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Modeling (some aspects of) the female reproductive system

Romain Yvinec

► **To cite this version:**

Romain Yvinec. Modeling (some aspects of) the female reproductive system. Thematic Month on Mathematical Issues in Biology - Mathematics of complex systems in biology and medicine, Feb 2020, Luminy, France. pp.1-65. hal-03115069

HAL Id: hal-03115069

<https://hal.science/hal-03115069>

Submitted on 19 Jan 2021

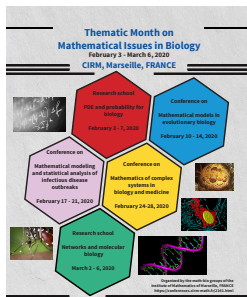
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Modeling (some aspects of) the female reproductive system

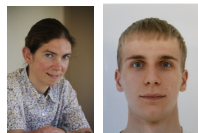
Romain Yvinec

Physiologie de la Reproduction et des Comportements
INRAe Tours



Acknowledgements

- ★ INRIA Saclay : Frédérique Clément, Guillaume Ballif, Frédérique Robin
- ★ INRAE PRC : Team BIOS, BINGO (Danielle Monniaux, Véronique Cadoret, Rozenn Dalbies-Tran)
- ★ INRAE LPGP (Julien Bobe, Violette Thermes)
- ★ CEMRACS 2018 (Céline Bonnet (CMAP, X), Kerloun Chahour (U. Côte d'Azur))



Inria INRAE

The Mammalian female reproductive system : a complex multiscale system

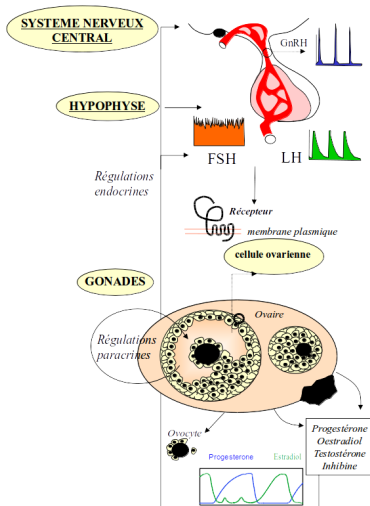
Encoding and decoding **neuro-hormonal signals**

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.



Scientific and societal issues in reproductive science

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

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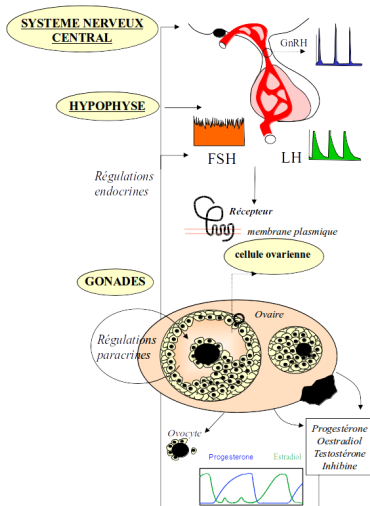
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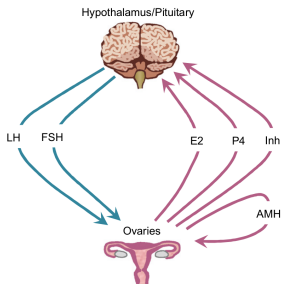


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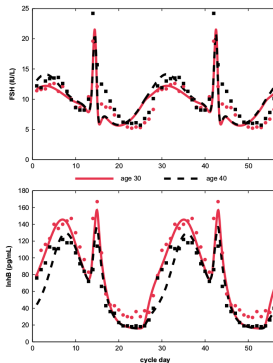


Neuro-hormonal signals (at the anatomic scale)

Mostly phenomenological equations (DDEs/SDEs) to represent measured levels of circulating hormones, on a daily basis.



Margolskee & Selgrade, JTB 2013

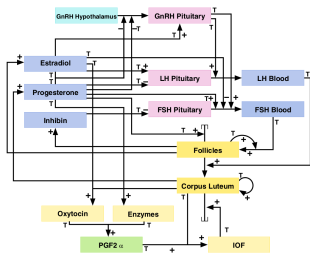


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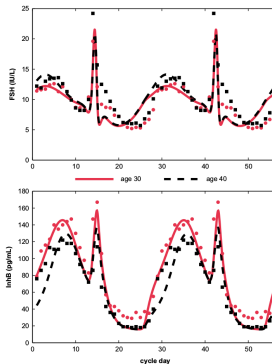
These models can explain some disorders in hormonal levels and predict the effect of pharmaceutical intervention.

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Stötzel et al., *Therio.* 2012



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

The Mammalian female reproductive system : a complex multiscale system

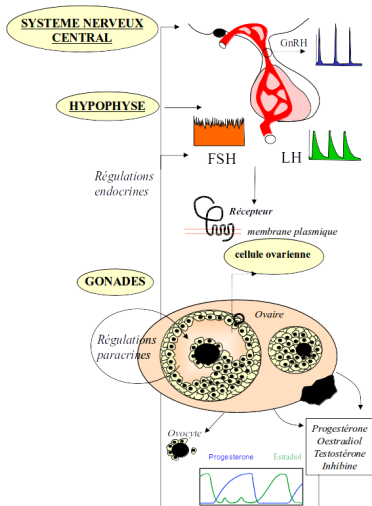
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Population dynamics : gametogenesis

Intra-cellular level : **signaling networks**



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Gametogenesis : Ovarian folliculogenesis

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

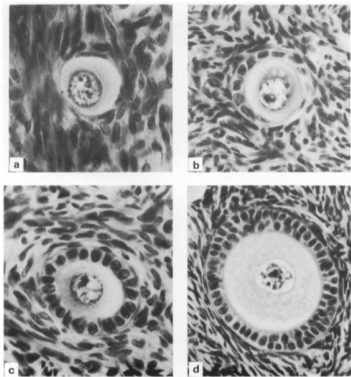
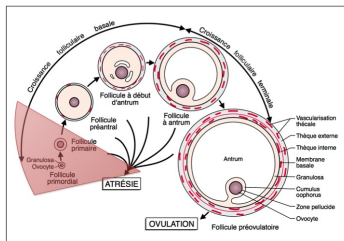


Fig. 1. Illustrations of follicle types: (a) Type B, $\times 570$; (b) Type B/C, $\times 570$; (c) Type C, $\times 570$; (d) Type D, $\times 410$.

Gougeon & Chainy, J. Reprod. Fert. 1987

Gametogenesis : Ovarian folliculogenesis

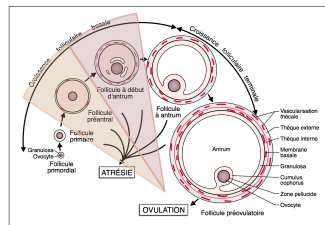
- Morphogenesis and maturation of ovarian follicles
somatic and germ (egg) cells
- Pool of Quiescent follicles
static reserve (perinatal in most mammals)
Slow activation



Monniaux, Theriogenology 2016

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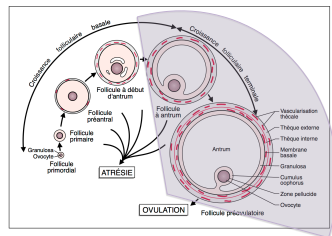
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Dynamic reserve (starting at birth)
 Spanning over several ovarian cycles



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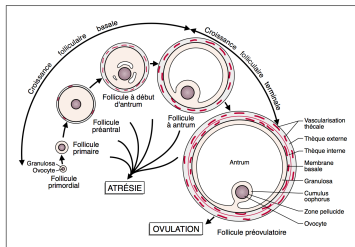
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- Terminal growth
 After puberty : ovulation within an ovarian cycle



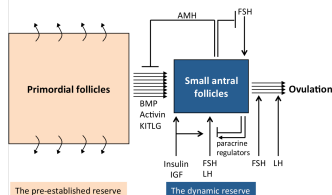
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After puberty : ovulation within an ovarian cycle
- Interactions between all follicles via complex (neuro-) hormonal signals



Ovarian reserves of follicles and their regulations



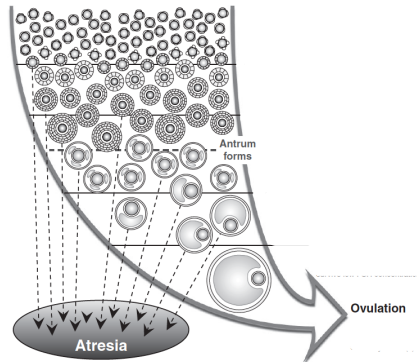
Monniaux, Theriogenology 2016

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

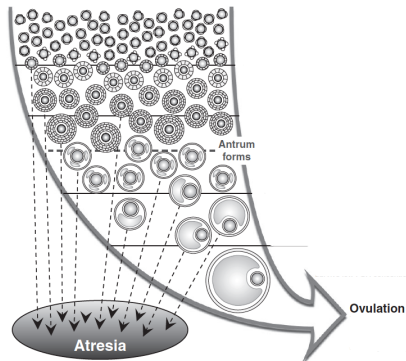
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- Growing follicles

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



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

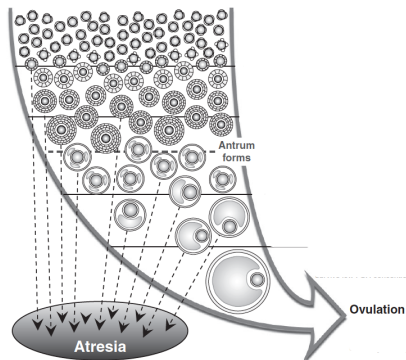
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- > **Only 400 follicles will ever reach the pre-ovulatory stage**

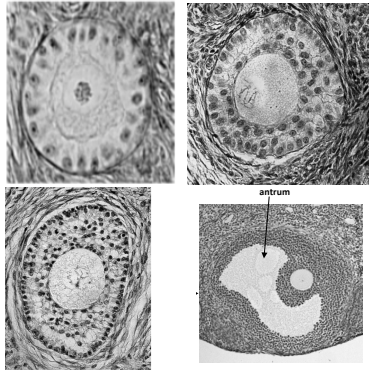


Scaramuzzi et al., *Reprod.Fert. Dev.* 2011

Order of magnitude

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

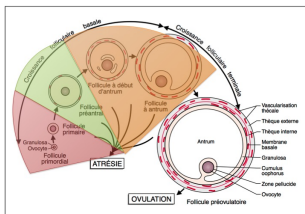
somatic cells diam.	$10\mu m$
ovocyte (egg cell) diam. :	$10 - 100\mu m$
follicle diam.	$0.03 - 20mm$
nb somatic cells	$10^2 - 10^7$



Courtesy of Danielle Monniaux.

Modeling ovarian folliculogenesis

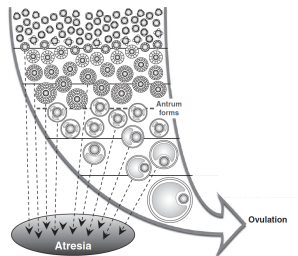
Growth of a single follicle



Monniaux et al., M/S. 1999

- Thesis of F. Robin, (co-supervised. F. Clément) 2016-2019

Populations of follicles

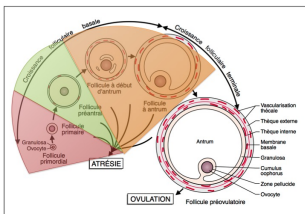


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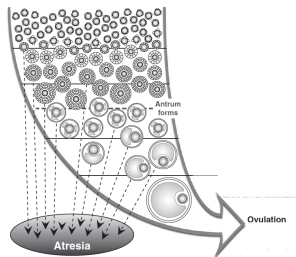
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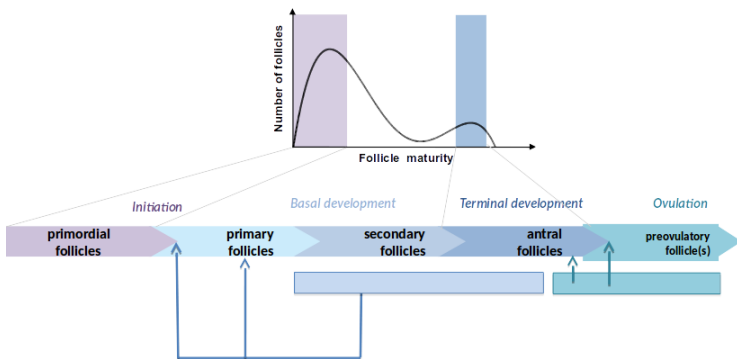


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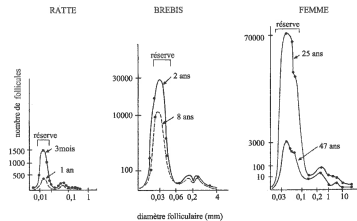
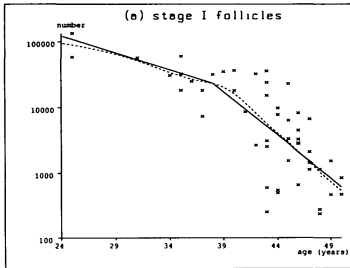
Models of population of follicles on the lifespan

- ⇒ Nonlinear interactions between follicles populations (endocrine and paracrine)
- ⇒ Slow decay of total follicles number and "stable" repartition in the maturity space

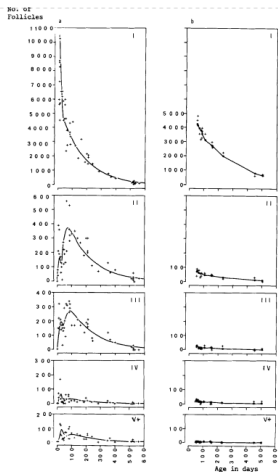


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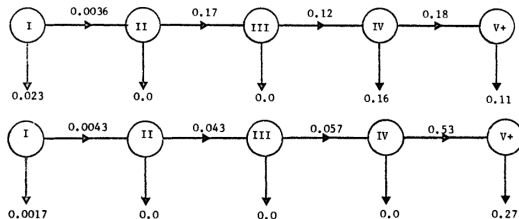
Models of population of follicles on the lifespan



An Analytical Model for Ovarian Follicle Dynamics

M. J. FADDY,¹ ESTHER C. JONES² AND R. G. EDWARDS³
¹ Department of Mathematical Statistics, University of Birmingham, Birmingham B15 2TT, U.K., ² Department of Anatomy, University of Birmingham, Birmingham B15 2TJ, U.K., and ³ Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG, U. K.

- "Migration-death" stochastic model
- Linear model with time-dependent coefficient



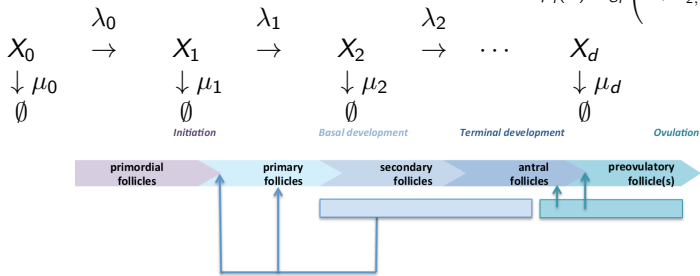
Faddy et al., J. Exp. Zool. 1976

Models of population of follicles on the lifespan

- Compartment based model (CTMC)
- Nonlinear interaction between follicles populations via λ 's and μ 's.
- Several time scales

$$\lambda_i(X) = m_i + \frac{f_i}{1 + K_{1,i} \sum_{j=0}^d \omega_{1,j} X_j},$$

$$\mu_i(X) = g_i \left(1 + K_{2,i} \sum_{j=0}^d \omega_{2,j} X_j \right)$$



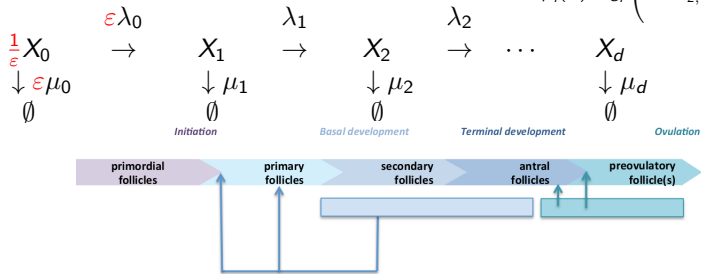
Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, to appear in ESAIM : PROCEEDINGS AND SURVEYS.

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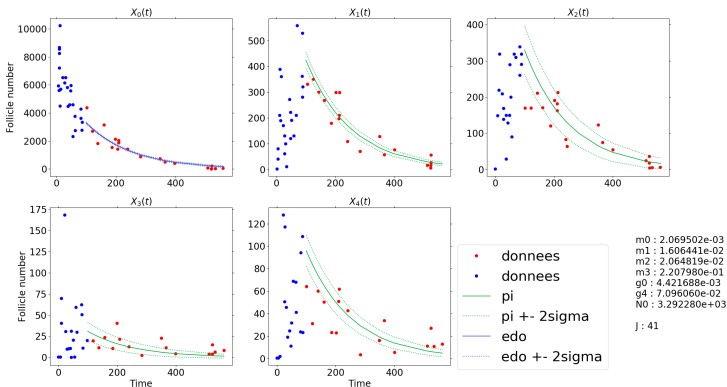
$$\begin{array}{ccccccc}
 \frac{1}{\varepsilon} X_0 & \xrightarrow{\varepsilon \lambda_0} & X_1 & \xrightarrow{\lambda_1} & X_2 & \xrightarrow{\lambda_2} & \dots & X_d \\
 \downarrow \varepsilon \mu_0 & & \downarrow \mu_1 & & \downarrow \mu_2 & & & \downarrow \mu_d \\
 \emptyset & & \emptyset & & \emptyset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

Theorem (G. Ballif, Averaging slow-fast dynamics)

For smooth and lower/upper bounded rates λ, μ , the CTMC converges as $\varepsilon \rightarrow 0$ (in $\mathcal{D}_{\mathbb{R}}[0, \infty[\times \mathcal{L}_m(\mathbb{N}^d)$) towards the solution of

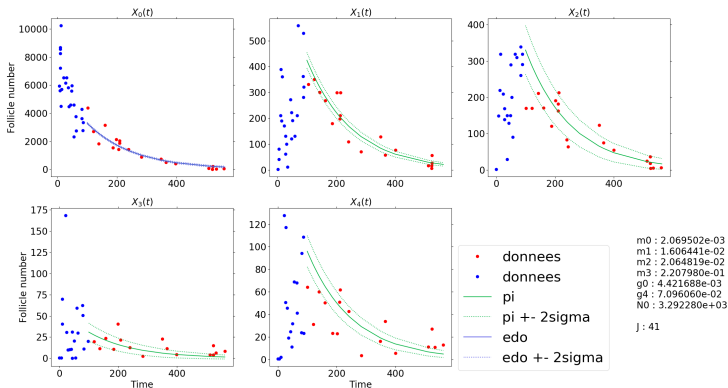
$$\left\{ \begin{array}{ll}
 \frac{dx_0}{dt}(t) = -\Lambda_0(x_0(t))x_0(t) & x_0(0) = x_0^{in}, \\
 \Lambda_0(x_0) = \sum_{y \in \mathbb{N}^d} (\lambda_0(x_0, y) + \mu_0(x_0, y)) \pi_{x_0}(y) & \forall x_0 \in \mathbb{R}_+, \\
 0 = \sum_{y \in \mathbb{N}^d} L_{x_0} f(y) \pi_{x_0}(y) & \forall f \in \mathcal{C}_b^2(\mathbb{N}^d), \\
 L_{x_0} f(y) = \lambda_0(x_0, y)x_0 \left[f(y + e_1) - f(y) \right] & \forall y \in \mathbb{N}^d, \\
 \quad + \sum_{i=1}^{d-1} \lambda_i(x_0, y)y_i \left[f(y + e_{i+1} - e_i) - f(y) \right] \\
 \quad + \sum_{i=1}^d \mu_i(x_0, y)y_i \left[f(y - e_i) - f(y) \right]
 \end{array} \right.$$

Models of population of follicles on the lifespan



- Separation of time scale is coherent with biological knowledge and follicles count data.

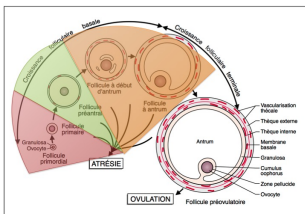
Models of population of follicles on the lifespan



- Separation of time scale is coherent with biological knowledge and follicles count data.
- **Work in progress...**
- Identifiability issues (even with the linear model)
- The limit model allows to test null hypothesis (no regulation)

Modeling ovarian folliculogenesis

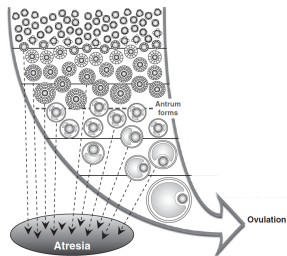
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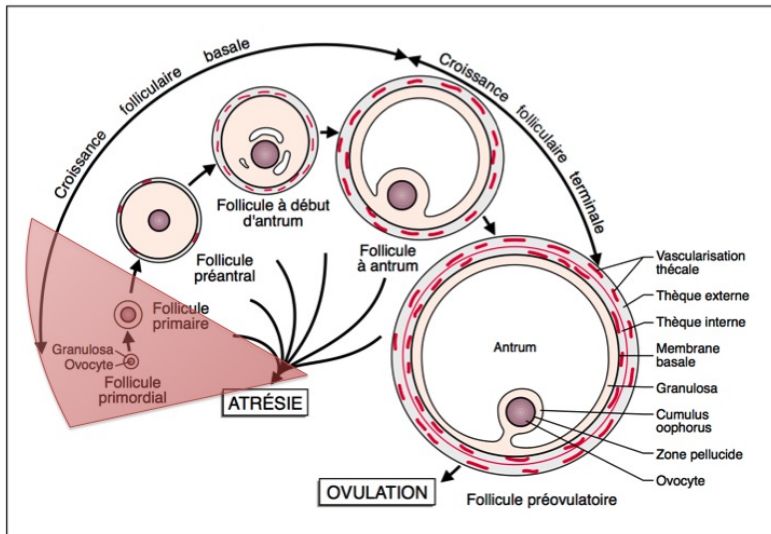
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Follicle initiation



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
- **"Awakening" signals both from external and internal cues**

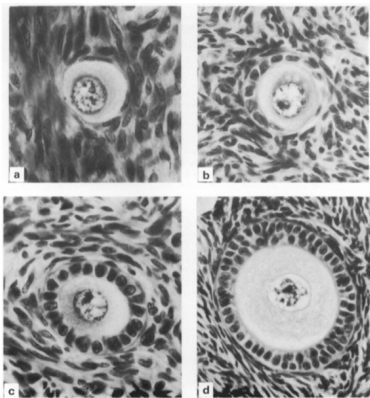
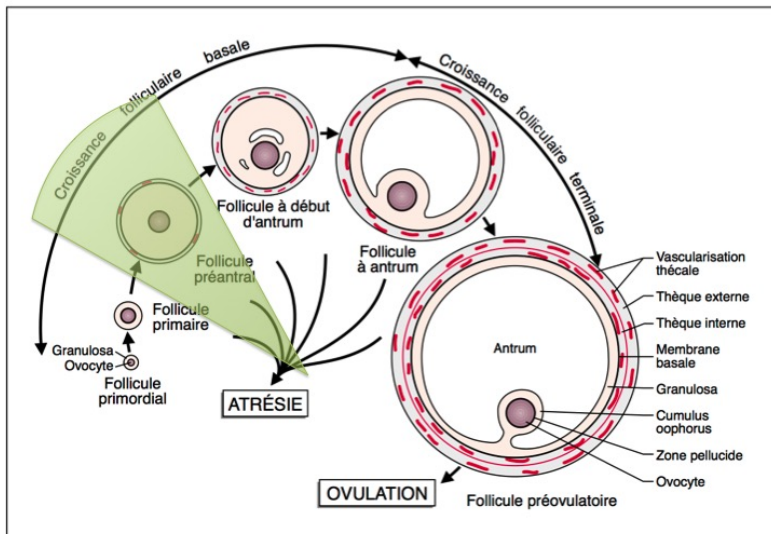


Fig. 1. Illustrations of follicle types: (a) Type B, $\times 570$; (b) Type B/C, $\times 570$; (c) Type C, $\times 570$; (d) Type D, $\times 410$.

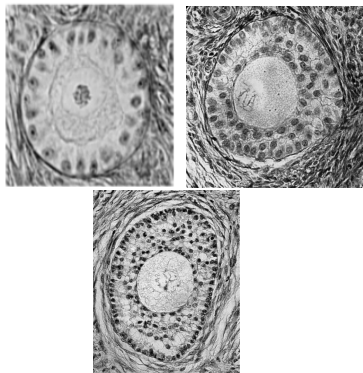
Gougeon & Chainy, J. Reprod. Fert. 1987

Basal growth



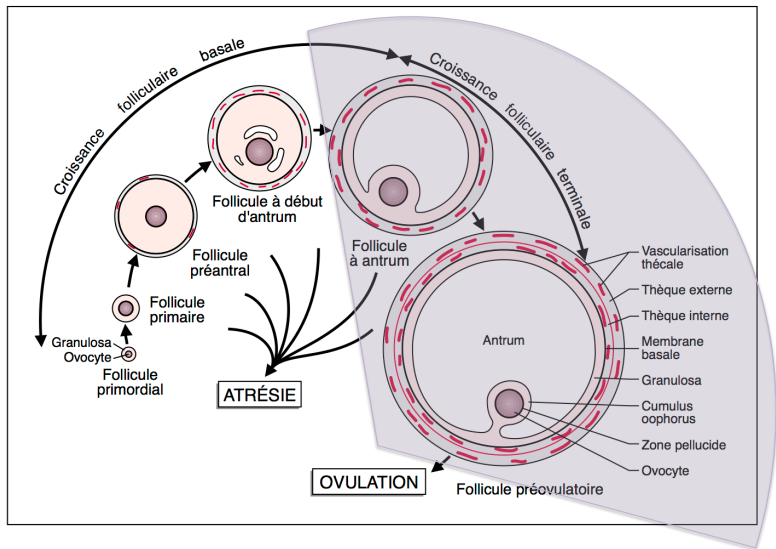
Key features of follicle basal growth

- Growth of a small follicle after initiation
- **Spherical Symmetry**
- Spatial structure of somatic cells in concentric **layers**
- Joint dynamic
 - ★ Ovocyte **growth**
 - ★ Somatic cells **Proliferation**
- Growth signals from the Ovocyte to somatic cells and *vice-versa*.



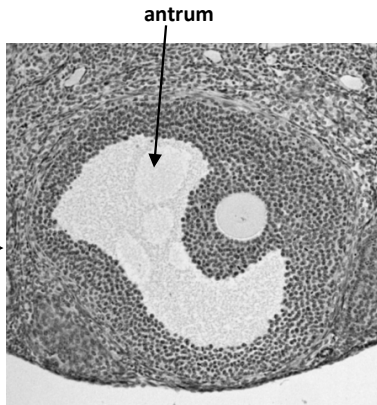
Courtesy of Danielle Monniaux.

Terminal growth



Key features of Follicle terminal growth

- Lost of spherical symmetry
- Joint Dynamic
 - ★ Liquid-filled cavity formation and growth
 - ★ Switch from proliferation to differentiation of somatic cells
 - ★ Morphogen gradient
- **Role of the Liquid-filled cavity ?**

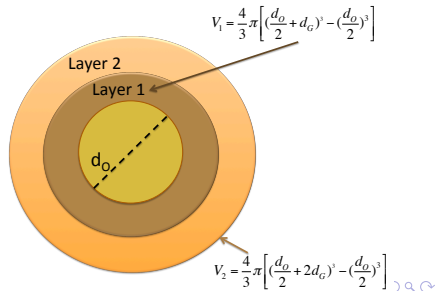
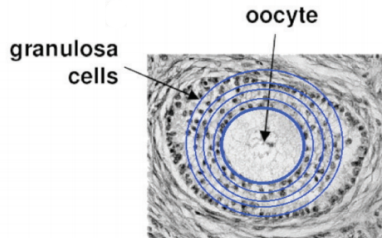


Tertiary (antral) follicle

Simple model : spatial compartment in successive layers

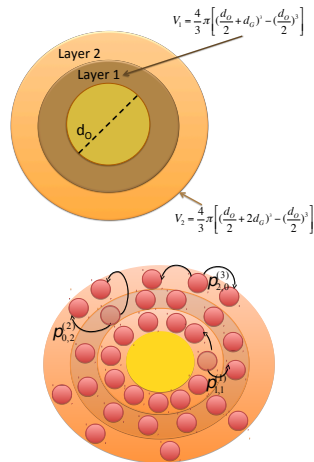
- Spherical ovocyte (d_o)
- Linear proliferation dynamics of somatics cells
- Layer dependent division rate
- Multi-type Bellman-Harris Branching process

Somatic cells divide and migrate to successive layers.



- The geometrical model allows a simple spatial description
- The model is linear and decomposable : **exponential growth**, with a stable asymptotic spatial profile : there exists a unique $\lambda > 0$ such that the process Z_t verifies

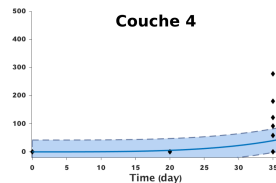
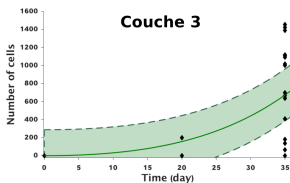
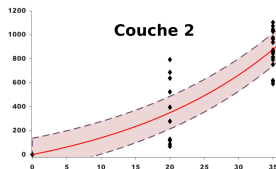
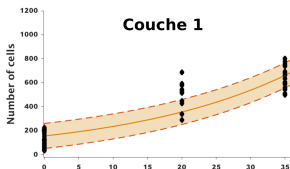
$$\lim_{t \rightarrow \infty} Z_t e^{-\lambda t} = \hat{Z} \quad (\text{in law})$$



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

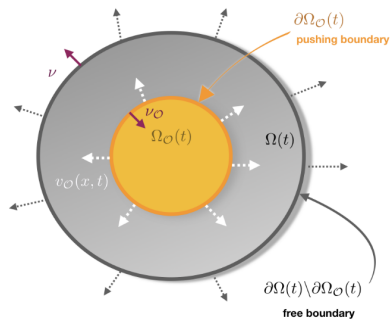
Fitting results

- ⇒ **Exponential** growth dominated by the first cell layer
- ⇒ Parameter identifiability and doubling time quantification (≈ 16 days) :
Cell-cycle time \nearrow with ovocyte distance



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 :

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

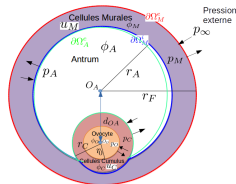
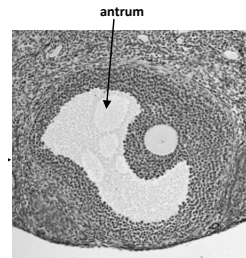
work in progress...

Antrum growth model

- Multiphasic advection-diffusion-reaction PDE

$$\begin{aligned}
 (\partial_t + \text{div}_x(v_M \cdot)) u_M &= R_M \\
 v_M &= -\mu_M \nabla_x p_M, \\
 p_M &= C_M (u_M - u_0)^{\gamma_M}, \\
 (\partial_t + \text{div}_x(v_a \cdot)) \Phi_a &= D \Delta \Phi_a + R_a \\
 \text{div}_x v_a &= 0, \\
 \nabla \Phi_a \cdot \vec{n}_a &= s(t) = \kappa \int_{\Omega_M} u_M(t, x) dx \\
 \frac{d}{dt} \left(\frac{4}{3} \pi r_a(t)^3 \right) &= J_{H_2O} = L_p(t) (\Delta \Pi - \Delta p) \\
 \Delta \Pi &= c_a \Phi_a^{\gamma_a} \\
 \Delta p &= p_M(t, |x| = r_a^+) - p_e \\
 L_p(t) &= \frac{\Pi(r_F(t) - r_a(t))^4}{8\eta\epsilon(u_M)} n(u_M),
 \end{aligned}$$

+ Boundary conditions and constitutive laws
work in progress...

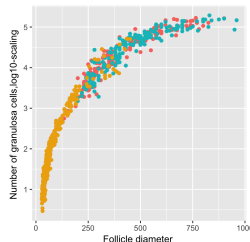


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+ Boundary conditions and constitutive laws
work in progress...



The Mammalian female reproductive system : a complex multiscale system

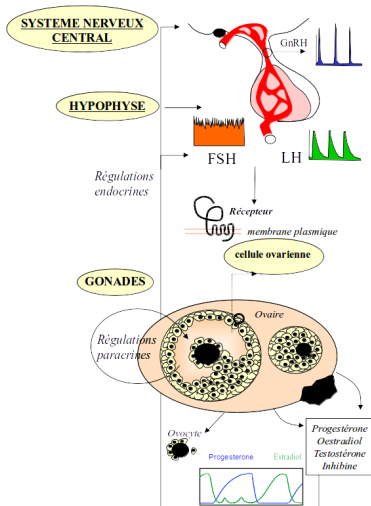
Encoding and decoding **neuro-hormonal signals**

Population dynamics : **gametogenesis**

Intra-cellular level : **signaling networks**

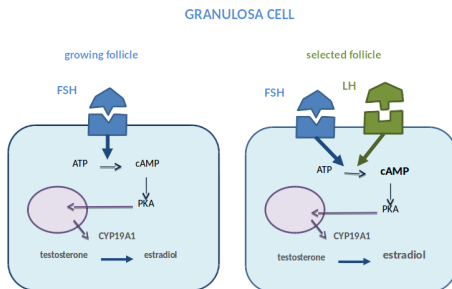


Yvinec et al., *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.

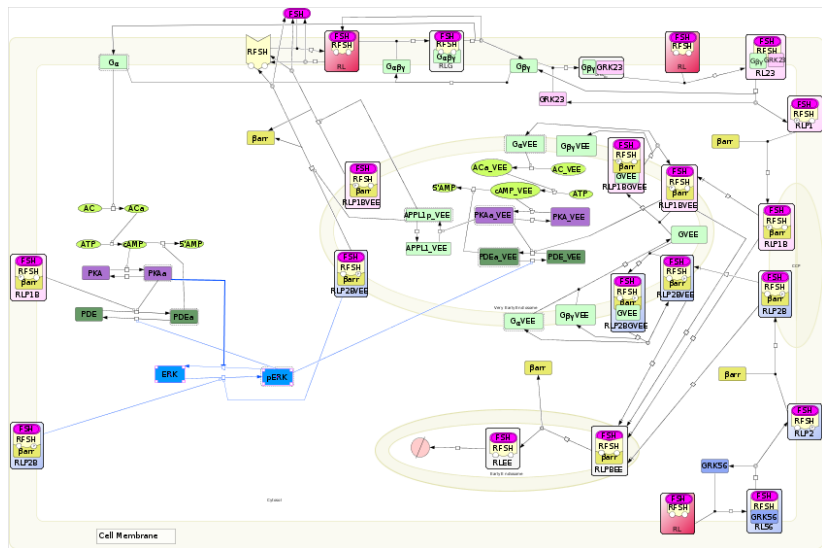


cAMP-induced FSH and its regulation at the cellular level

- FSHR signaling network and short-term cAMP induction.
 - Long-term regulation of the FSHR network during follicular selection.
- ⇒ The Cellular "switch" is a pre-requisite for follicle selection .
- ⇒ This switch is implemented at molecular level by the FSHR network and cAMP output (which is a good marker of follicle maturity).



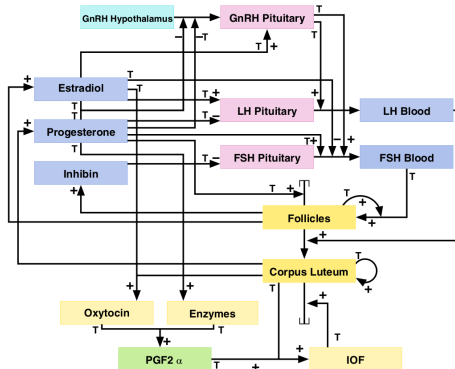
FSHR networks : very complicated dynamics !



"Network Biology"-> next week !

Summary

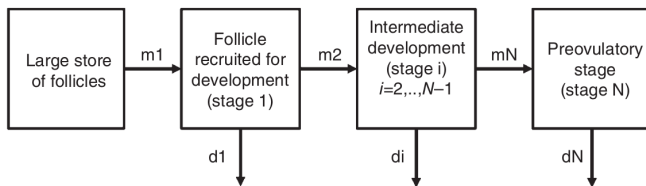
- Circulating hormones dynamical models (Selgrade's model)
 - ★ Purely hormonal dynamics
 - ★ limit cycles in compact delay differential equation models of the ovarian cycle



Stötzel et al., *Therio*. 2012

Summary

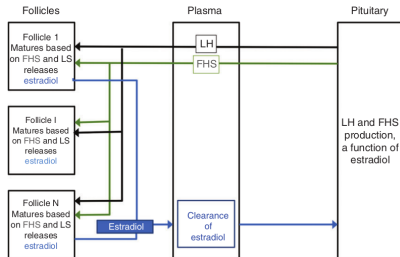
- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
 - ★ Reproductive lifespan timescale
 - ★ Follicle communication and "hormonal control" through population feedback



Clark & Kruger, WIREs Syst Biol Med 2017

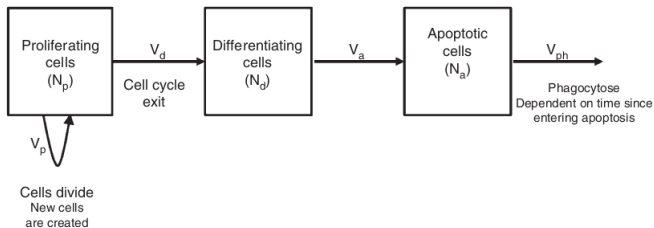
Summary

- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
 - ★ Ovarian cycle / follicle cohort timescale
 - ★ Follicle cohort subject to a shared hormonal environment
 - ★ The individual follicle maturity rate has local positive feedback and global negative feedback.



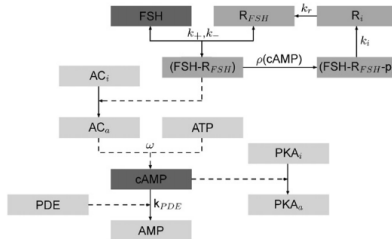
Summary

- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
- Cell dynamics in a single follicle (Clément's model)
 - ★ Cell cycle time scale
 - ★ Pool of different cell types within a single follicle
 - ★ Complex geometry and moving boundary problems



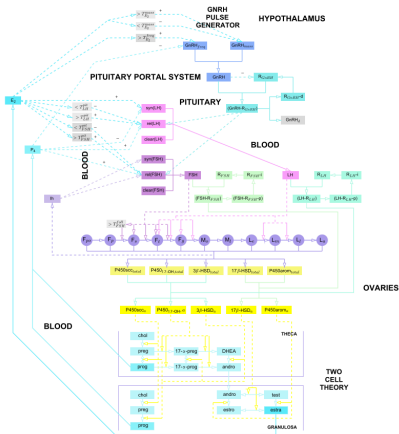
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- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
- Cell dynamics in a single follicle (Clément's model)
- Intra-cellular dynamics (Clément / Quignot & Bois)
 - ★ Steroidogenesis, cAMP response



Multiscale Models of ovarian follicle selection

- Putting "many" pieces together (Reinecke & Deuflhard)



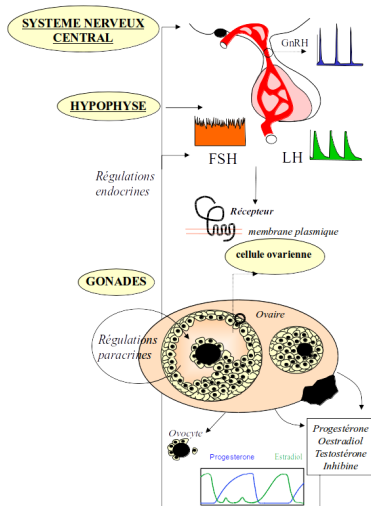
- ★ From (stochastic) GnRH pulse generator to detailed steroid metabolism through (compartment-based) follicle development
- ★ *Focus in this paper is on the model development*
- ★ 43 equations (stochastic input and delay differential equations), 191 parameters.

Reinecke & Deuflhard, JTB 2007

Summary

Population dynamics in ovarian folliculogenesis

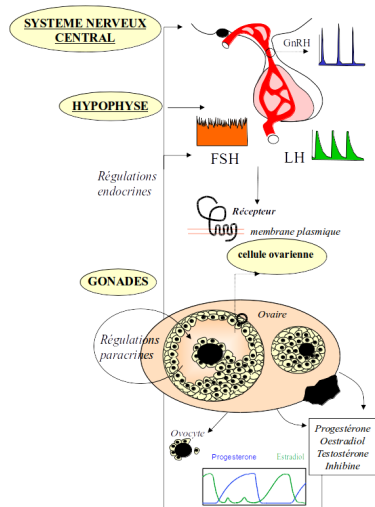
- Somatic cells proliferation, differentiation, and migration during follicle initiation & growth
- Multiscale nonlinear dynamics shape the follicle population distribution into different maturity stages.



Summary

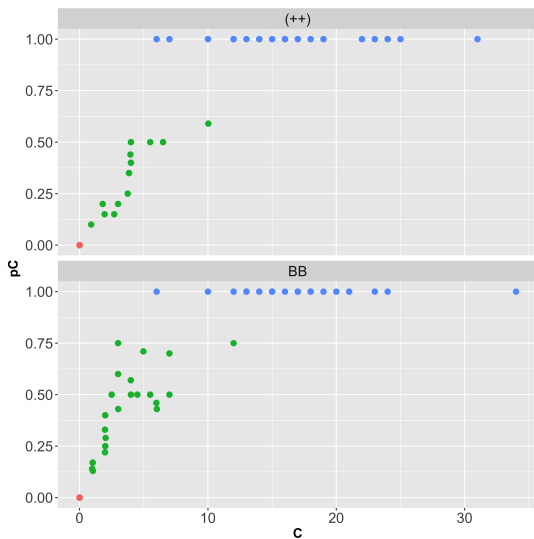
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Thank you for your attention !

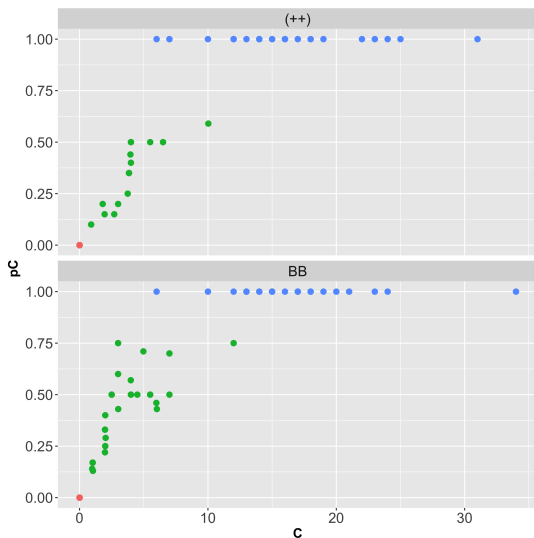
Ex vivo data (snapshot data)



- 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**

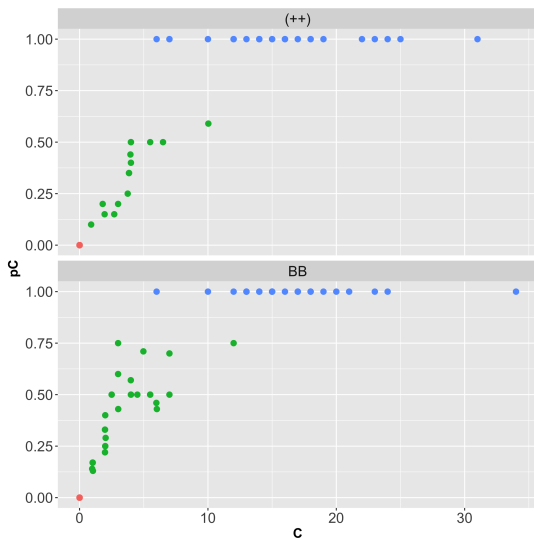
Ex vivo data (snapshot data)



- 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 ?**

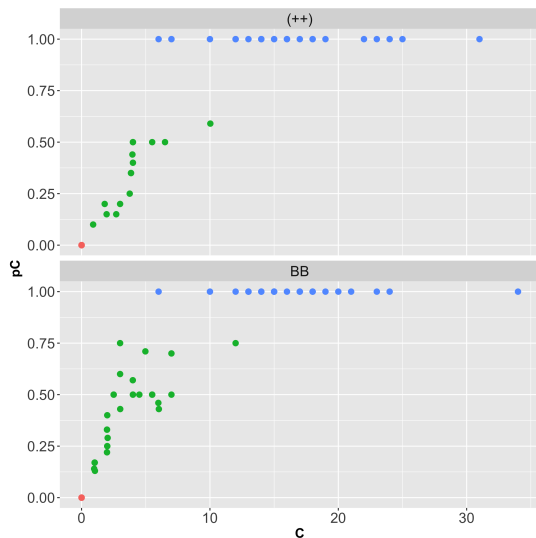
Ex vivo data (snapshot data)



- 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	$C \rightarrow C + C$	γC

- ↔ Two cell populations : F (flattened) and C (cuboid)
- ↔ Small number of cells
- ↔ Retro-action of cuboid cells on the differentiation rate : is it relevant ?
- ↔ From $(F_0, 0)$ to $(0, C_T)$

- Theoretical study

- ⇒ Statistics of the "transition" time τ to reach $F = 0$.

- ⇒ Variability of final cuboid cells ($\mathbb{E}[C_\tau] < \infty$ if $\gamma < \alpha + \beta$)

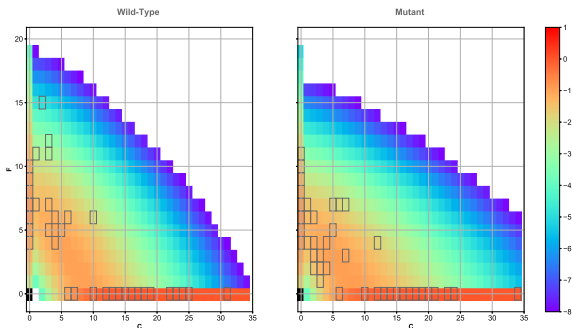
- ⇒ Impact of parameters e.g. on qualitative dynamics (progressive vs abrupt)

- Parameter calibration : lack of identifiability. Either $\gamma \ll 1$ and β 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



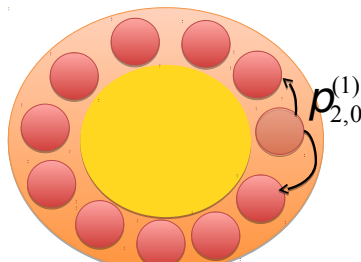
- ⇒ The model can capture both data sets
- ⇒ Lack of identifiability (non-conclusive on retro-action)
- ⇒ First differentiation, then proliferation (slightly more concomitant in mutant case)



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

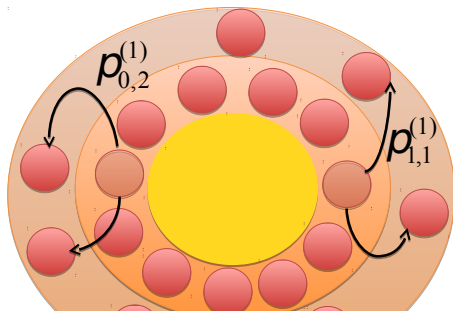
Dynamical model (Multi-type Bellman-Harris Branching process)

- **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)



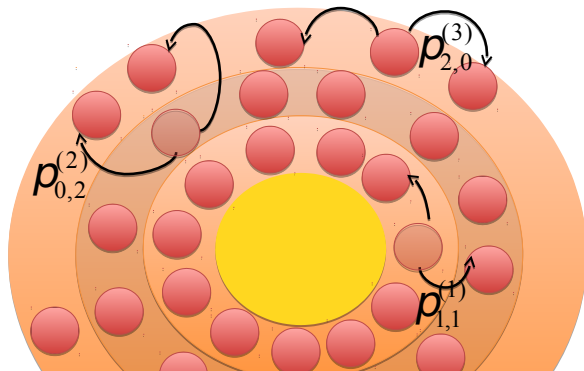
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Data

- 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 ± 57.76	885.75 ± 380.89	2241.75 ± 786.26
Oocyte diameter (μm)	49.31 ± 8.15	75.94 ± 10.89	88.08 ± 7.43
Follicle diameter (μm)	71.68 ± 13.36	141.59 ± 17.11	195.36 ± 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?

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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 ?