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Romain Yvinec. Time scale separation in life-long ovarian follicles population dynamics model. 12. European Conference on Mathematical and Theoretical Biology - ECMTB 2022, European Society for Mathematical and Theoretical Biology (ESMTB); Society for Mathematical Biology (SMB), Sep 2022, Heidelberg, Germany. pp.110-111. <hal-04194057>

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Submitted on 1 Sep 2023

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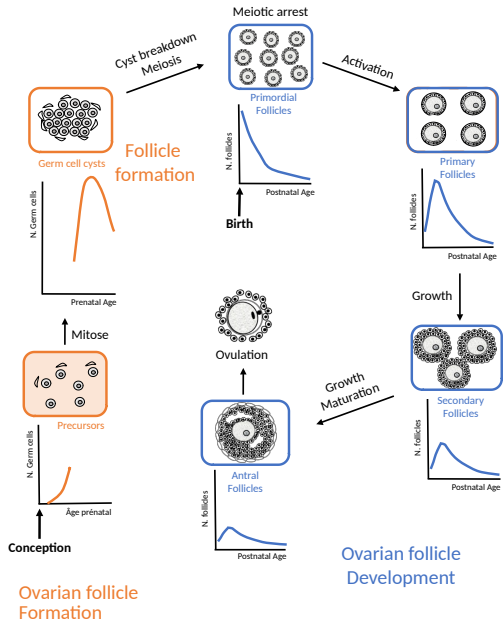


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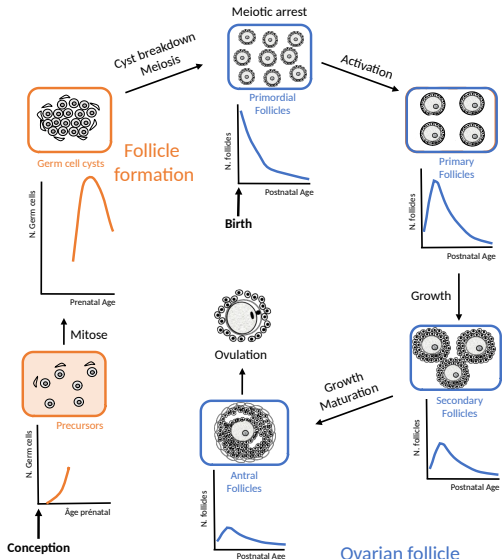
Time scale separation in life-long ovarian follicles population dynamics model

Romain Yvinec

BIOS Team, Physiologie de la Reproduction et des Comportements, INRAE
CNRS, Université de Tours, (Tours, France)
MUSCA Team, INRIA-INRAE-CNRS (Saclay, France)



Ovarian follicle Development



Ovarian follicle Formation

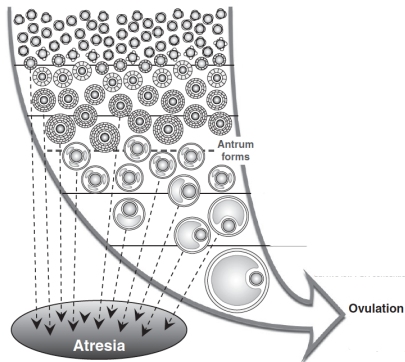
Ovarian follicle Development

- Pool of Quiescent follicles **static reserve** (perinatal in most mammals)
Slow activation
- Basal growth **Dynamic reserve** (starting at birth) Spanning over several ovarian cycles
- Terminal growth
After puberty : **ovulation** within an ovarian cycle

Order of magnitude (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"



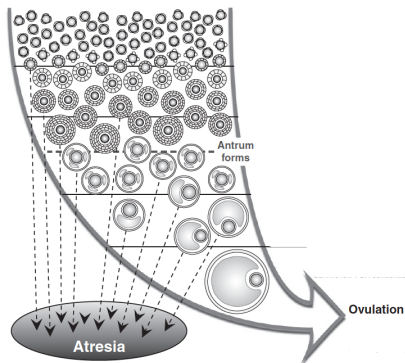
Scaramuzzi et al., *Reprod.Fert. Dev.* 2011

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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 ther



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

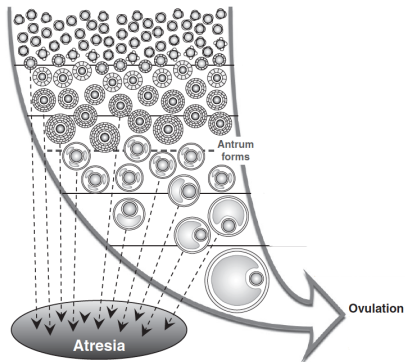
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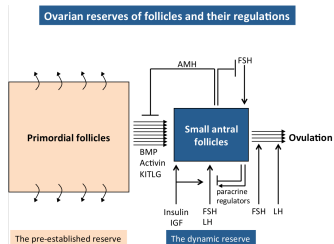
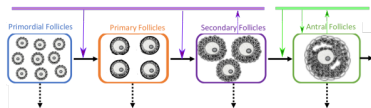
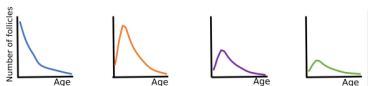
> **Only 400 follicles will ever reach the pre-ovulatory stage**



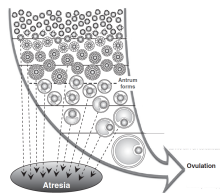
Scaramuzzi et al., *Reprod.Fert. Dev.* 2011

Population dynamics in female gametogenesis

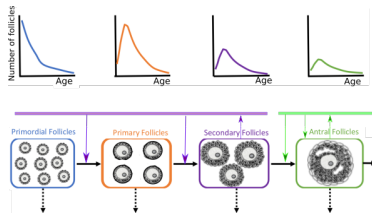
- Asynchronous growth
- Several timescales : Ten of years / Months / Weeks
- Interactions between subpopulations



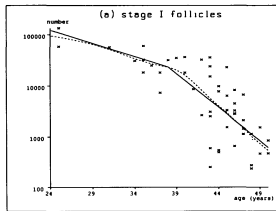
Monniaux, *Theriogenology* 2016



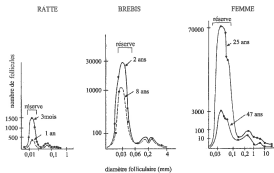
Scaramuzzi et al., *Reprod.Fert. Dev.* 2011



- ⇒ Irreversible (slow) decay of an initial pool of quiescent follicle
- ⇒ "Stable" repartition of growing follicle

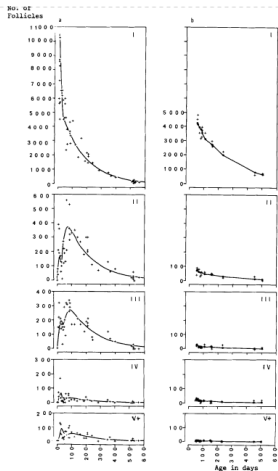


Faddy and Gosden 1995



Thibault and Levasseur, 2001

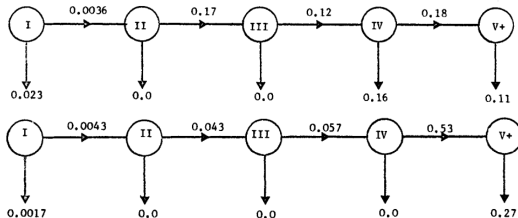
Previous compartmental model (mice data)



An Analytical Model for Ovarian Follicle Dynamics

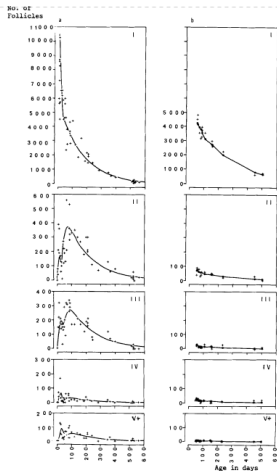
M. J. FADDY,¹ ESTHER C. JONES² AND R. G. EDWARDS³
¹ Department of Mathematical Statistics, University of Birmingham, Birmingham B15 2TT, U.K., ² Department of Anatomy, University of Birmingham, Birmingham B15 2TJ, U.K., and ³ Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG, U.K.

- "Migration-death" model
- Linear Model



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

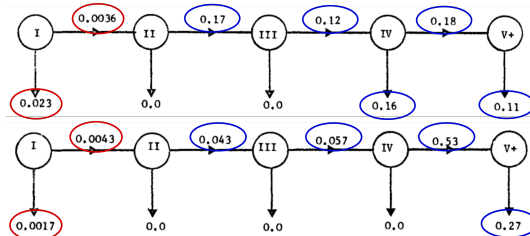
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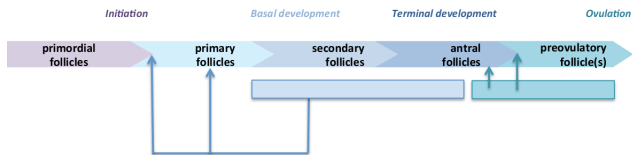
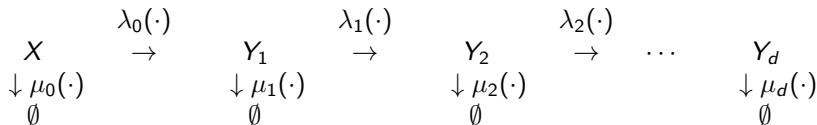
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Lifespan follicle population model

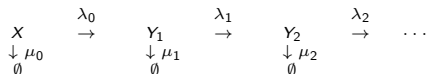
- Structured Population in compartments
- Non linear interaction between follicles via λ 's and μ 's.



Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, ESAIM : PROCEEDINGS AND SURVEYS, 2020.

Lifespan follicle population model

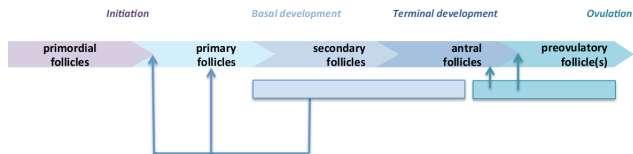
- Structured Population in compartments
- Non linear interaction between follicles *via* λ 's and μ 's.



Typical choice

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

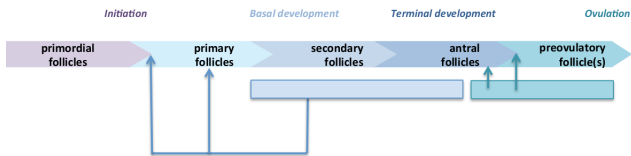
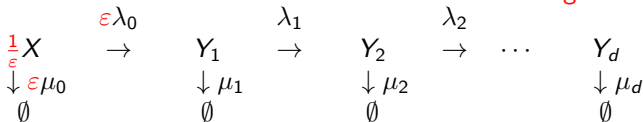
$$\mu_i(Y) = g_i \left(1 + K_{2,i} \sum_{j=0}^d \omega_{2,j} Y_j \right)$$



Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, ESAIM : PROCEEDINGS AND SURVEYS, 2020.

Lifespan follicle population model

- Structured Population in compartments
- Non linear interaction between follicles *via* λ 's and μ 's.
- Two time and abundance scales
- Quiescent Pool \gg Growing Follicles
- Slow Activation \ll Fast growth



Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, ESAIM : PROCEEDINGS AND SURVEYS, 2020.

Singular Perturbation Theory

$$\begin{array}{ccccccc}
 \frac{1}{\varepsilon} X & \xrightarrow{\varepsilon \lambda_0} & Y_1 & \xrightarrow{\lambda_1} & Y_2 & \xrightarrow{\lambda_2} & \dots & Y_d \\
 \downarrow \varepsilon \mu_0 & & \downarrow \mu_1 & & \downarrow \mu_2 & & & \downarrow \mu_d \\
 \emptyset & & \emptyset & & \emptyset & & & \emptyset
 \end{array}$$

In the limit $\varepsilon \rightarrow 0$ We expect X and $Y = (Y_1, \dots, Y_d)$ to converge to a differential-algebraic equation :

$$\begin{cases} \frac{dx}{dt}(t) = F(x(t), y(t)), & x(0) = x^{\text{in}}, \\ 0 = G(x(t), y(t)), & t > 0 \end{cases}$$

$$\begin{array}{ccccccc}
 & \varepsilon \lambda_0 & & \lambda_1 & & \lambda_2 & & \dots & & Y_d \\
 \frac{1}{\varepsilon} X & \rightarrow & Y_1 & \rightarrow & Y_2 & \rightarrow & \dots & & & \\
 \downarrow \varepsilon \mu_0 & & \downarrow \mu_1 & & \downarrow \mu_2 & & & & & \downarrow \mu_d \\
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 \end{array}$$

Theorem (G. Ballif, F. Clément, R.Y. SIAP 2022)

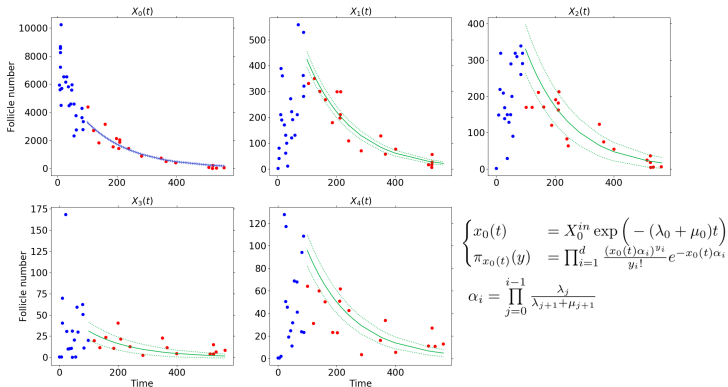
(...) $(X^\varepsilon, Y^\varepsilon)$ converges in $\mathcal{D}_{\mathbb{R}}[0, \infty[\times \mathcal{L}_m(\mathbb{N}^d)$ to the unique solution of

$$\begin{cases} \frac{dx}{dt}(t) & = \Lambda_0(x(t))x(t), & x(0) = x^{\text{in}}, \\ \Lambda_0(x(t)) & = - \sum_{y \in \mathbb{N}^d} (\lambda_0(y) + \mu_0(y)) \pi_{x(t)}(y), \end{cases}$$

$$\sum_{y \in \mathbb{N}^d} L_x \psi(y) \pi_x(y) = 0, \quad \forall \psi \text{ bounded on } \mathbb{N}^d,$$

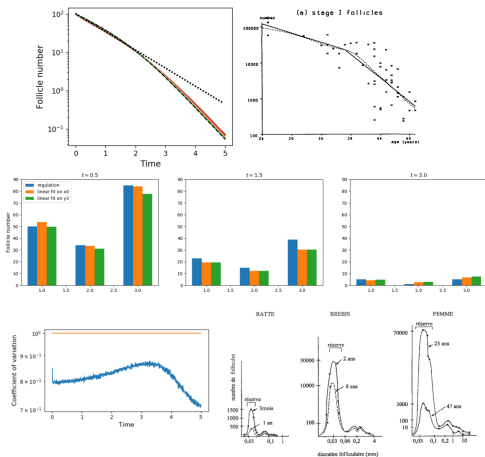
$$\begin{aligned}
 L_x \psi(y) = \lambda_0(y) x \left[\psi(y + e_1) - \psi(y) \right] &+ \sum_{i=1}^{d-1} \lambda_i(y) y_i \left[\psi(y + e_{i+1} - e_i) - \psi(y) \right] \\
 &+ \sum_{i=1}^d \mu_i(y) y_i \left[\psi(y - e_i) - \psi(y) \right].
 \end{aligned}$$

Does it works in practice ?



- Timescale separation is coherent with published data on follicle counts in mice at the lifespan time scale, *away from a transient period*.

What is it useful for ?



- ✓ acceleration of reserve decay with age :

$$\frac{dx}{dt} = -\left(a + \frac{b}{1+cx}\right)x$$

-> Mechanistic

explanation of
previously published
statistical regression
model (Coxworth and Hawkes
2010)

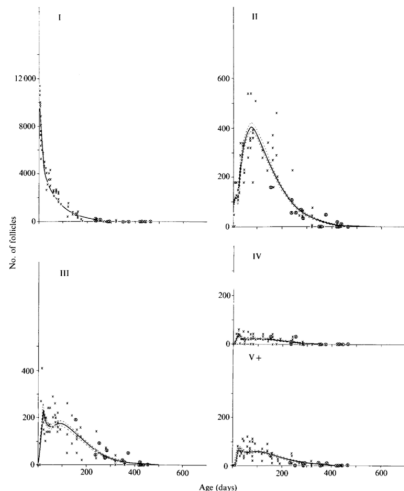
- ✓ "stable" evolution of
growing follicles Y

Going further

- Can we infer the regulation mechanism that control follicle activation ?
- Can we refine the model to model the transient phase (reserve establishment / early post-natal dynamics)?

"Time" course

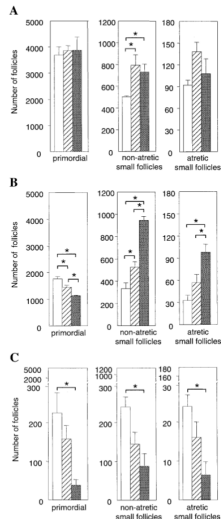
- Follicle count in mice from birth until 500 days.
- Reserve + 4 compartments (Faddy's classification)
- (Recovery of points by hand)



Faddy, Gosden and Edwards, J. Endo., 1983
 Faddy, Telfer and Gosden, Cell Proliferation, 1987

Perturbation data : KO AMH

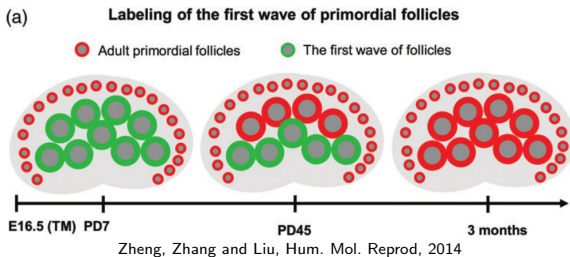
- AMH Inhibition *in vivo* on mice
- 3 genotypes : control group (+/+), heterozygous mice KO AMH (+/-) homozygous mice KO AMH (-/-).
- Follicle counts at 3 ages :
 - 25 days (A)
 - 120 days (B)
 - 390 days (C)



Durlinger and al, Endocrinology, 1999

Ovarian Reserve build-up

- Two distinct population of follicles are present initially
- Labelling of each population

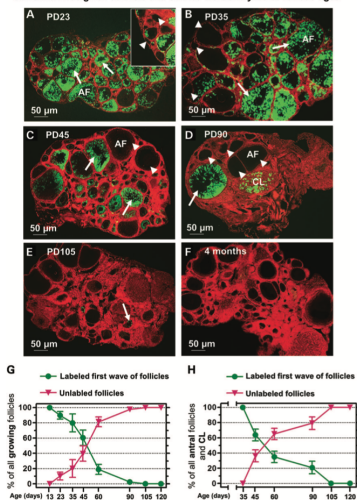


Ovarian Reserve build-up

- Tracing follicles of the first wave of activated follicles.
- Proportion of first wave activated follicles among growing follicles.

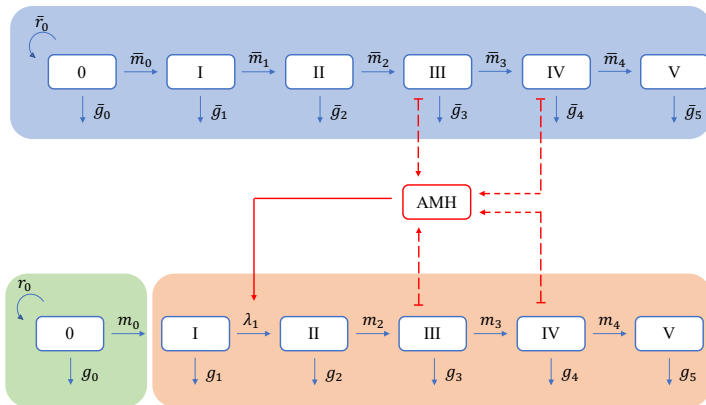
$$p(t) = \frac{\sum_{i=1}^4 X_i^1(t)}{\sum_{i=1}^4 X_i^{tot}(t)}$$

Tamoxifen was given at E16.5 and ovaries were analyzed at various ages

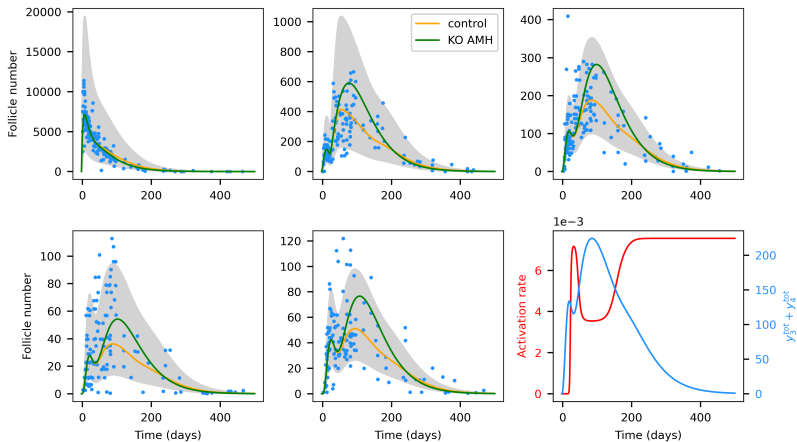


Zheng, Zhang and al, Hum. Mol. Gen, 2014

ODE model



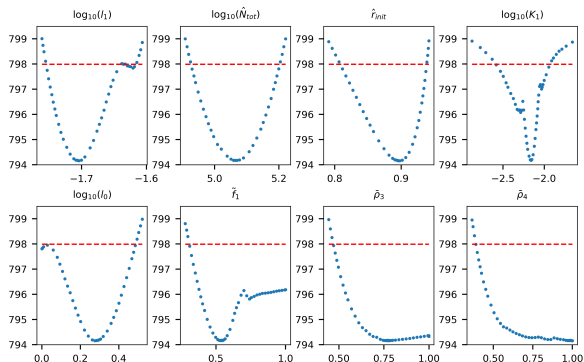
Data fitting



Identifiability

Theoretical (*Structural Identifiability Julia package*) and practical identifiability

(*Data2Dynamics Matlab package*) .

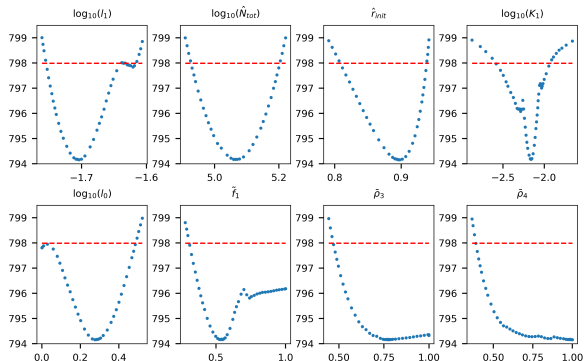


- 20 of 31 parameters are practically identifiable.
- Mean activation time is around 200 days, while growing time is around 50 days.

Identifiability

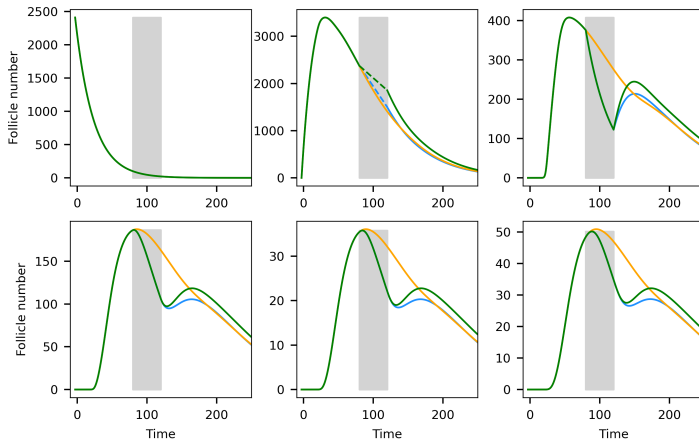
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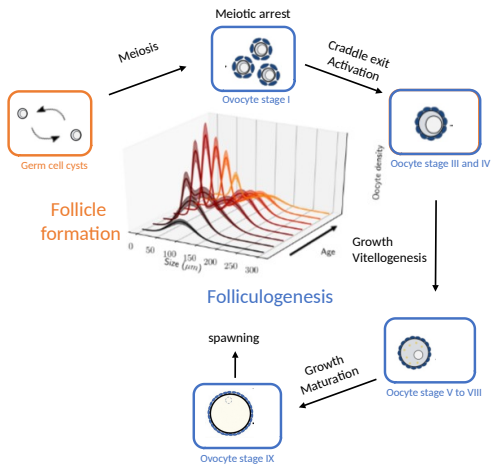


- 20 of 31 parameters are practically identifiable.
- Additional Data on germ cell dynamics would greatly improve identifiability

Prediction of AMH administration

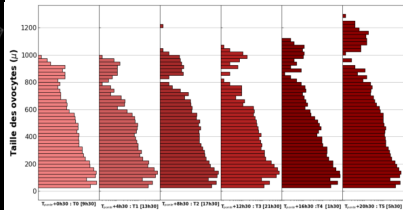
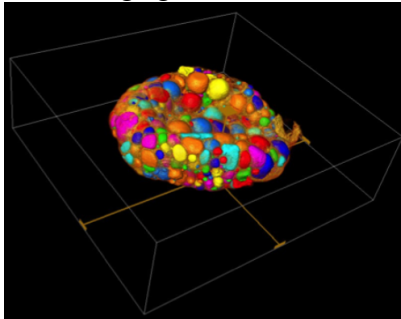


Comparison with fish oogenesis



Continuous structuring variable

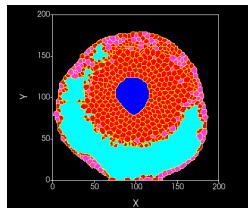
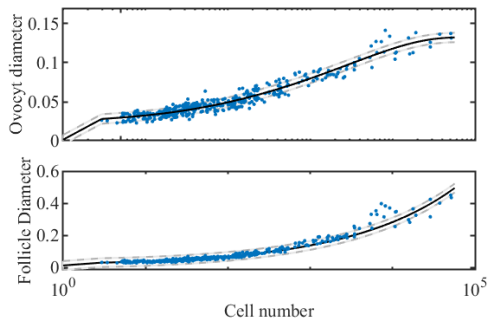
3D imaging data : whole Follicle count and size measurement



-> The bulk size distribution is ovarian-cycle independent (slow variable).

$$\begin{cases} \frac{d\rho_0(t)}{dt} & = -(\lambda_0(\rho(t, \cdot)) + \mu_0(\rho(t, \cdot)))\rho_0(t), \\ \varepsilon \partial_t \rho(t, x) & = -\partial_x (\lambda(\rho(t, \cdot), x)\rho(t, x)) - \mu(\rho(t, \cdot), x)\rho(t, x), \\ \lim_{x \rightarrow 0} \lambda(\rho(t, \cdot), x)\rho(t, x) & = \lambda_0(\rho(t, \cdot))\rho_0(t), \end{cases}$$

More than one structuring variable



Conclusion and perspective

- ✓ Lifespan ovarian follicle population dynamics model
- ✓ Separation of time scale explains slow decay of the reserve and quasi stable growing follicle repartition
- ✓ Follicle count data and perturbation experiments may reveal feedback mechanisms
 - Extension to three timescale (reserve, basal growth and terminal growth)
 - Extension to (several) continuous structuring variable
 - Comparative physiology approach

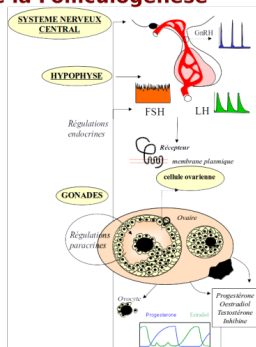
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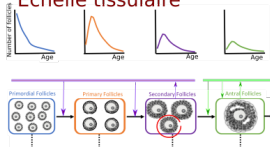
Open Post-position available in 2023 !

Thanks for your attention !

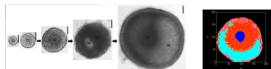
Modélisation Multi-échelle de la Folliculogénèse



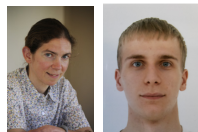
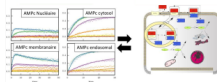
Echelle tissulaire



Echelle cellulaire



Echelle intra-cellulaire



Inria

INRAE

- ★ INRIA Saclay : Frédérique Clément, Guillaume Ballif, Frédérique Robin
- ★ INRAE PRC : Team BIOS, BINGO (Danielle Monniaux, Véronique Cadoret, Rozenn Dalbies-Tran)
- ★ INRAE LPGP (Violette Thermes)
- ★ INSERM - Paris Cité (Céline Guigon)
- ★ CEMRACS 2018 (Céline Bonnet, Keltoum Chahour)