Modeling (some aspects of) the female reproductive system

Gonadotropin and follicular dynamics

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Scientific and societal issues

Understanding of a complex process of developmental biology, occuring 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)

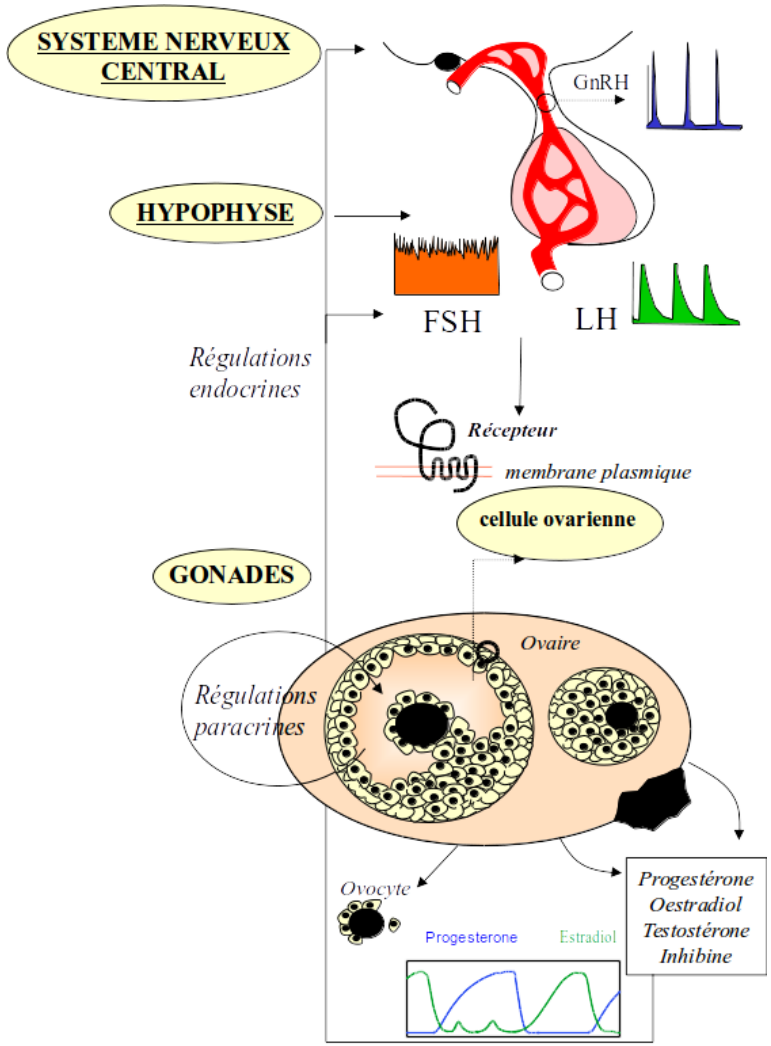
- Biotechnology of reproduction (*in vivo*, *ex vivo*, *in vitro*)
- Clinical, economical and environmental issues

Multiscale biology and Folliculogenesis

Encoding et decoding complex neuro-hormonal signals

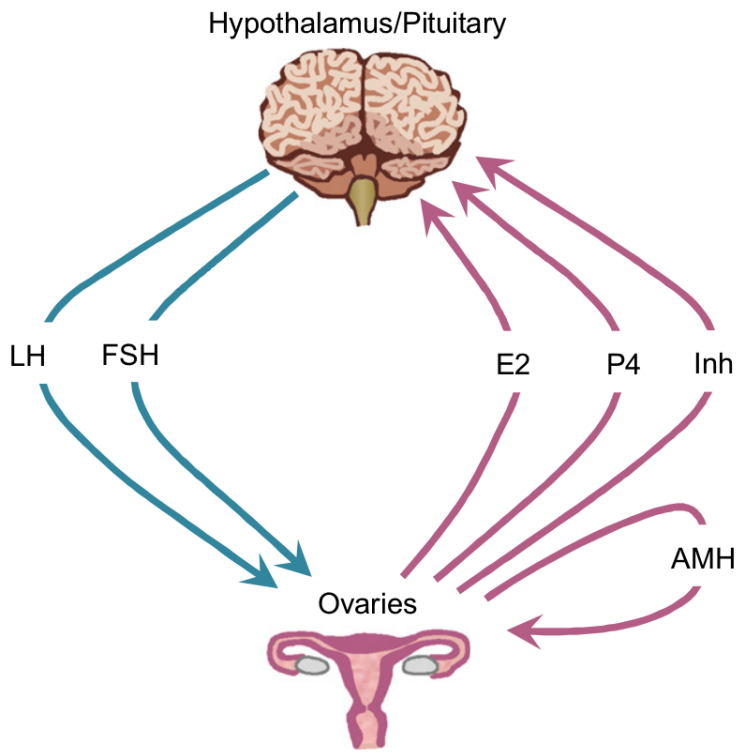
Population dynamics : gametogenesis

Intra-cellular level : signaling networks

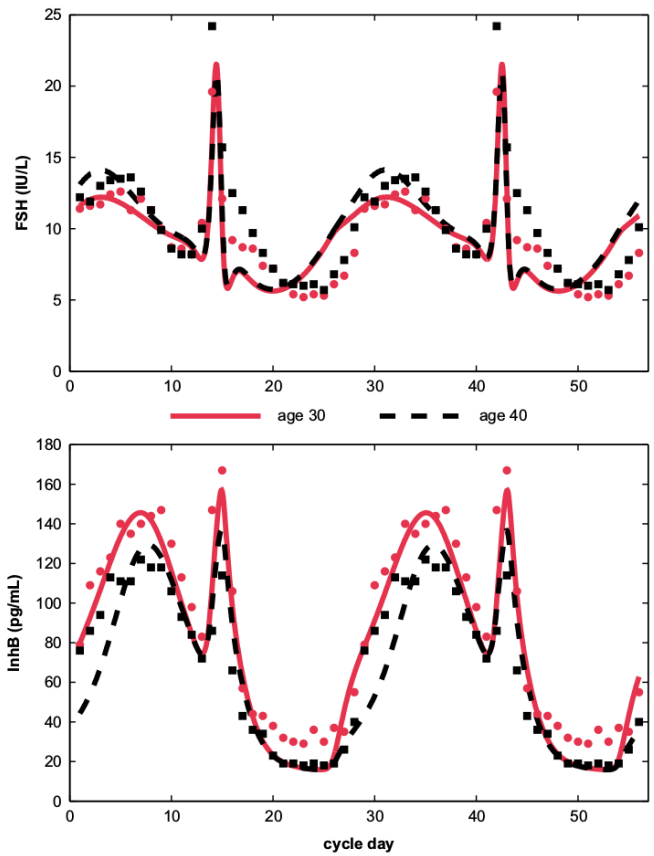


Hormonal signals (at the anatomic scale)

Mostly phenomenological equations (DDEs/SDEs) to represent measured levels of circulating hormones.



Margolskee & Selgrade, JTB 2013



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These models can explain some disorders in hormonal levels and predict the effect of pharmaceutical intervention.

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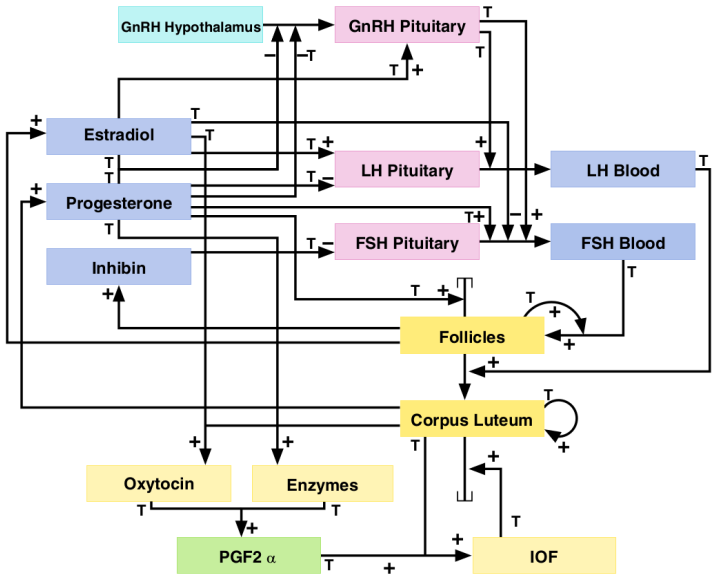
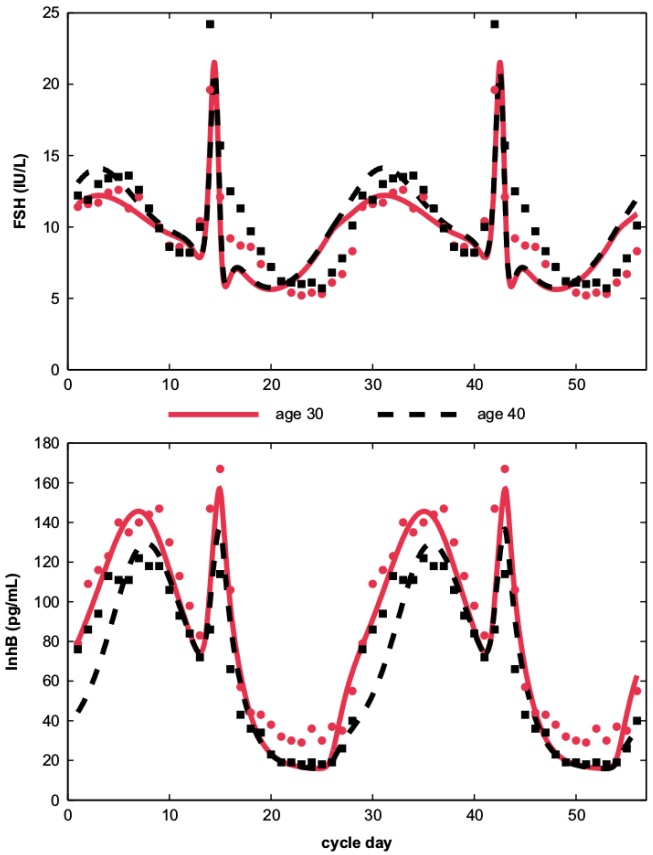


Stötzel et al., Therio. 2012

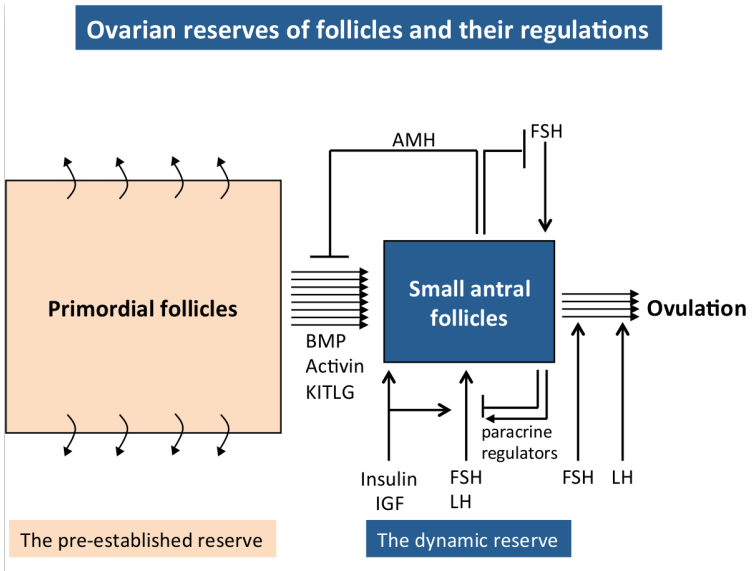


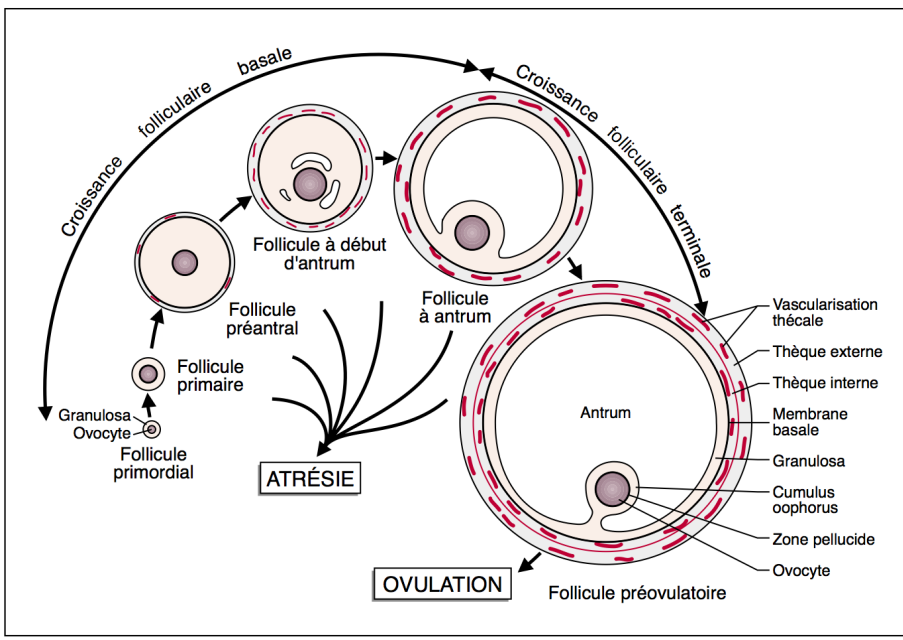
Margolskee & Selgrade, JTB 2013

These models can explain some disorders in hormonal levels and predict the effect of pharmaceutical intervention. **Theoretical analysis gets rapidly challenging !**

Gametogenesis : Ovarian folliculogenesis

- Morphogenesis and maturation of ovarian follicles
  somatic and germ (egg) cells





Monniaux, Theriogenology 2016

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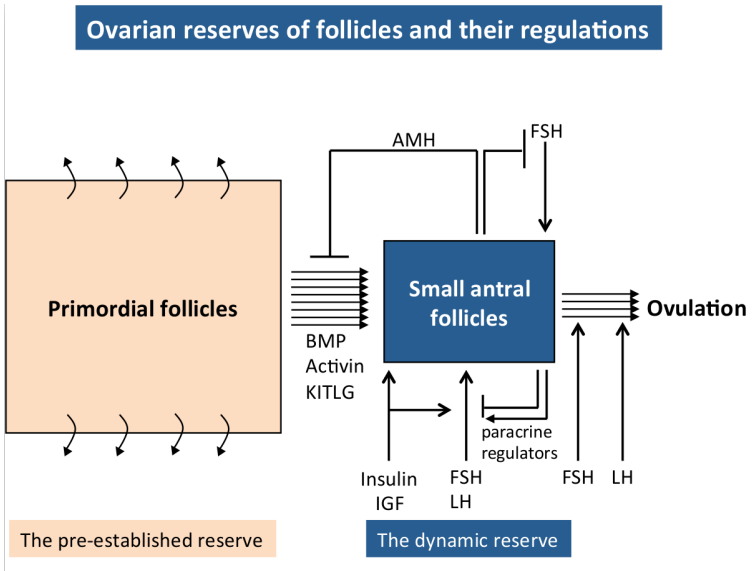
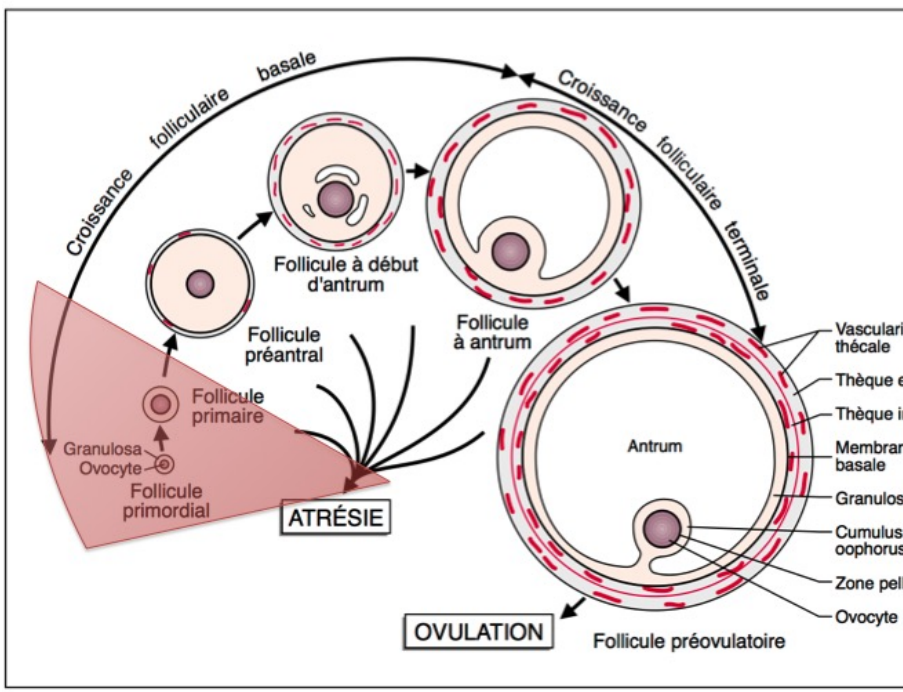
  static reserve (perinatal in most mammals)
  Slow activation





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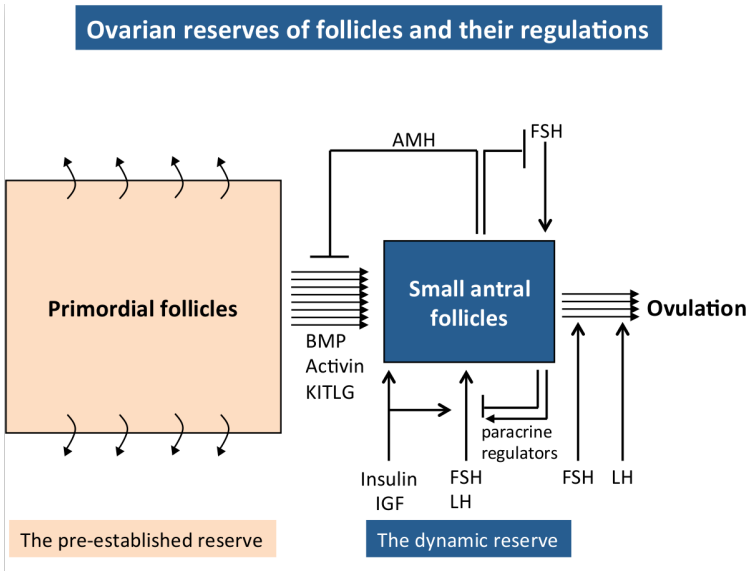

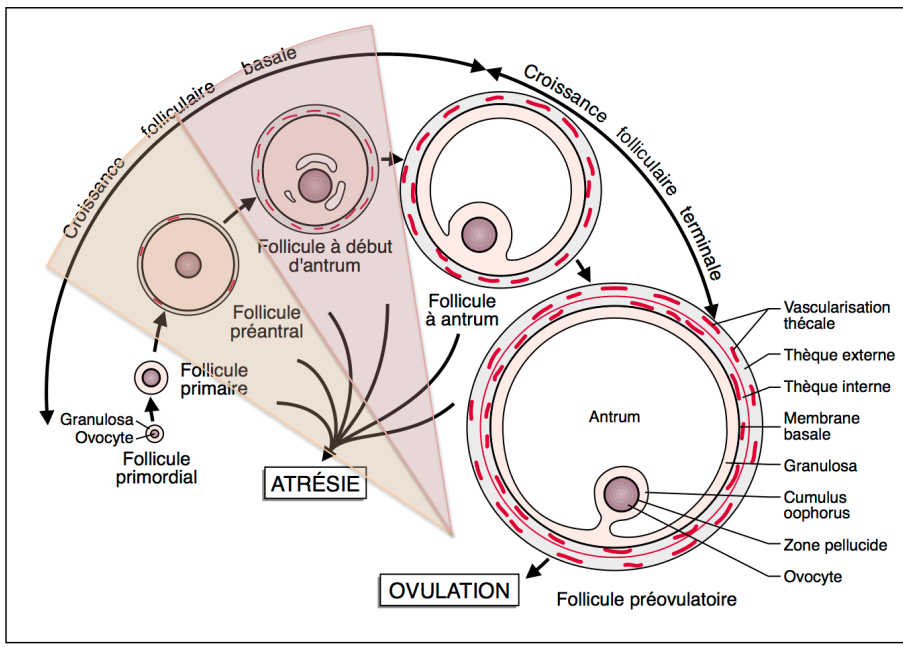

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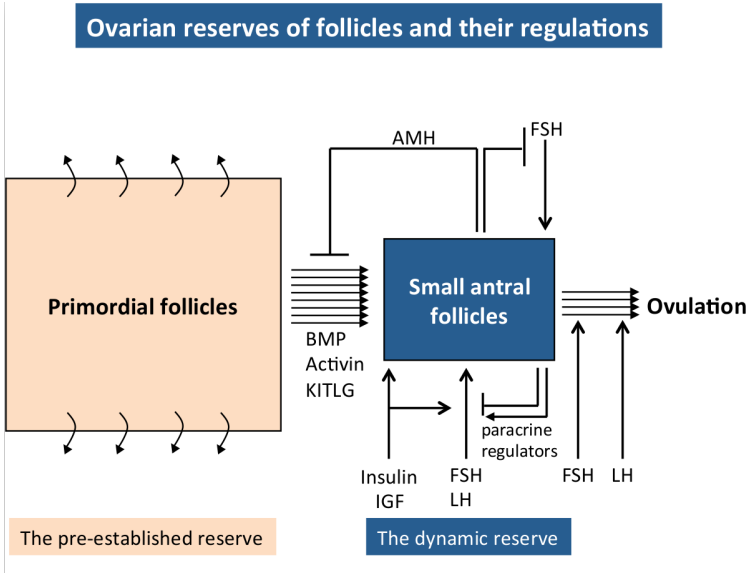
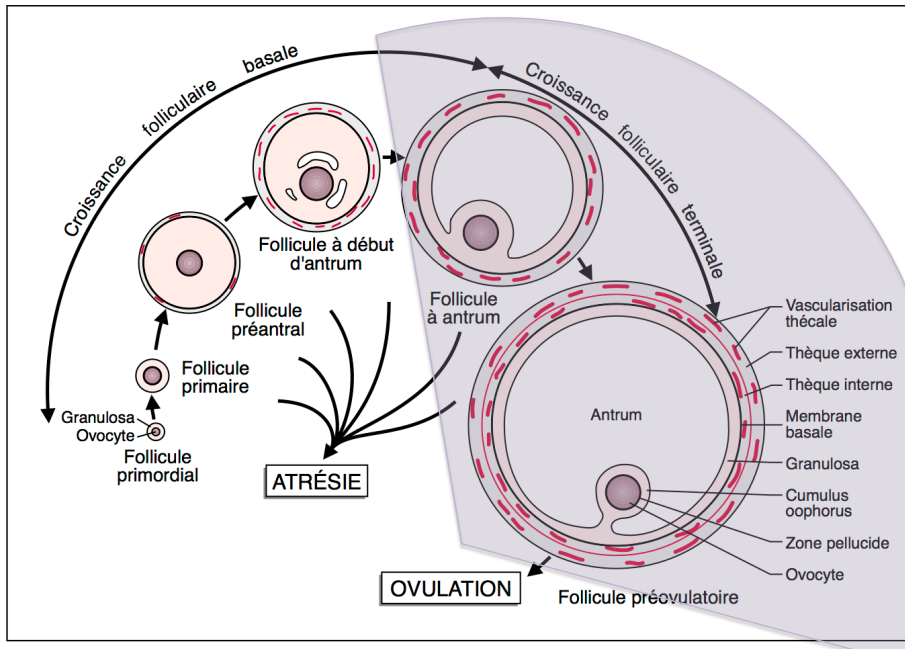
- Terminal growth
  After puberty : ovulation within an ovarian cycle



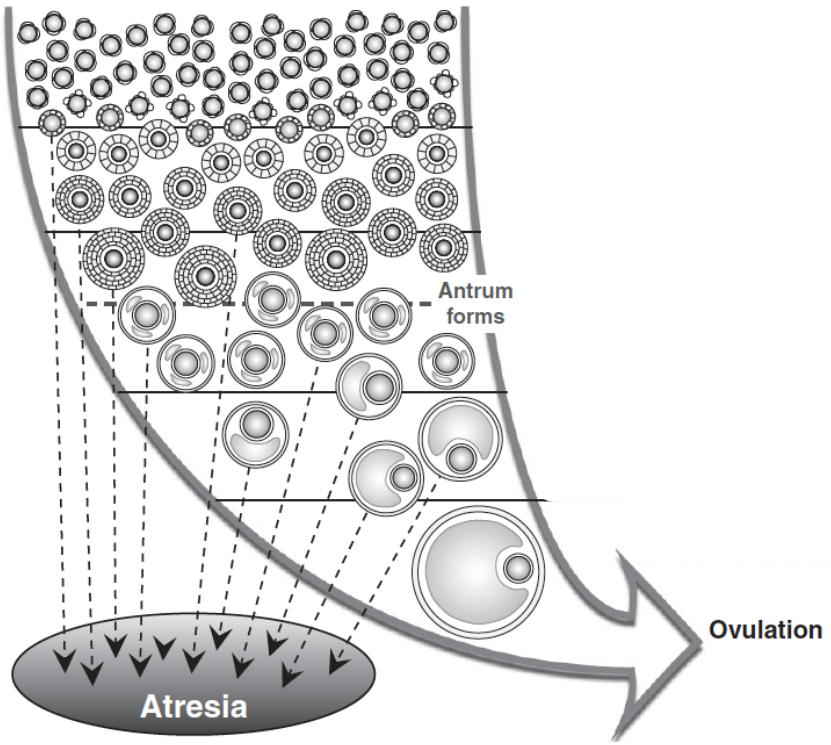


Gametogenesis : Ovarian folliculogenesis

Order of magnitude of the follicle population in women

- Quiescent follicles

peri-natal	$\approx 5.10^6$
At birth	$\approx 1.10^6$
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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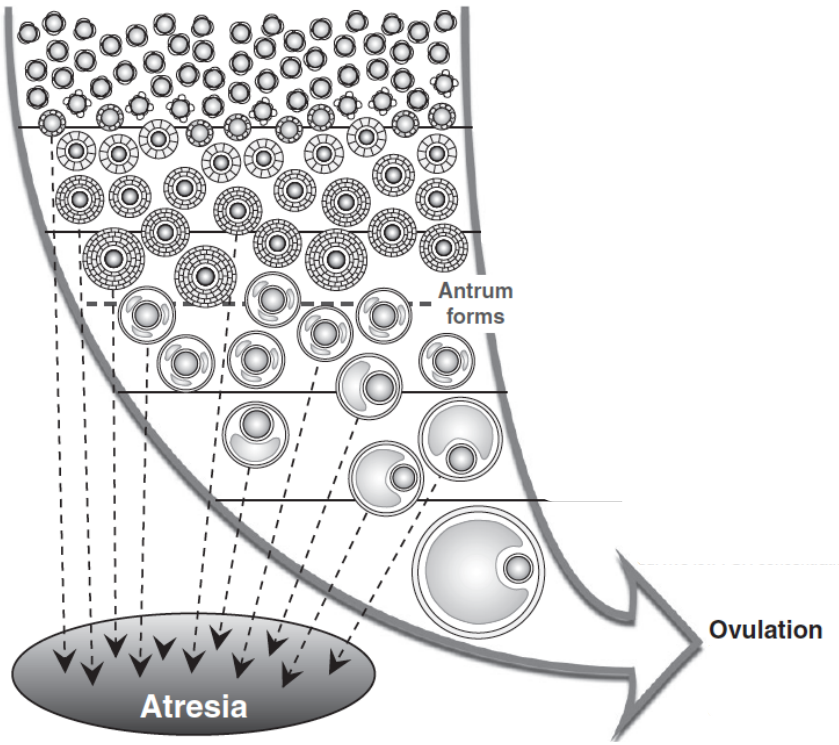
- Growing follicles
  - Maturation time $120 - 180j$
  - Basal follicles $10^3 - 10^4$
  - Terminal follicles 10^2
  - Pre-Ovulatory follicles a few
  - Atresia Most of them !



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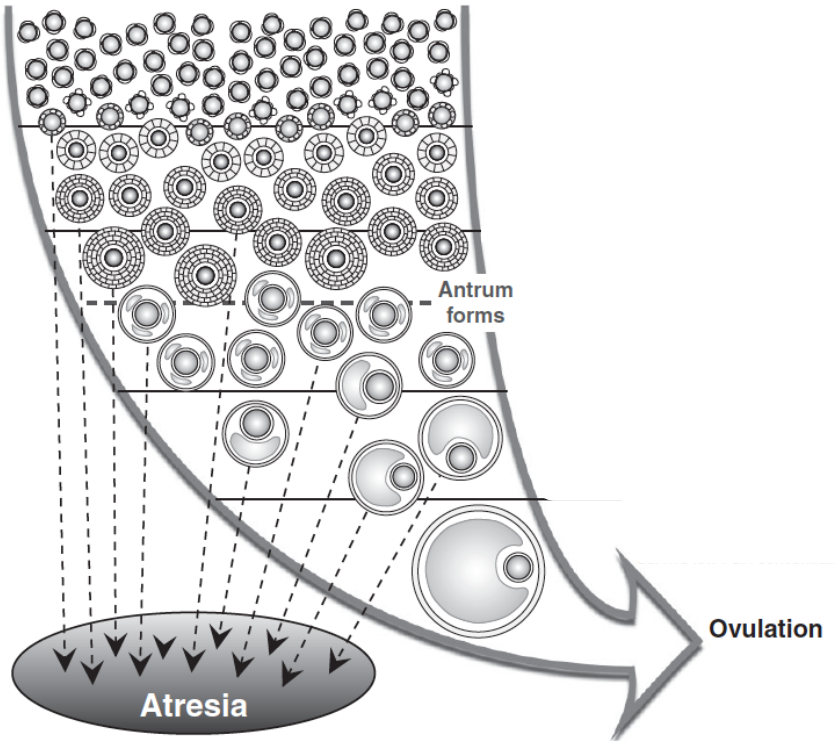
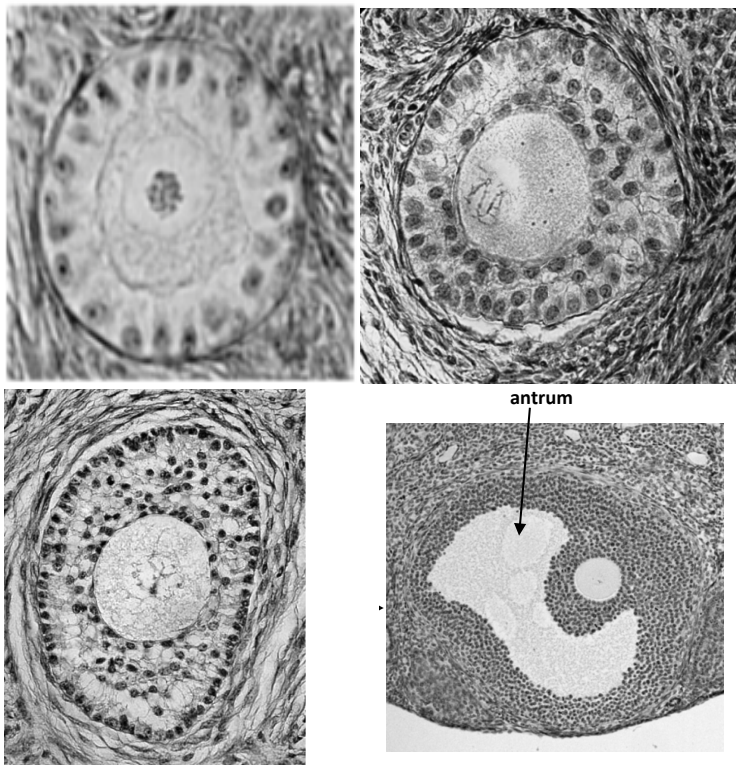
-> **Only** 400 **follicles will ever reach the pre-ovulatory stage**



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

Gametogenesis : Ovarian folliculogenesis

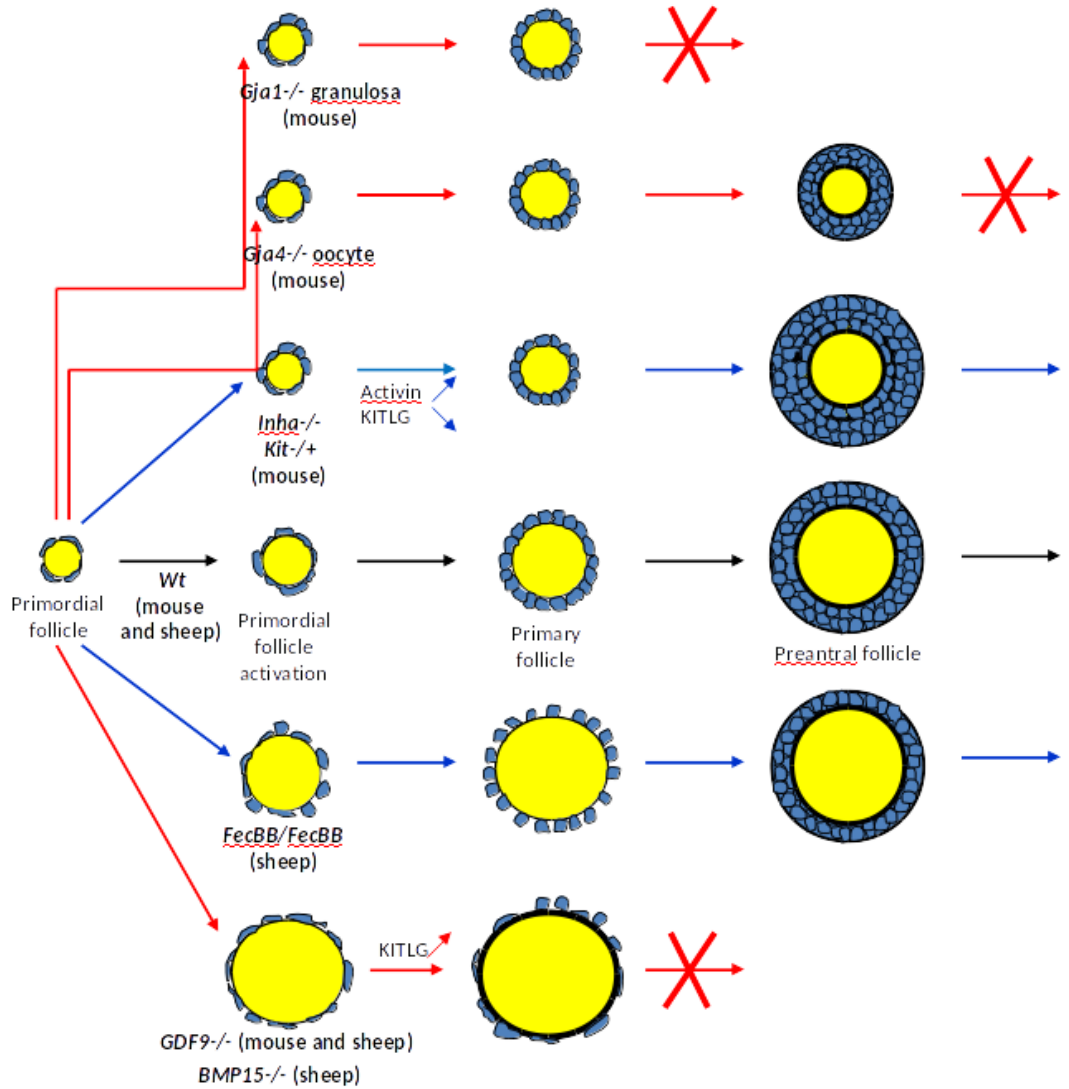
- Order of magnitude for a single follicle (women) at different maturation stages
  - ovocyte (egg cell) diam. : $0.01 - 0.1mm$
  - follicle diam. $0.03 - 20mm$
  - somatic cells diam. $\approx 0.01mm$
  - nb somatic cells $10^2 - 10^7$



Courtesy of Danielle Monniaux.

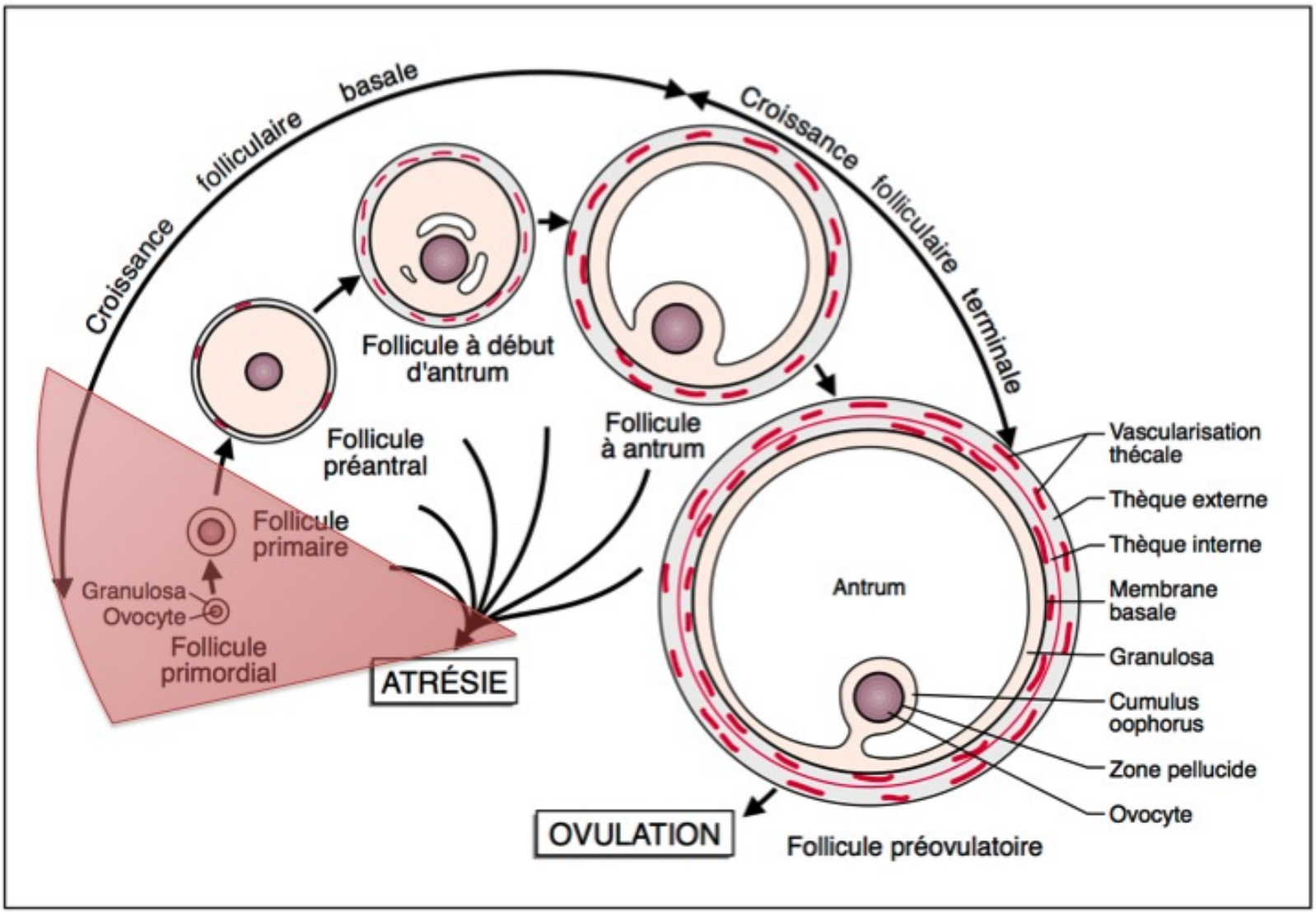
Morphogenesis of a single follicle

Possible physiological or pathological disorders



Monniaux, Theriogenology 2016

Initiation of a follicle



Key points of follicle initiation

Exiting of a quiescent state

A single layer of somatic cells

Two somatic cell types : flattened and cuboid

Irreversible transition from flattened to cuboid

Proliferation of cuboid cells

Auto-amplification ?

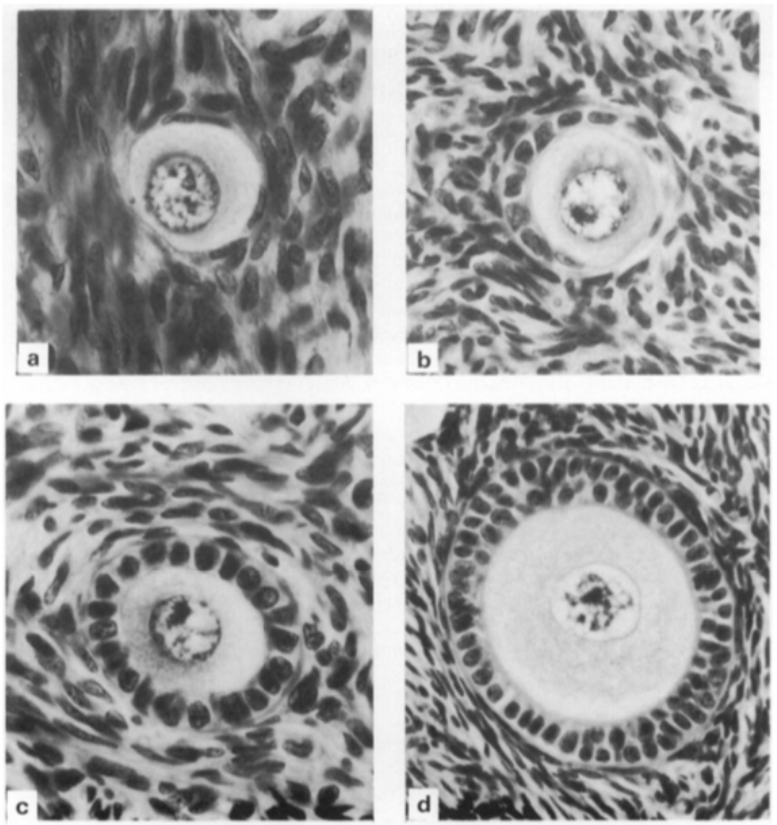


Fig. 1. Illustrations of follicle types: (a) Type B, × 570; (b) Type B/C, × 570; (c) Type C, × 570; (d) Type D, × 410.

Histological section of women ovarian follicles, Gougeon et al, 1987

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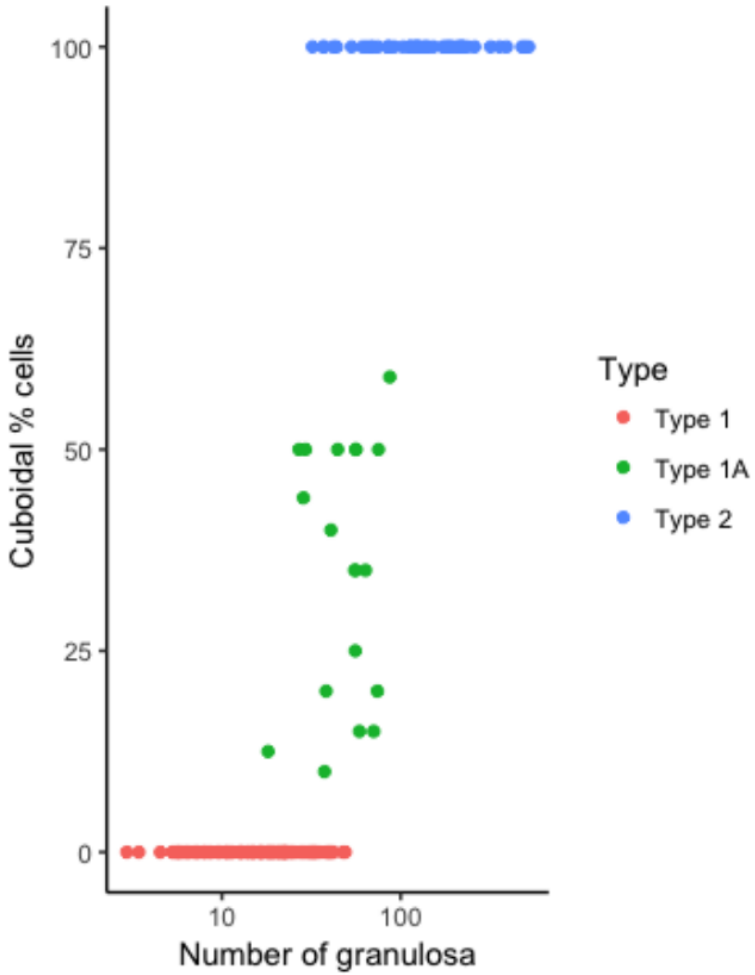


Courtesy of Mc Natty

Dynamical model

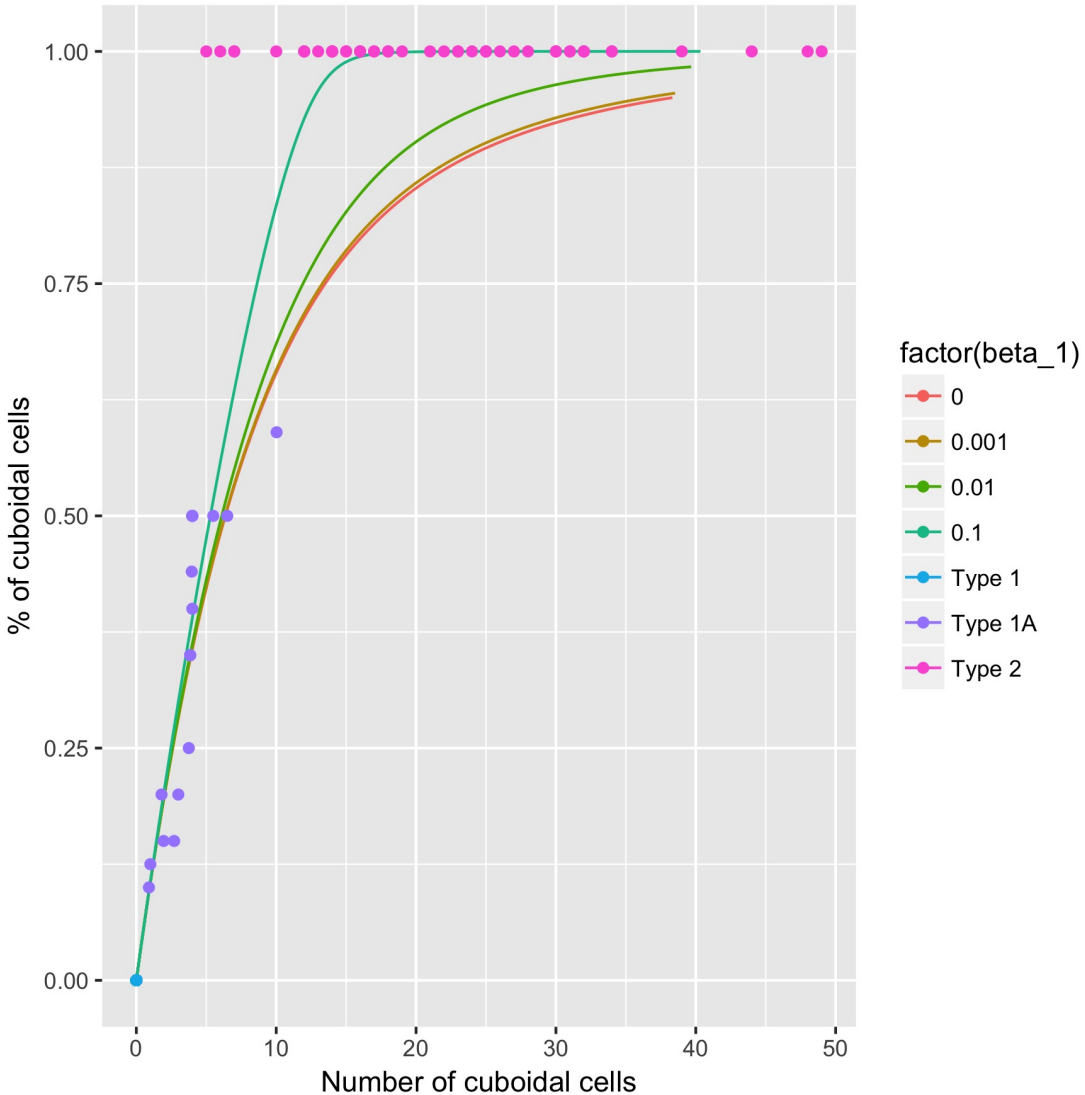
↪ Two population of cells : F (flattened) and C (cuboid)

↪ Small number of cells : Markov chain model

Events	Reaction	Intensity function
differentiation	$F \to C$	$\alpha F + \beta \dfrac{FC}{F+C}$
division	$C \to C + C$	γC

↪ Feedback of cuboid cells on the differentiation rate

Comparison with data *ex vivo*

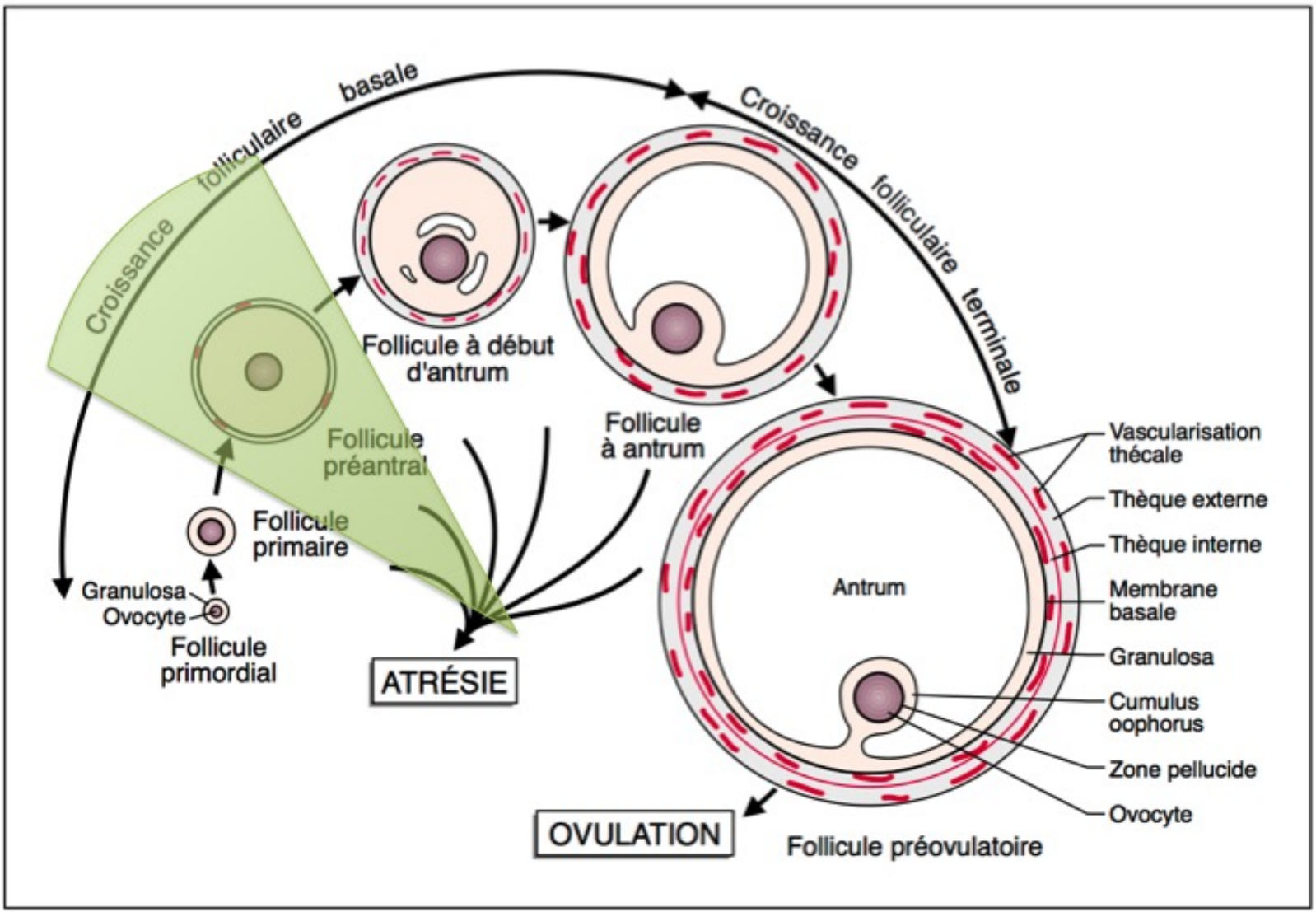


- Ex vivo data in sheep fetus (Courtesy of K. McNatty)

$\Rightarrow$ superposition of proliferation and differentiation processes

$\Rightarrow$ Prediction of the statistics of the initiation time

Basal growth of a follicle



Key points of the basal growth of a follicle

Growth of a follicle after initiation

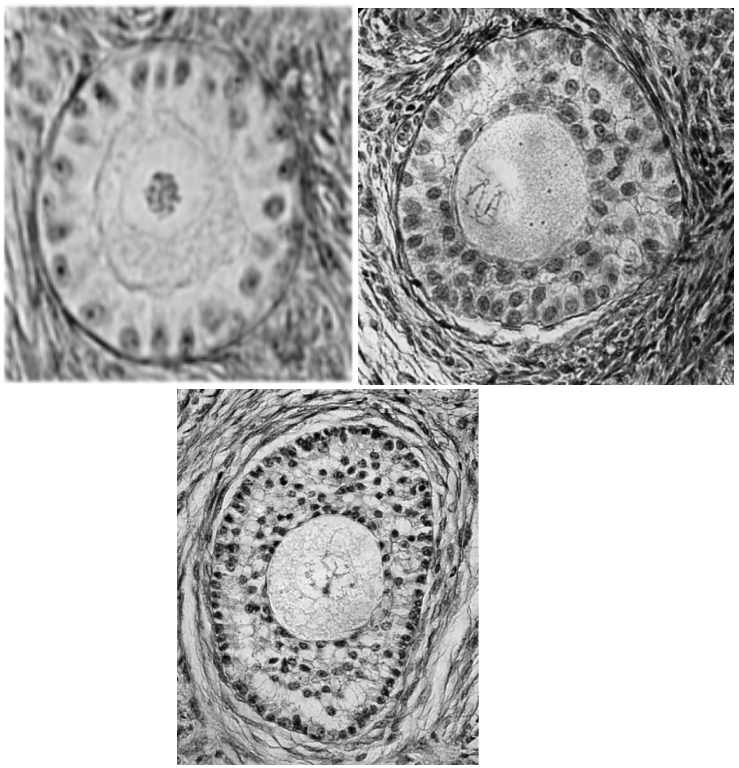
Spherical symmetry

Concentric layers of somatic cells

Joint dynamic
oocyte Growth
somatic cells proliferation

Feedback mechanism ?

Dynamical characteristic ?

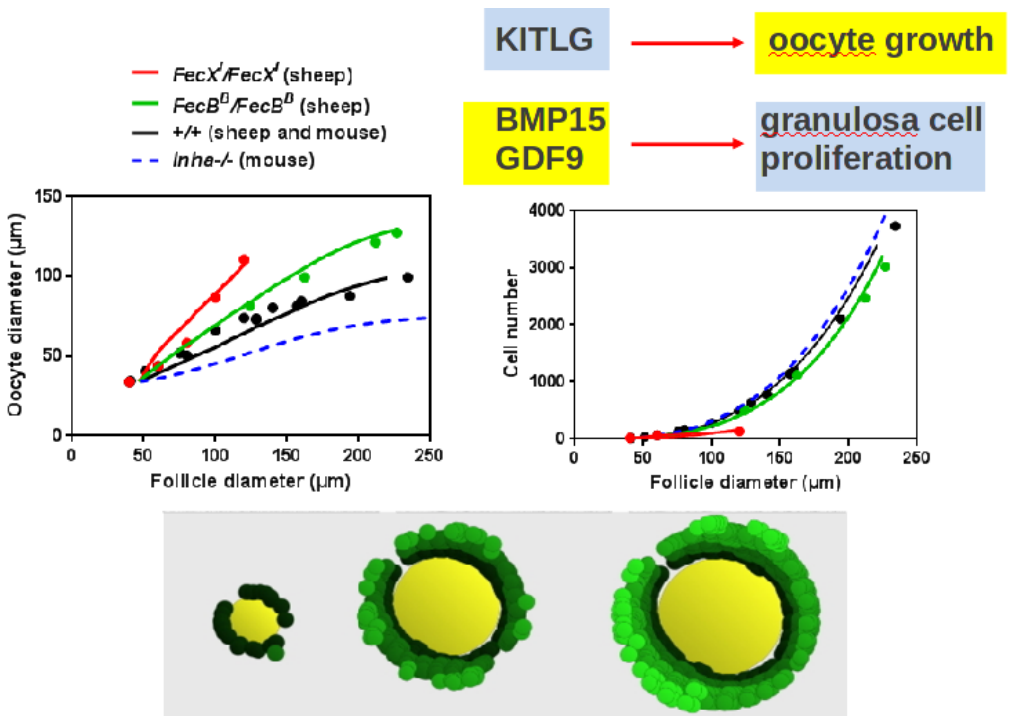


Courtesy of Danielle Monniaux.

Dynamical model

Individual-based spatial model (that started in CEMRACS 2009 !)

- Growth of the ovocyte given by an ODE, modulated by the number of somatic cells
- Age-dependent division and Displacement of somatic cells driven by local crowding
- Free Boundary problem



Michel et al., Multiscale Model. & Simul. 2013

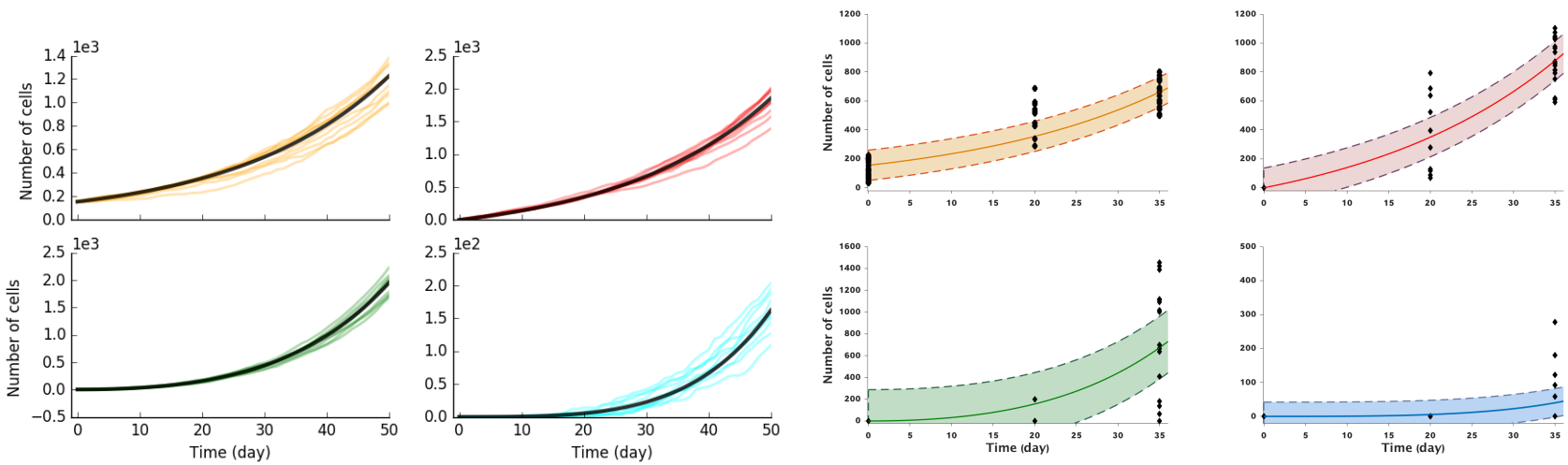
Study of a linear model and "kinetic" data

Bellman-Harris multi-types // McKendrick-von Foerster multi-dim

Quantification of the doubling time
Malthusian exponential growth

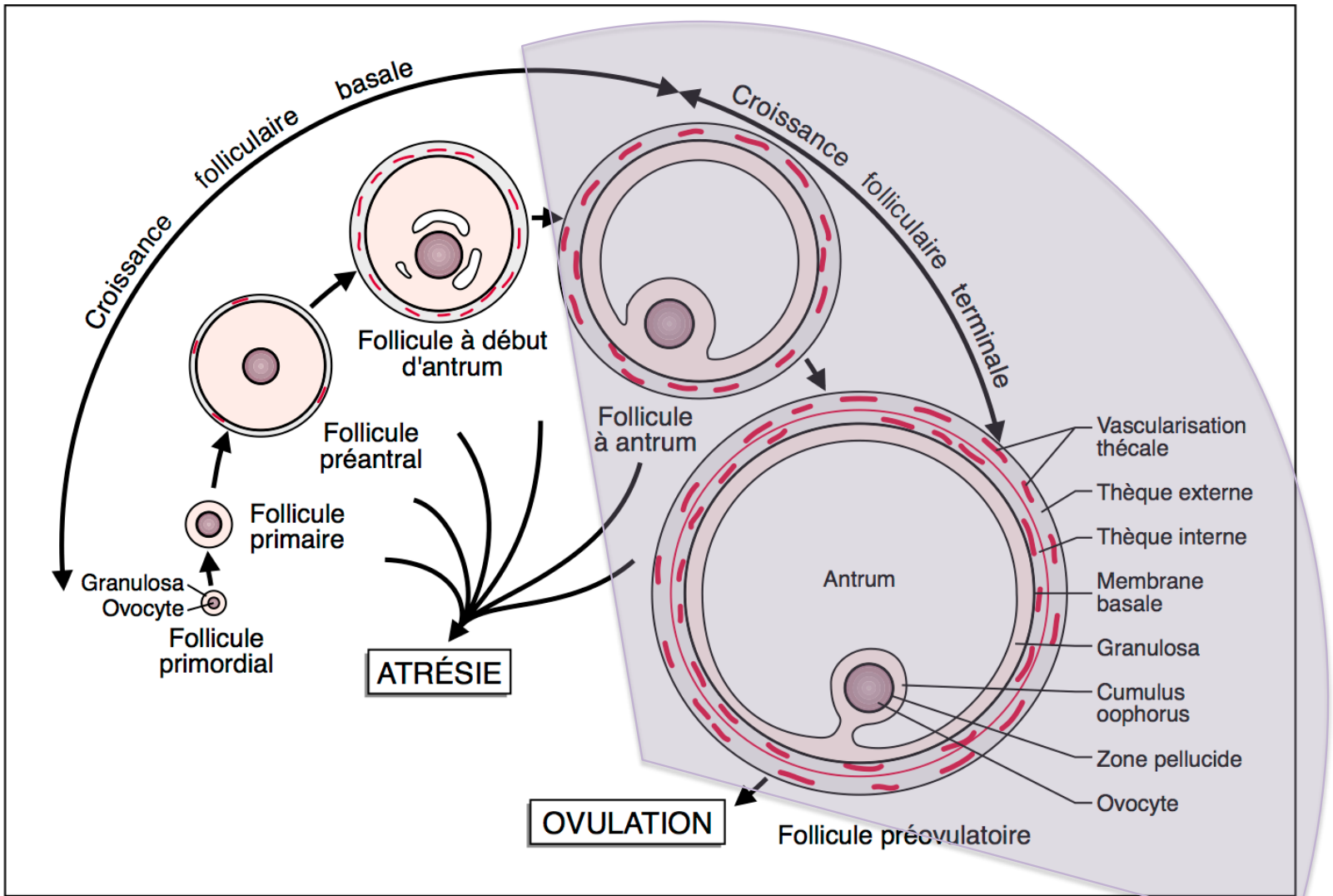
Long time stable age-spatial distribution ($\lim_{t\to\infty} \varrho(t,x)e^{-\lambda t} = \hat{\varrho}(x)$)

Calibration of the model with reconstructed kinetic data
parameter values



Robin et al., arXiv :1712.05372

Terminal growth



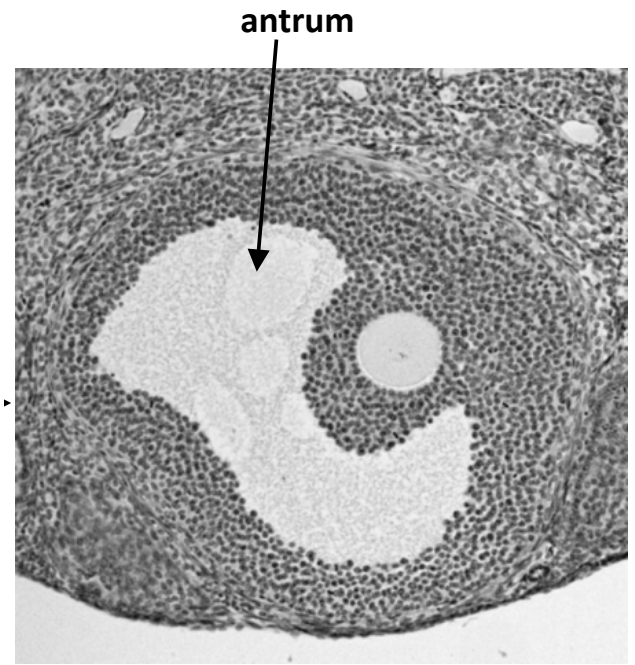
Antral growth

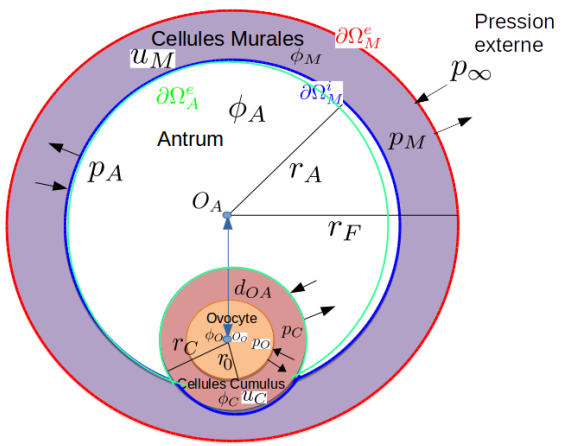
- No more spherical symmetry
- Joint dynamics
  Antrum growth
  Proliferation and Differentiation of somatic cells
  Morphogen gradient

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

+ Boundary conditions and constitutive laws

work in progress...

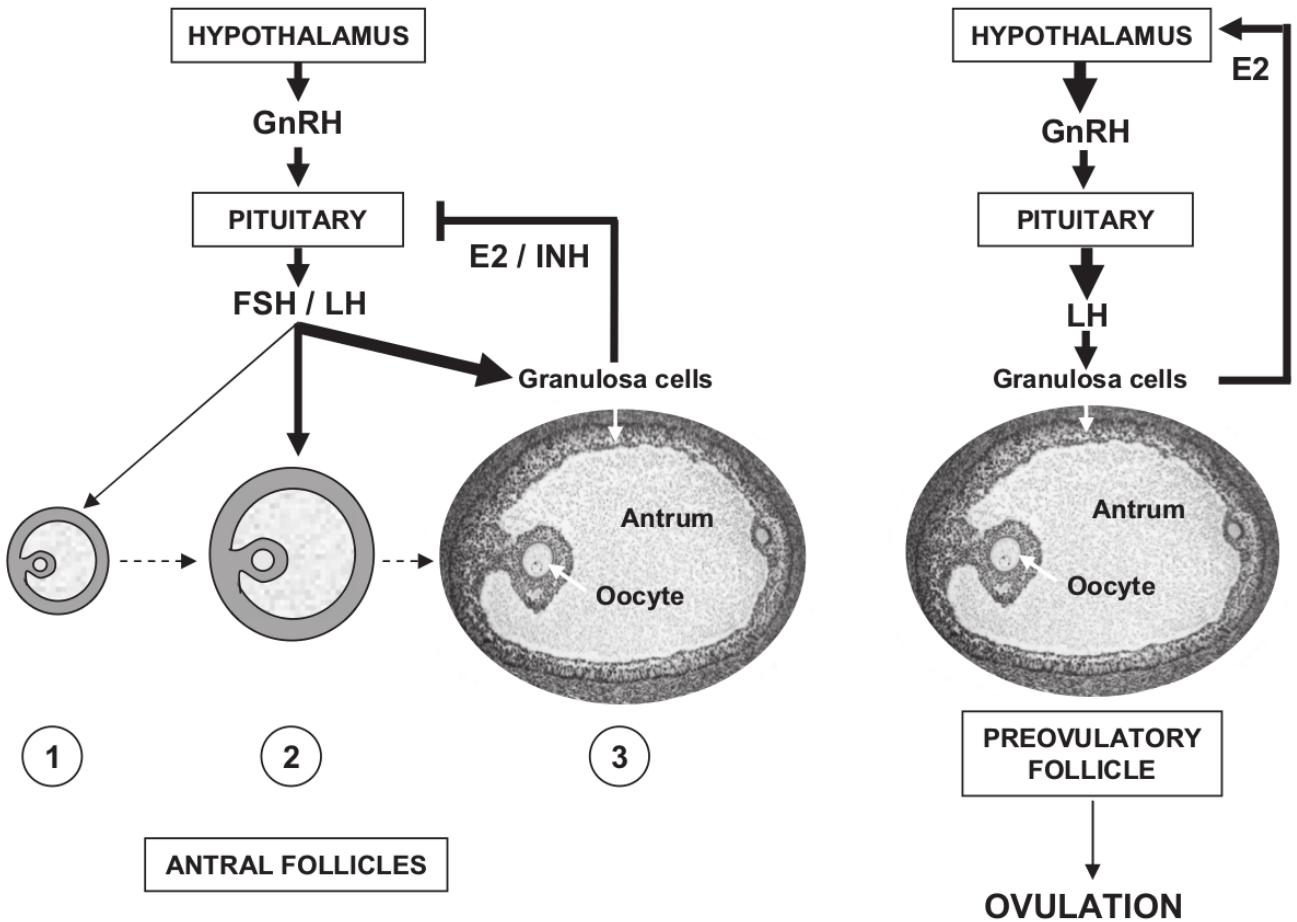




Tertiary (antral) follicle

Models of population of follicles : selection model

In reality, the growth process of follicles are not independent but are highly coordinated, both by steric/biophysical constraints and hormonal feedbacks.



Clément and Monniaux, PBMB 2013

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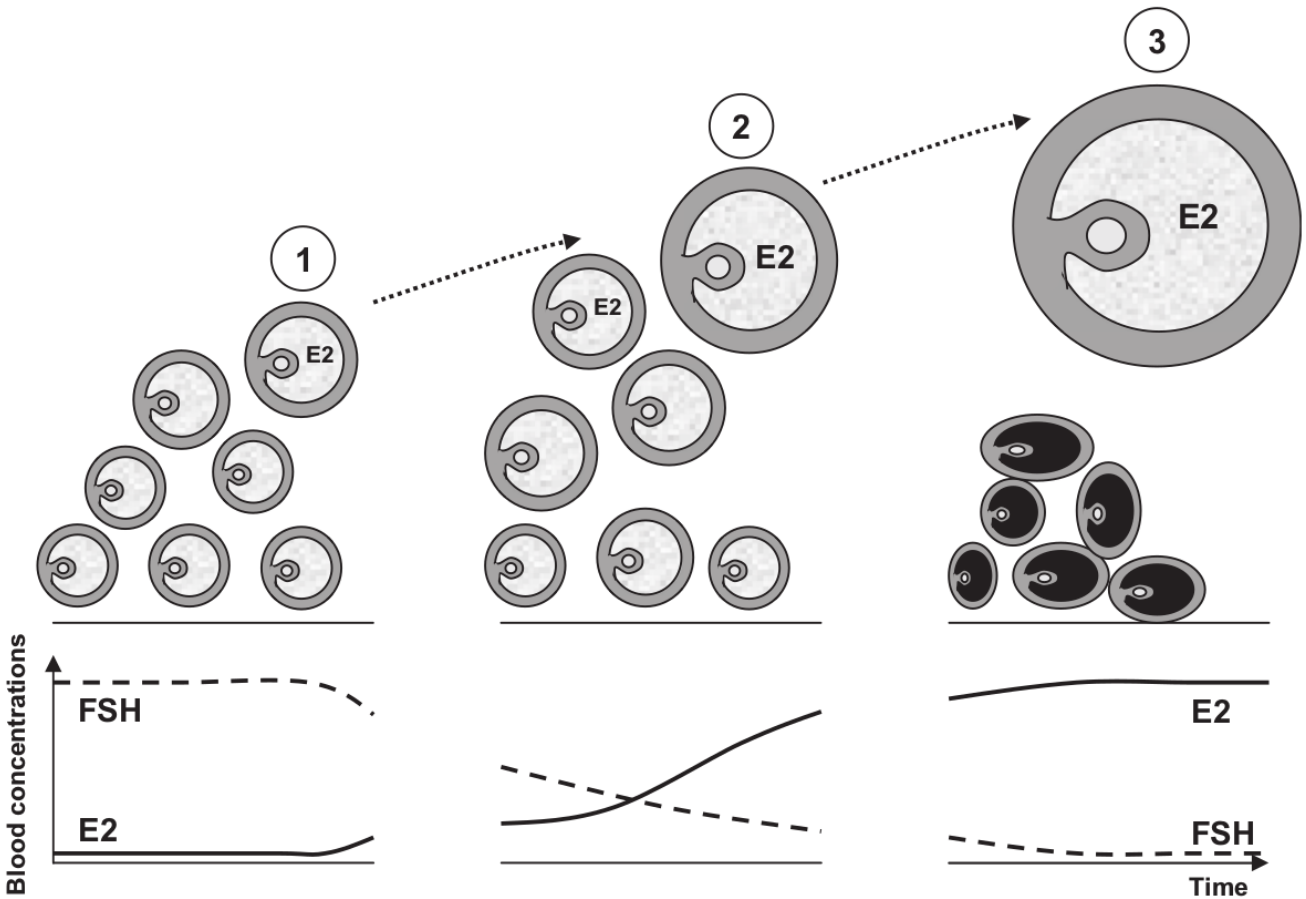
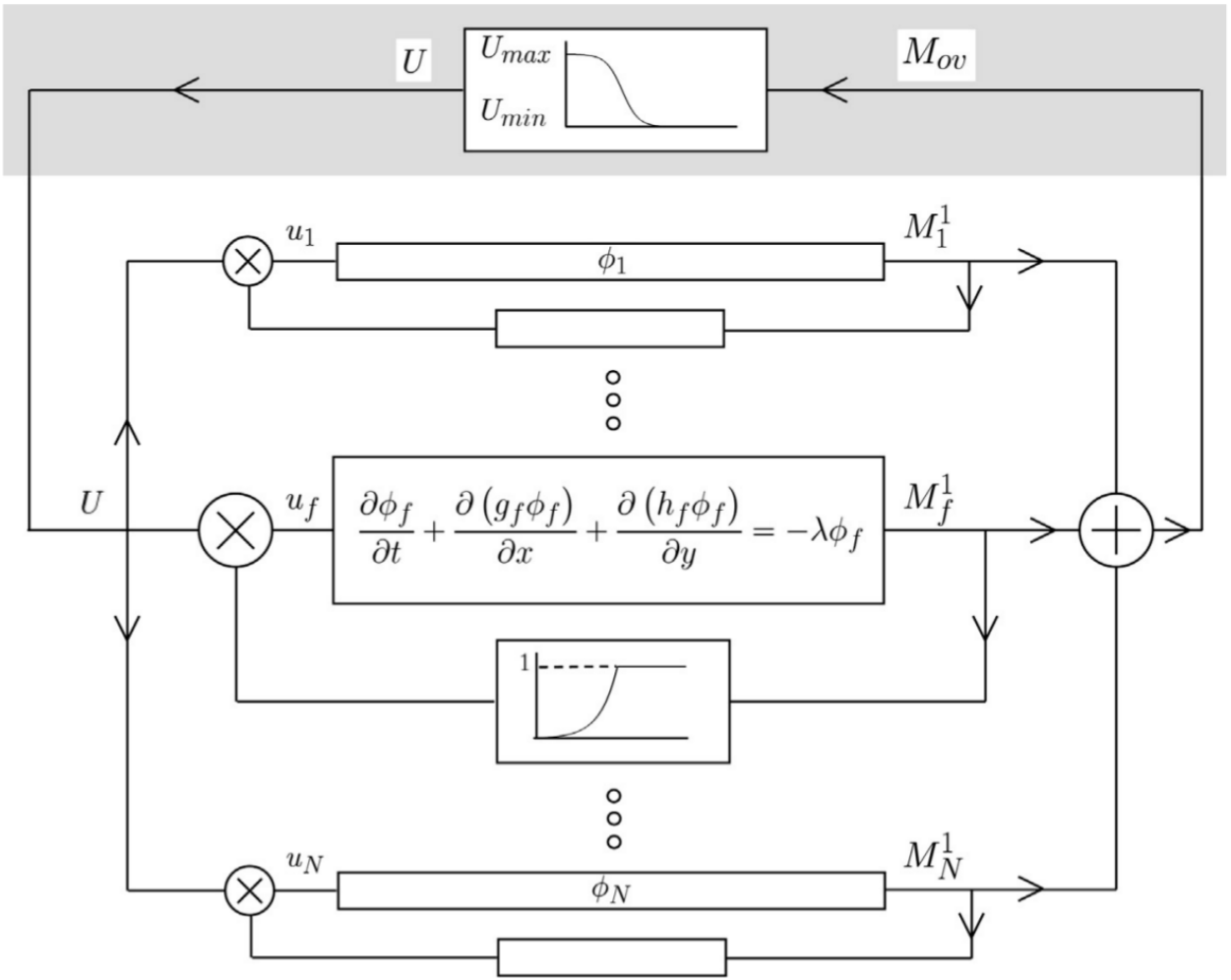


Clément and Monniaux, PBMB 2013

Models of population of follicles : selection model

Nonlinearly coupled conservation laws, one for each follicle
(somatic cells density population, structured by age and maturity)



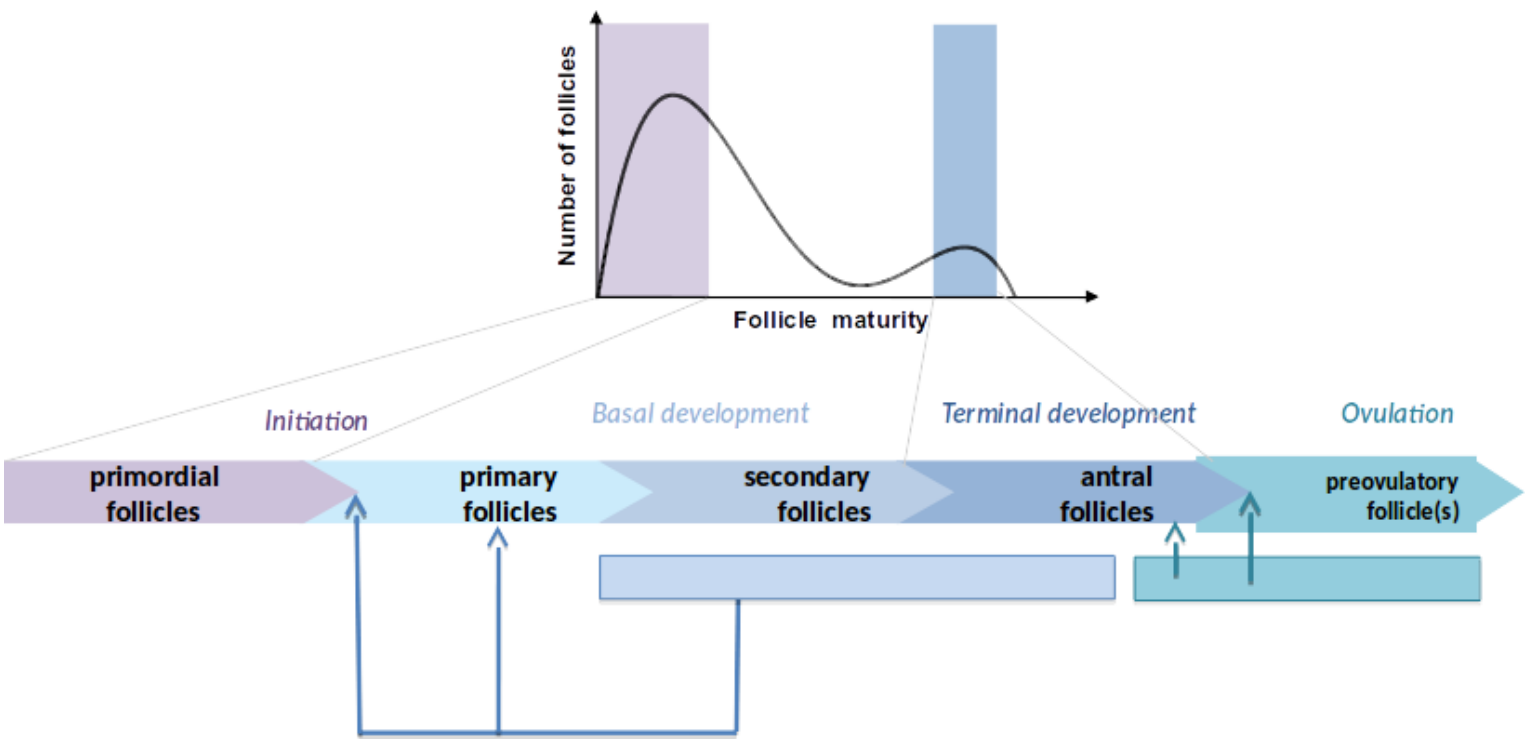
Clément and Monniaux, PBMB 2013

Models of population of follicles : on the lifespan

Folliculogenesis on the lifespan

⇒ Nonlinear interactions between follicles populations (endocrine and paracrine)

⇒ (Slow) (decay) of total follicles number and "stable" repartition in the maturity space



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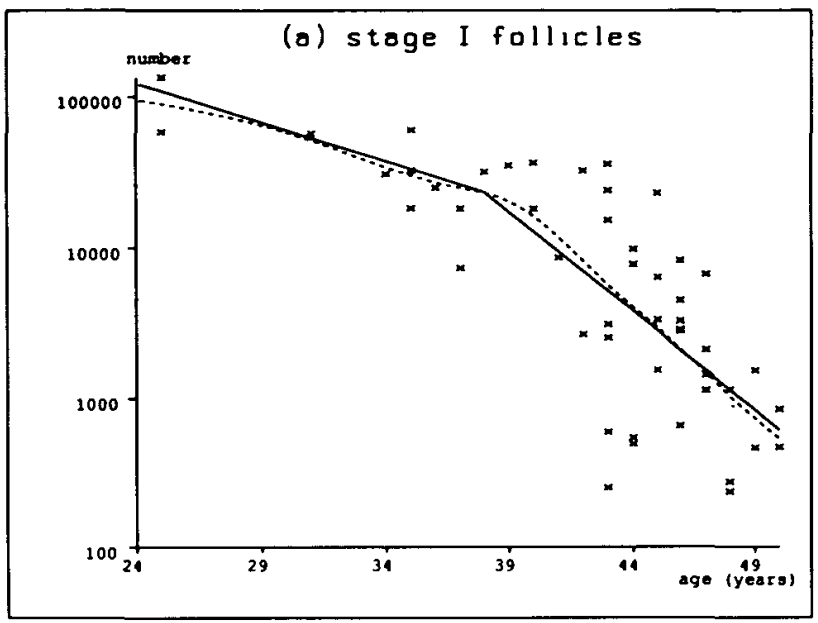
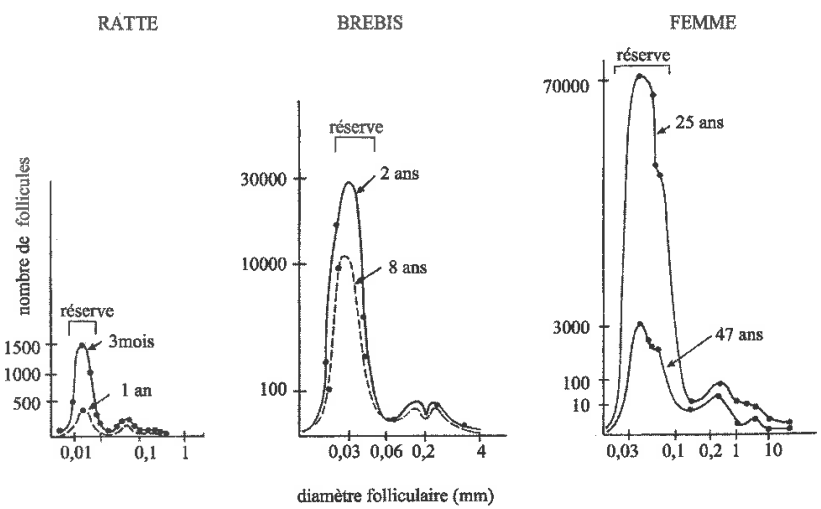
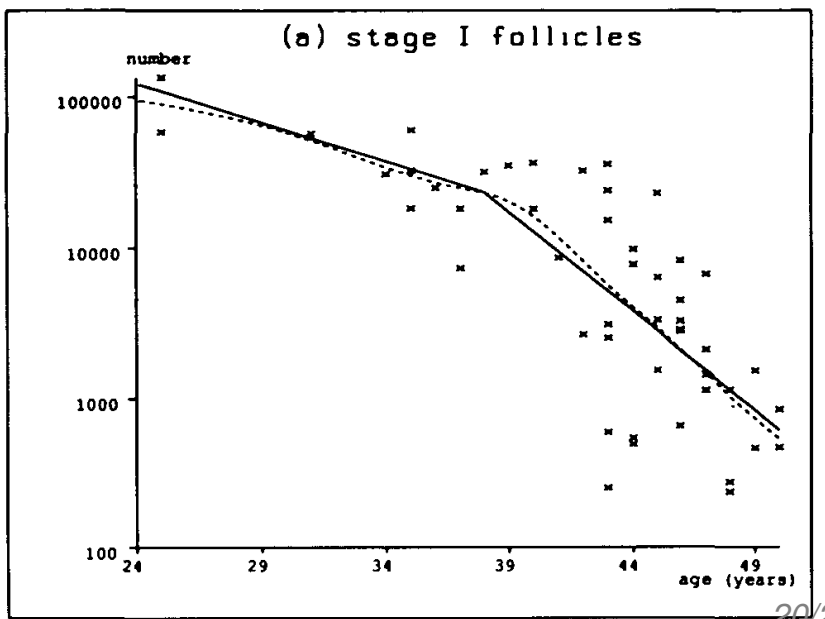


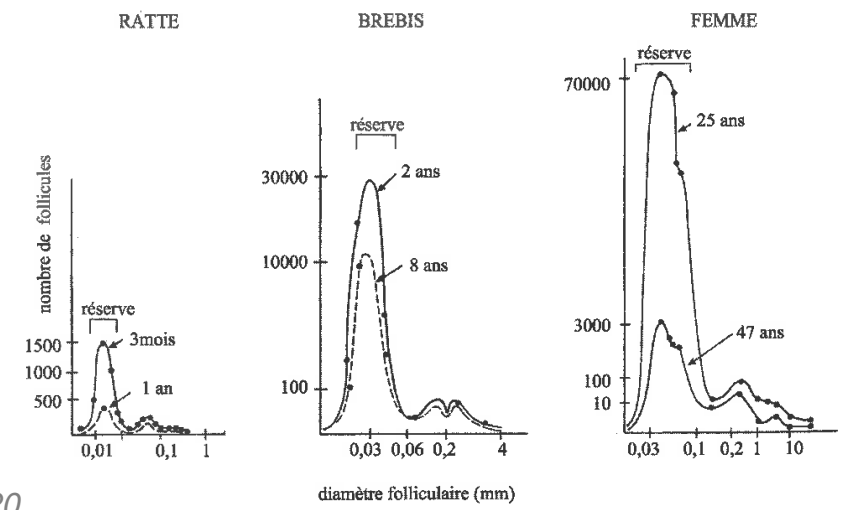


Models of population of follicles

Cemracs project

$$
\begin{aligned}
\frac{\partial \rho(t,x)}{\partial t} + \frac{\partial \left(\lambda(t,x)\rho(t,x)\right)}{\partial x} &= -\mu(t,x)\rho(t,x)\,, t>0, 0<x<1\,,\\
\lim_{x\to 0} \left(\lambda(t,x)\rho(t,x)\right) &= \lambda_0(t)\rho_0(t)\,,\\
\frac{d\rho_0(t)}{dt} &= -\lambda_0(t)\rho_0(t) - \mu_0(t)\rho_0(t)\,.
\end{aligned}
$$





Thanks

- ⋆ Frédérique Clément, Frédérique Robin (INRIA Saclay,projet EPC)
- ⋆ Danielle Monniaux, team BIOS, BINGO (PRC INRA)
- ⋆ Marie Postel (LJLL, UPMC)
- ⋆ Celine Bonnet, Keltoum Chahour (cemracs)
- ⋆ Fundings (INRA PHASE department)

PHYSIOLOGIE ANIMALE ET SYSTÈMES D'ÉLEVAGE

F. Robin et al., arXiv :1712.05372
Analysis and calibration of a linear model for structured cell populations with unidirectional motion : Application to the morphogenesis of ovarian follicles

R. Y. et al., In press
Advances in computational modeling approaches of pituitary gonadotropin signaling

D. Monniaux. et al., Biol. Cell (2016)
Multi-scale modelling of ovarian follicular development : From follicular morphogenesis to selection for ovulation

Initiation Model

$$
\begin{aligned}
F(t) &= F_0 - Y_1 \left(\int_0^t \alpha F(s) + \beta \frac{F(s)C(s)}{F(s)+C(s)} ds \right) \\
C(t) &= Y_1 \left(\int_0^t \alpha F(s) + \beta \frac{F(s)C(s)}{F(s)+C(s)} ds \right) + Y_2 \left(\int_0^t \gamma C(s) ds \right)
\end{aligned}
$$

We are interested in the initiation time $\tau = \inf\{t \geqslant 0, F(t) = 0\}$ and the number of cells at that time $C(\tau)$.

Basal Model

$$
\begin{aligned}
Z(t) &= \sum_{k=1}^{N_0} \delta_{X_k(0),A_k(0)+t} + \int_0^t \mathbf{1}_{k<N_{s^-}} Q\left(ds, n(dk), d\theta, J(dj)\right) \\
&\quad \Bigg[\left(2\delta_{X_k(s^-),t-s} - \delta_{X_k(s^-),A_k(s^-)+t-s}\right) \mathbf{1}_{\theta<m_1(s,Z_s,k)} \\
&\quad \left(\delta_{J,A_k(s^-)+t-s} - \delta_{X_k(s^-),A_k(s^-)+t-s}\right) \mathbf{1}_{m_1(s,Z_s,k)<\theta<m_2(s,Z_s,k,J)} \Bigg] \\
\frac{d}{dt} d_0 &= d_0^{\alpha}(1-d_0)^{\beta} f(Z_s)\,.
\end{aligned}
$$

m_1 and m_2 gives the birth rates (age and position dependent) and displacement rate (crowing dependent). We are interested in the respective growth rate of the somatic cell population versus the oocyte diameter.

Linear basal Model

$$Z_t = \sum_{k=1}^{N(0)} \delta_{i_k(0),a_k(0)+t} + \int_0^t \int \overbrace{\mathbf{1}_{k \leqslant N(s^-)}}^{\text{Mother } \not\in} \cdot \overbrace{\mathbf{1}_{\theta < b_k(s^-)}}^{\text{division time}} Q(ds, dk, d\theta, du)$$

$$\Big[\underbrace{2\delta_{i_k+1,t-s}\mathbf{1}_{E_1}}_{\text{2 displacements}} + \underbrace{\left(\delta_{i_k,t-s} + \delta_{i_k+1,t-s}\right)\mathbf{1}_{E_2}}_{\text{daugther } \not\in \text{ :1 displacement}} + \underbrace{2\delta_{i_k,t-s}\mathbf{1}_{E_3}}_{\text{0 displacement}} - \delta_{i_k,a_k+t-s} \Big]$$

where Q Poisson measure on $\mathbb{R}^+ \times \mathbb{N}^* \times \mathbb{R}^+ \times [0,1]$,

$$E_1 = \{u \leqslant p_{0,2}^{i_k}\}, E_2 = \{p_{0,2}^{i_k} < u \leqslant p_{0,2}^{i_k} + p_{1,1}^{i_k}\}, E_3 = \{p_{0,2}^{i_k} + p_{1,1}^{i_k} < u\}$$

and $b_k(s) = b_{i_k(s)}(a_k(s))$

Linear basal Model

Starting with one cell on layer i and age 0,

$$Z_t^{[i]} := \delta_{i,t} + \int_0^t \int \overbrace{\mathbf{1}_{k \leqslant N(s^-)}}^{\not\subset \text{ Mère}} \cdot \overbrace{\mathbf{1}_{\theta < b_k(s^-)}}^{\text{Temps de division}} \; Q(ds, dk, d\theta, du)$$

$$\Big[\underbrace{2\delta_{i_k+1,t-s}\mathbf{1}_{E_3}}_{\text{2 déplacements}} + \underbrace{\Big(\delta_{i_k,t-s} + \delta_{i_k+1,t-s}\Big)\mathbf{1}_{E_1}}_{\not\subset \text{ filles :1 déplacement}} + \underbrace{2\delta_{i_k,t-s}\mathbf{1}_{E_2}}_{\text{0 déplacement}} - \delta_{i_k,a_k+t-s} \Big]$$

we have the **branching property**

$$Z^{[i]}(t) = \begin{cases} \delta_{i,t}, & t < \tau(i) \\ Z_1^{[i_1]}(t-\tau) +_{\amalg} Z_2^{[i_2]}(t-\tau), & t \geqslant \tau(i) \end{cases}$$

where $\mathbb{P}\{\tau(i) > t\} = \exp\left(-\int_0^t b_i(s)ds\right)$
and (i_1, i_2) randomly drawn according to $p^i_{1,1}, p^i_{2,0}, p^i_{0,2}$.

Linear basal Model

Starting with one cell on layer i and age 0,

$$Z_t^{[i]} := \delta_{i,t} + \int_0^t \int \overbrace{\mathbf{1}_{k \leqslant N(s^-)}}^{\not\subset \text{ Mère}} \cdot \overbrace{\mathbf{1}_{\theta < b_k(s^-)}}^{\text{Temps de division}} Q(ds, dk, d\theta, du)$$

$$\Big[\underbrace{2\delta_{i_k+1,t-s}\mathbf{1}_{E_3}}_{\text{2 déplacements}} + \underbrace{\Big(\delta_{i_k,t-s} + \delta_{i_k+1,t-s}\Big)\mathbf{1}_{E_1}}_{\not\subset \text{ filles :1 déplacement}} + \underbrace{2\delta_{i_k,t-s}\mathbf{1}_{E_2}}_{\text{0 déplacement}} - \delta_{i_k,a_k+t-s} \Big]$$

We show that there exists λ such that

$$\lim_{t\to\infty} Z_t e^{-\lambda t} = \hat{Z}\,.$$

◇ The Malthus parameter λ exists when the ensemble

$$\mathcal{M} := \{\lambda_j, \overbrace{\int_0^{+\infty} b_j(a) e^{-\lambda_j a - \int_0^a b_j(u)du} da}^{\mathbb{E}\left[e^{-\lambda_j \tau(j)}\right]} = \frac{1}{2p_S^{(j)}}\}$$

admits a unique maximal element, et $\lambda = \max \mathcal{M}$.

Let $\rho(t, \dot{)} = \mathbb{E}Z_t$.

Theorem (Robin et al., submitted)

If $\forall j\,, \forall a$, $0 < \underline{b_j} \leqslant b_j(a) \leqslant \overline{b}_j < \infty$, *Then there exists a polynomial* β *of degree at most* $J-1$, η *et* $\mu > 0$ *such that*

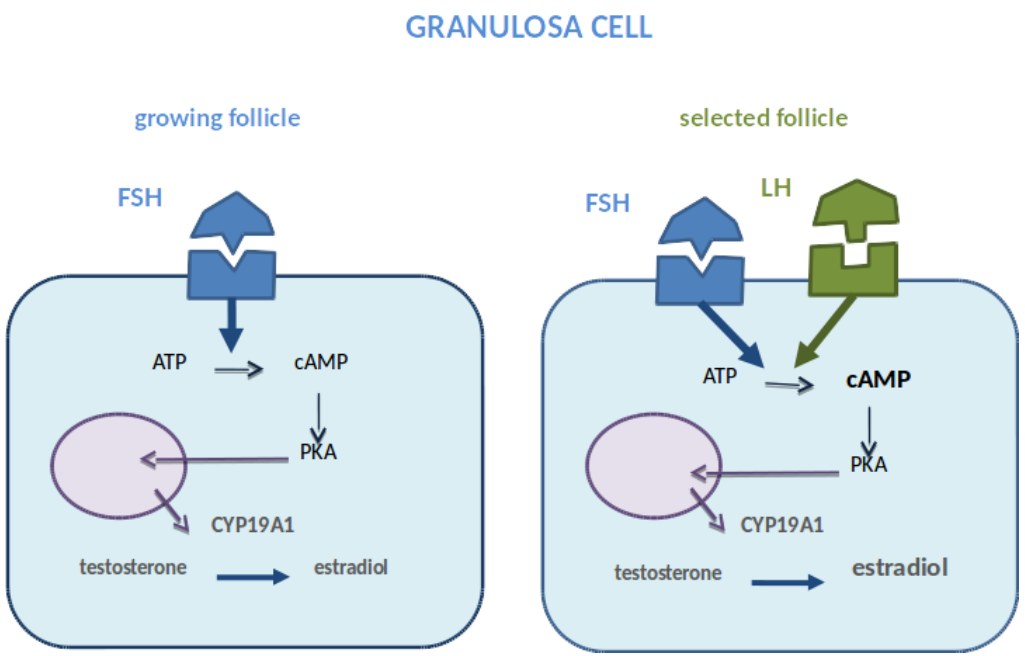
$$\ll \left| e^{-\lambda t} \varrho(t, \cdot) - \eta \hat{\varrho} \right| \gg \leqslant \beta(t) e^{-\mu t} \ll \left| \varrho_0 - \eta \hat{\varrho} \right| \gg \ .$$

where $(\lambda, \hat{\varrho}, \hat{\varphi})$ *are maximal eigenelements , and* $\eta = \langle \varrho_0, \hat{\varphi} \rangle$.

$+$ analogous results on asymptotic higher moments of Z_t.

Signaling

⇒ Signaling model of FSH in somatic cells

⇒ Auto-amplification of the FSH signaling that could explain the selection process

⇒ Coupling of a follicle population model and a modèle de signalisation cellulaire "bi-stable".