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

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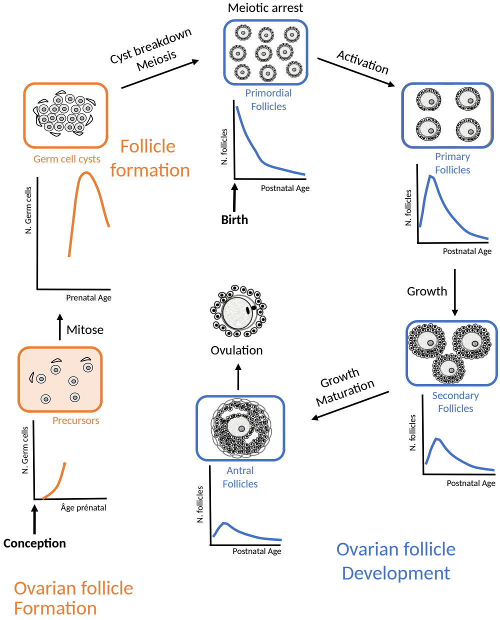
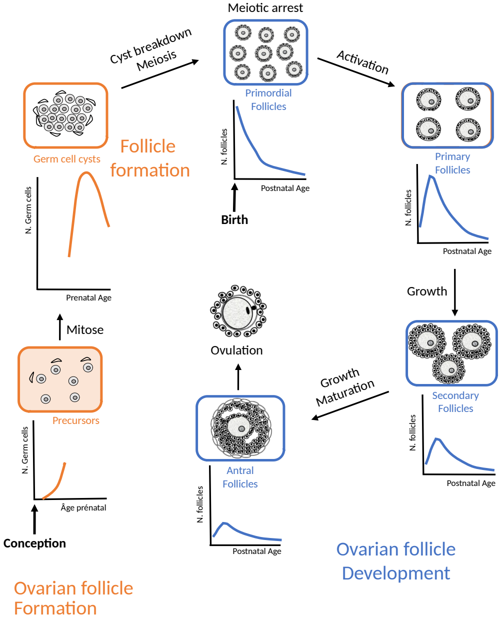

Meiotic arrest
Cyst breakdown
Meiosis
Activation
Primordial
Follicles
N. follicles
Postnatal Age
Birth
Germ cell cysts
Follicle
formation
N. Germ cells
Prenatal Age
Primary
Follicles
N. follicles
Postnatal Age
Growth
Mitose
Ovulation
Precursors
N. Germ cells
Âge prénatal
Conception
Growth
Maturation
Secondary
Follicles
N. follicles
Postnatal Age
Antral
Follicles
N. follicles
Postnatal Age
Ovarian follicle
Development
Ovarian follicle
Formation

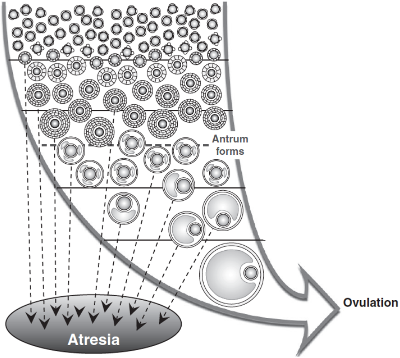


- Pool of Quiescent follicles
  static reserve (perinatal in most mammals)
  Slow activation
- Basal growth
  Dynamic reserve (starting at birth) Spanning over several ovarian cycles
- Terminal growth
  After puberty : ovulation within an ovarian cycle

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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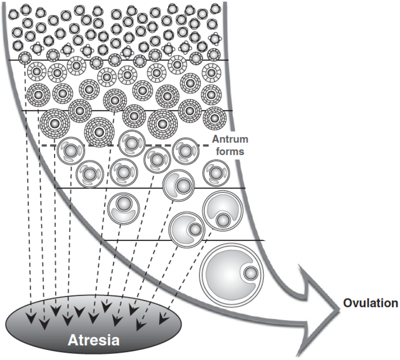
- Growing follicles

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



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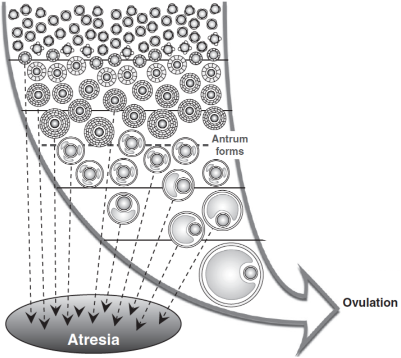
$>$**Only** 400 **follicles will ever reach the pre-ovulatory stage**



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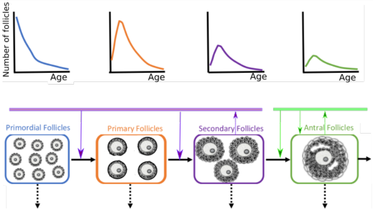
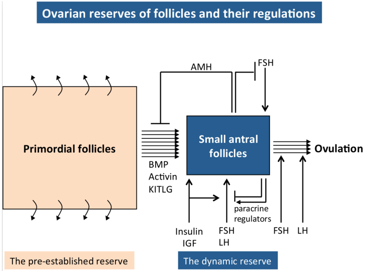
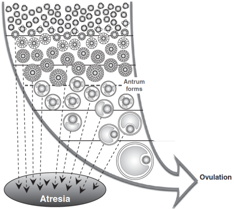
Population dynamics in female gametogenesis

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





Monniaux, Theriogenology 2016



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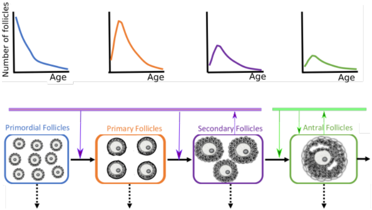
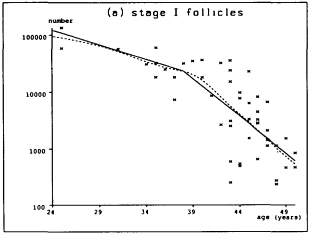
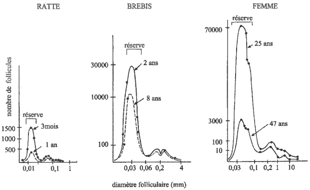


⇒ Irreversible (slow) decay of an initial pool of quiescent follicle

⇒ ”Stable” repartition of growing follicle



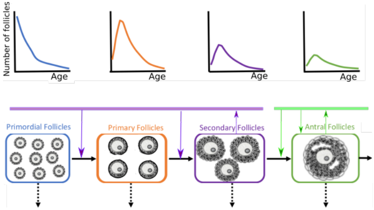
Faddy and Gosden 1995

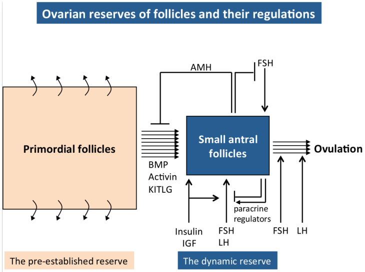


Thibault and Levasseur, 2001

Societal challenges : to preserve the reproductive ability

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



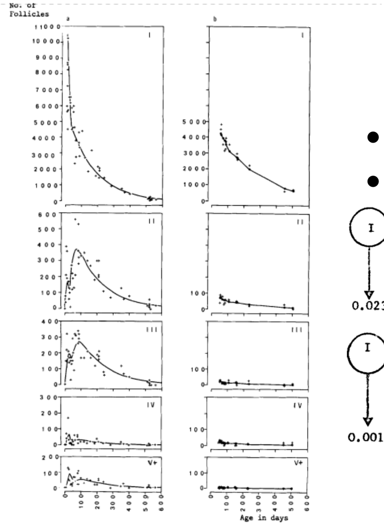


Monniaux, Theriogenology 2016

Economic and environmental challenges

- Biotechnology of reproduction
- Endocrine disruptors
- Non-hormonal contraception

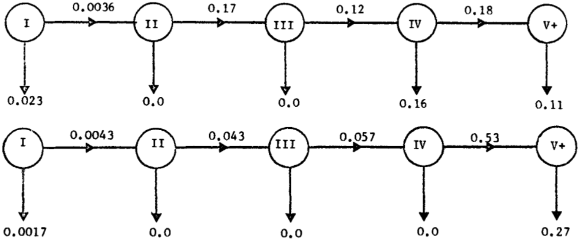
Aim : revisit compartmental model with nonlinear interaction and timescale analysis



An Analytical Model for Ovarian Follicle Dynamics

M. J. FADDY,[1] ESTHER C. JONES[2] AND R. G. EDWARDS[3]
[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



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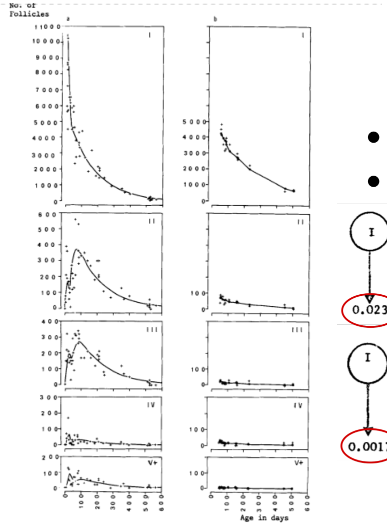

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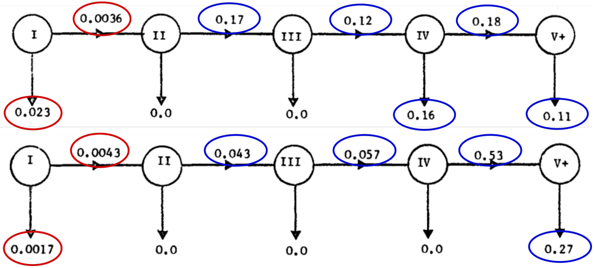
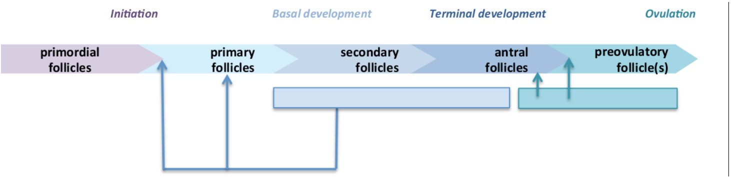


Lifespan follicle population model

- Structured Population in compartments
- Non linear interaction between follicles *via* $\lambda's$ and $\mu's$.

$$
\begin{array}{ccccccccc}
 & \lambda_0(\cdot) & & \lambda_1(\cdot) & & \lambda_2(\cdot) & & & \\
X & \to & Y_1 & \to & Y_2 & \to & \cdots & & Y_d \\
\downarrow \mu_0(\cdot) & & \downarrow \mu_1(\cdot) & & \downarrow \mu_2(\cdot) & & & & \downarrow \mu_d(\cdot) \\
\emptyset & & \emptyset & & \emptyset & & & & \emptyset
\end{array}
$$



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

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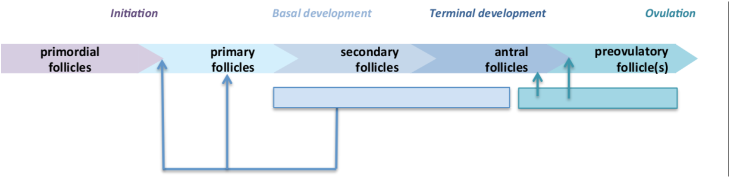
\downarrow \mu_0 & & \downarrow \mu_1 & & \downarrow \mu_2 & & & & \downarrow \mu_d \\
\emptyset & & \emptyset & & \emptyset & & & & \emptyset
\end{array}
$$

Typical choice

$$
\begin{aligned}
\lambda_i(Y) &= m_i + \frac{f_i}{1 + K_{1,i} \sum_{j=1}^{d} \omega_{1,j} Y_j}, \\
\mu_i(Y) &= g_i \left(1 + K_{2,i} \sum_{j=0}^{d} \omega_{2,j} Y_j \right)
\end{aligned}
$$



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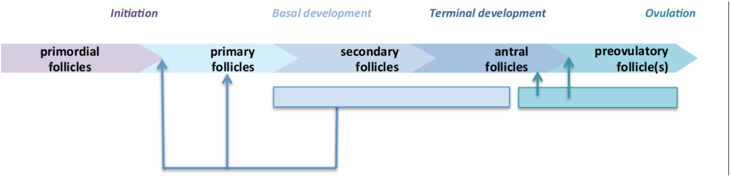
Lifespan follicle population model

- Structured Population in compartments
- Non linear interaction between follicles *via* $\lambda's$ and $\mu's$.
- Two time and abundance scales

- Quiescent Pool $\gg$ Growing Follicles
- Slow Activation $\ll$ Fast growth

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



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Singular Perturbation Theory (deterministic ODEs)

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

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

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

Singular Perturbation Theory (stochastic CTMC)

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

Re-scaled Continuous Time Markov Chain :

$(X^\varepsilon(t) = \varepsilon X_0(t/\varepsilon),\ Y^\varepsilon(t) = (X_1(t/\varepsilon), \cdots, X_d(t/\varepsilon)))$:

	Events	Rate
self-renew :	$(X, Y) \rightarrow (X + \varepsilon, Y)$,	$\frac{1}{\varepsilon} r_0(Y)X$,
activation :	$(X, Y) \rightarrow (X - \varepsilon, Y + e_1)$,	$\frac{1}{\varepsilon}\lambda_0(Y)X$,
atresia :	$(X, Y) \rightarrow (X - \varepsilon, Y)$,	$\frac{1}{\varepsilon}\mu_0(Y)X$,
growth :	$(X, Y) \rightarrow (X, Y + e_{i+1} - e_i)$,	$\frac{1}{\varepsilon}\lambda_i(Y)Y_i$, $i = 1..d-1$,
atresia :	$(X, Y) \rightarrow (X, Y - e_i)$,	$\frac{1}{\varepsilon}\mu_i(Y)Y_i$, $i = 1..d$,

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

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*

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

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

$$L_x\psi(y) = \lambda_0(y)x\Big[\psi(y+e_1) - \psi(y)\Big] + \sum_{i=1}^{d-1}\lambda_i(y)y_i\Big[\psi(y+e_{i+1}-e_i) - \psi(y)\Big]$$
$$+ \sum_{i=1}^{d}\mu_i(y)y_i\Big[\psi(y-e_i) - \psi(y)\Big]\,.$$

Schéma de preuve

- Compacité / Estimée sur les moments :
  $\forall p \geq 1, \ \sup_{\varepsilon} \mathbb{E}\Big(\sup_{t \geq 0} \Big| X^{\varepsilon}(t) + \sum_{i=1}^{d} Y_i^{\varepsilon}(t) \Big|^p \Big) < \infty$
- Identification de la martingale "lente" :
  $M_f^{\varepsilon}(t) = f\Big(X^{\varepsilon}(t)\Big) - \int_0^t Af\Big(X^{\varepsilon}(s), Y^{\varepsilon}(s)\Big)\d{s} + R_f^{\varepsilon}(t)$ où
  $Af(x,y) = \Big(r_0(y) - \lambda_0(y) - \mu_0(y)\Big)xf'(x)$
- Identification de la martingale "rapide" :
  $M_g^{\varepsilon}(t) := \varepsilon\Big[g\big(Y^{\varepsilon}(t)\big) - g\big(Y^{\varepsilon}(0)\big)\Big] - \int_0^t \int_{\mathbb{N}^d} L_{X^{\varepsilon}(s)} g\big(Y^{\varepsilon}(s)\big)ds$

	Events	Rate
self-renew :	$(X,Y) \to (X+\varepsilon, Y)$,	$\frac{1}{\varepsilon} r_0(Y)X$,
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Hypothèses

- ⋆ $r_0(y) < R_0, \forall y$
- ⋆ $\lambda_0(y) \leq B_0, \forall y$
- ⋆ $\lambda_i(y) > 0$, $i \in [\![0, d-1]\!], \forall y$
- ⋆ $\mu_d(y) > 0, \forall y$
- ⋆ $\alpha_i > 0$ tel que $\lambda_i(y) + \mu_i(y) \geq \alpha_i$, $\forall i \in [\![0, d]\!], \forall y$

Éléments de preuves

- Processus majorant linéaire :

$$\begin{array}{ll} (U,V) \to (U+\varepsilon, V), & \frac{1}{\varepsilon} R_0 U\,, \\ (U,V) \to (U, V+e_1), & \frac{1}{\varepsilon} B_0 U\,, \\ (U,V) \to (U-\varepsilon, V+1), & \frac{1}{\varepsilon} \alpha_0 U\,, \\ (U,V) \to (U, V+e_{i+1}-e_i), & \frac{1}{\varepsilon} \alpha_i V_i\,. \end{array}$$

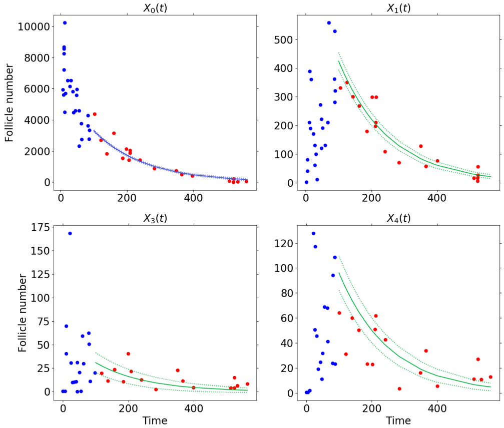
- Par couplage : $X \leq U$ et $\sum_{j=1}^{i} Y_j \leq \sum_{j=1}^{i} V_j$.
- Lyapounov $F(y) = \sum_{i=1}^{d} \left(\sum_{j=1}^{i} y_j \right)^{p_i}$ pour $p_i \searrow$.

Pour l'unicité :

$\frac{dx}{dt}(t) = \langle r_0 - \lambda_0 - \mu_0, \pi_{x(t)} \rangle x(t)$

- Lyapounov F : $\langle \pi_x, F \rangle < \infty$.
- Pour toute fonction f tel que $| f | \leq F$
  $\langle f, \pi_x - \pi_{x'} \rangle = (x - x') \langle (g_x(\cdot + 1) - g_x(\cdot)) \lambda_0, \pi_{x'} \rangle$
  où g_x est solution de l'équation de Poisson : $L_x g_x = \langle f, \pi_x \rangle - f$ et vérifie $| g_x | \leq F$

Does it works in practice ?

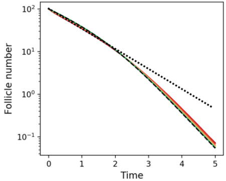


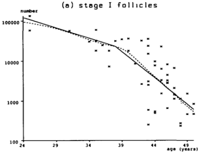
$$\begin{cases} x_0(t) & = X_0^{in} \exp\Big(-(\lambda_0 + \mu_0)t \Big) \\ \pi_{x_0(t)}(y) & = \prod_{i=1}^{d} \frac{(x_0(t)\alpha_i)^{y_i}}{y_i!} e^{-x_0(t)\alpha_i} \end{cases}$$

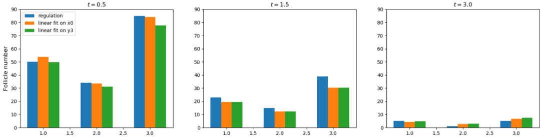
$$\alpha_i = \prod_{j=0}^{i-1} \frac{\lambda_j}{\lambda_{j+1}+\mu_{j+1}}$$

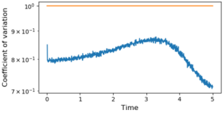
- Timescale separation is coherent with published data on follicle counts in mice at the lifespan time scale, *away from a transient period*.

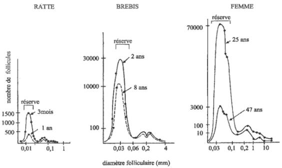
What is it useful for ?











- ✓ acceleration of reserve decay with age : $\frac{dx}{dt} = -(a + \frac{b}{1+cx})x$ -> Mechanistic explanation of previously published statistical regression model (*Coxworth and Hawkes 2010*)

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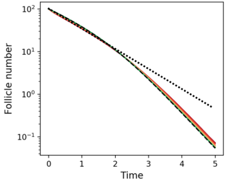
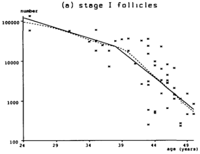
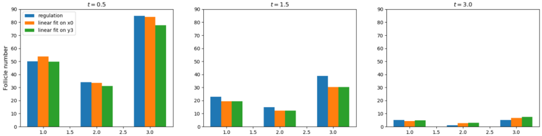
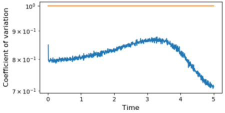
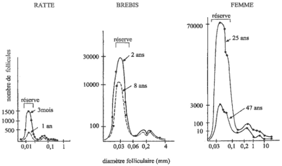










- ✓ acceleration of reserve decay with age : $\frac{dx}{dt} = -(a + \frac{b}{1+cx})x$ -> Mechanistic explanation of previously published statistical regression model (*Coxworth and Hawkes 2010*)
- ✓ "stable" evolution of growing follicles Y -> Antral Follicle Count for fertility test and primary ovarian insufficiency detection

Going further

- What about fluctuations ?
- 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) ?

Fluctuations

At leading order, fluctuations are Gaussian of order $\sqrt{\varepsilon}$: $U^\varepsilon = \frac{X^\varepsilon - x}{\sqrt{\varepsilon}}$

CLT

... U^ε converges towards U that satisfies

$$U(t) = U^{in} + \int_0^t \left[\lambda_0'(x(s))x(s) + \lambda(x(s))\right] U(s)\dot{s} + \int_0^t \sqrt{\langle G(x(s),\cdot),\pi_{x(s)}\rangle}\dot{W}_s$$

Fluctuations with more than two timescales

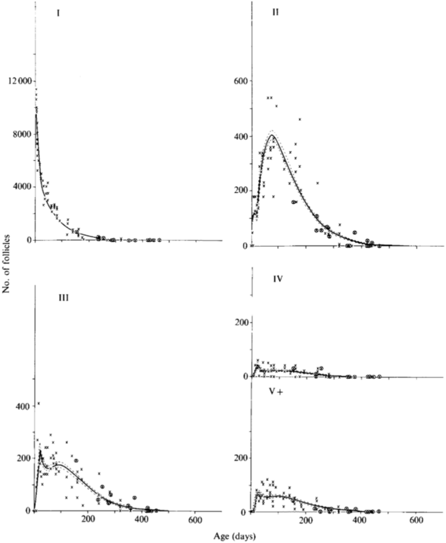
X=quiescent follicles ; Y=small growing follicles ; Z large terminal

$$\text{follicles :}\quad \begin{array}{ccccc} \frac{1}{\varepsilon}X & \overset{\varepsilon\lambda_0}{\to} & \frac{1}{\varepsilon^p}Y & \overset{\varepsilon^p\lambda_1}{\to} & Z \\ \downarrow \varepsilon\mu_0 & & \downarrow \varepsilon^p\mu_1 & & \downarrow \mu_2 \\ \emptyset & & \emptyset & & \emptyset \end{array}$$

For $p > 1/2$, fluctuations on X are still on order $\sqrt{\varepsilon}$, with Y and Z contributing *equally*.
For $p \leq 1/2$: undergoing work !

"Time" course

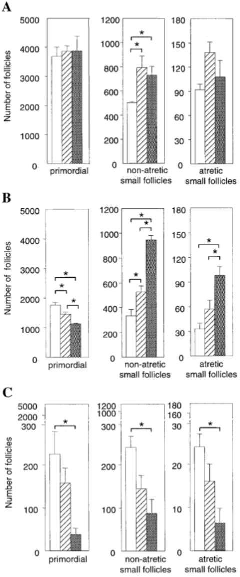
- Follicle count in mice from birth until 500 days.
- Reserve + 4 compartments (Faddy's classification)
- (Recovery of points by hand)



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

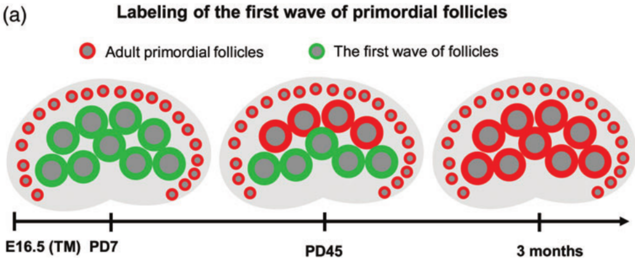
Perturbation data : KO AMH

- 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)



Ovarian Reserve build-up

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

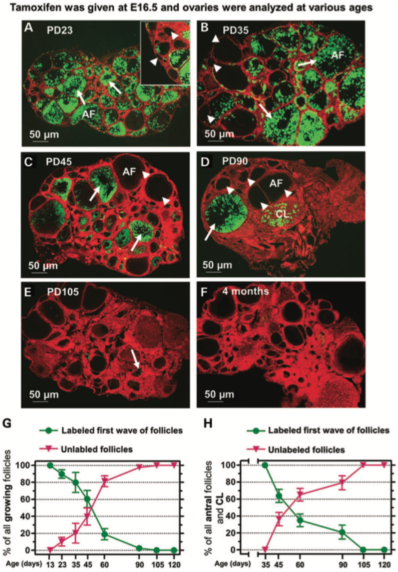


Zheng, Zhang and Liu, Hum. Mol. Reprod, 2014

Ovarian Reserve build-up

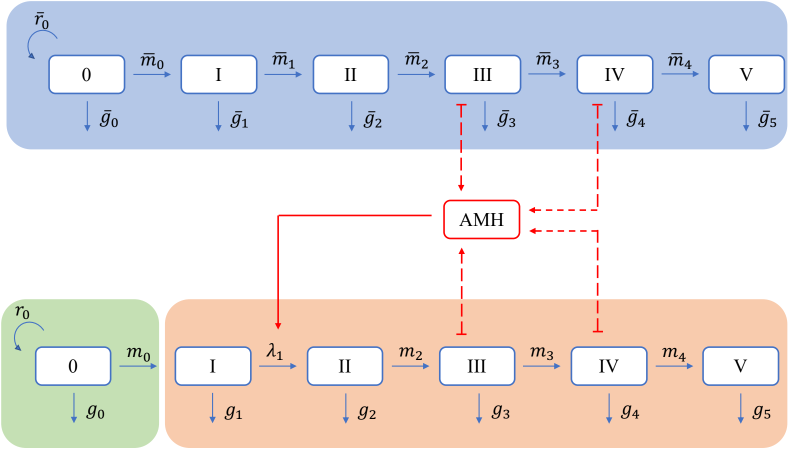
- Tracing follicles of the first wave of activated follicles.
- Proportion of first wave activated follicles among growing follicles.

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

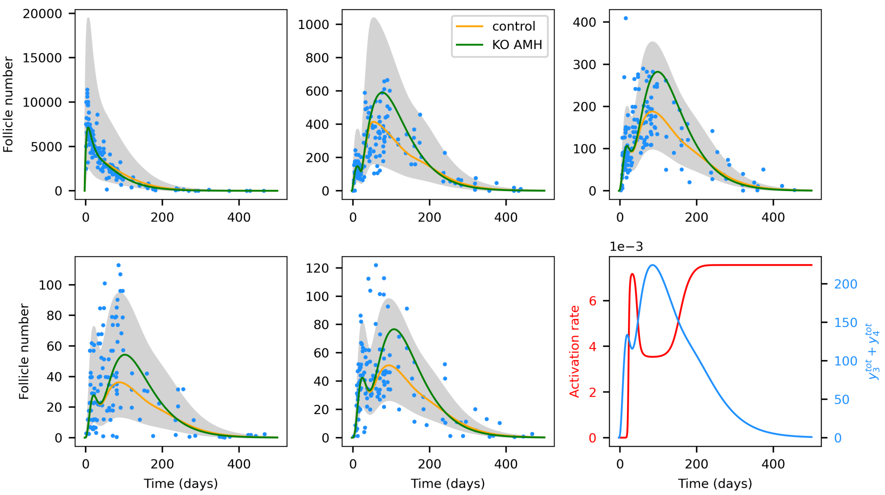


Zhang, Zhang and al. Hum. Mol. Gen. 2014

ODE model

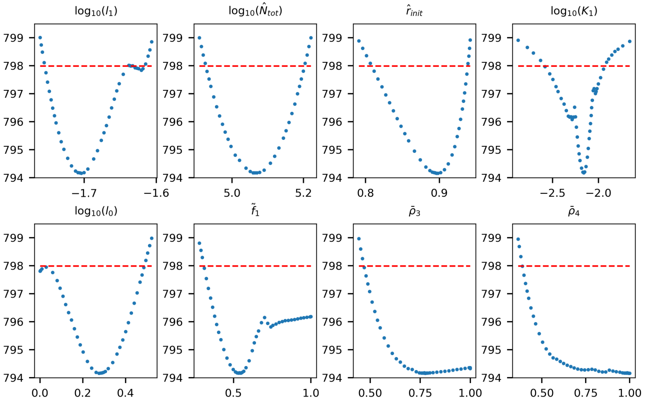

$\bar{r}_0$
0
$\bar{m}_0$
I
$\bar{m}_1$
II
$\bar{m}_2$
III
$\bar{m}_3$
IV
$\bar{m}_4$
V
$\bar{g}_0$
$\bar{g}_1$
$\bar{g}_2$
$\bar{g}_3$
$\bar{g}_4$
$\bar{g}_5$
AMH
r_0
0
m_0
I
λ_1
II
m_2
III
m_3
IV
m_4
V
g_0
g_1
g_2
g_3
g_4
g_5

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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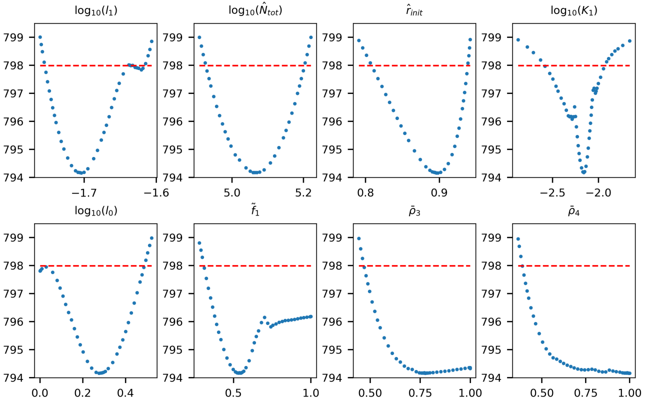
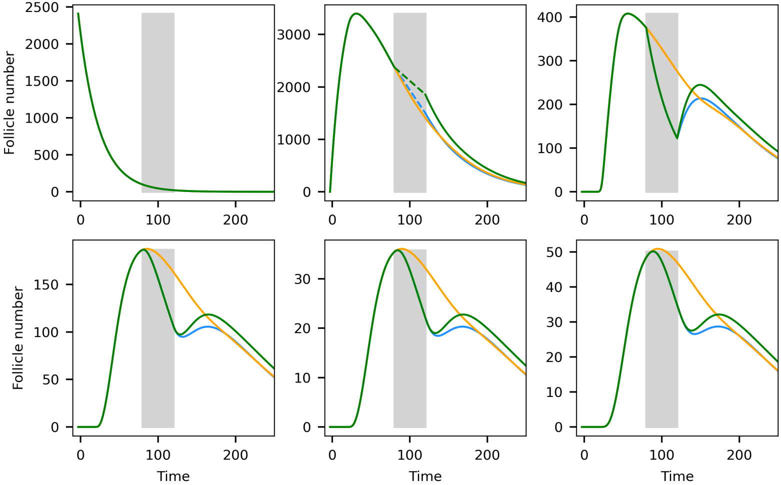


- 20 of 31 parameters are practically identifiable.
- Additional Data on germ cell dynamics would greatly improve identifiability

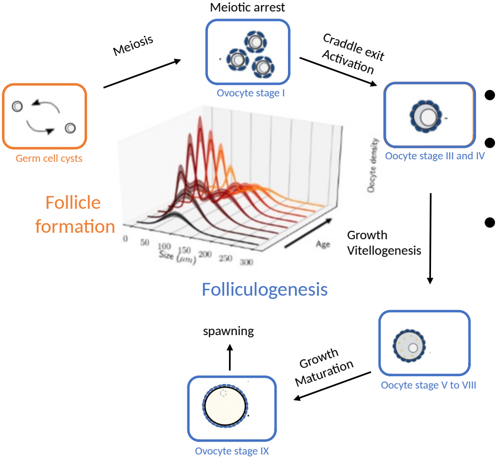
Parameter values interpretation

- Mean activation time is around 200 days, while growing time is around 50 days.
- The first-wave follicles is approx. 5 times faster than the second wave for compartments 0,1,2
- Follicles atresia is negligible in compartment 2,3,4

Prediction of AMH administration



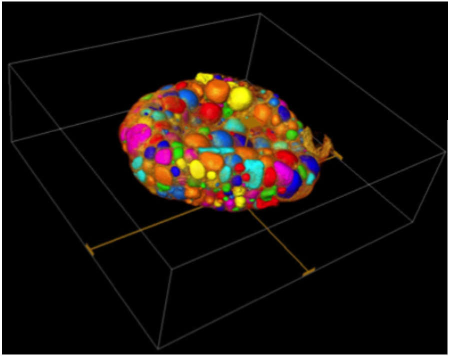
Comparison with fish oogenesis

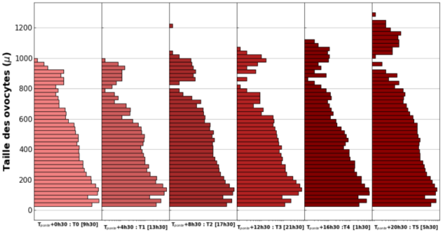


- Study of Medaka oogenesis
- Renewed asynchronous oogenesis
- Useful for Eco-Toxicology studies

3D imaging of whole ovary in Medaka

3D imaging data : whole Follicle count and size measurement





Modèle structuré en taille

$$
\begin{cases}
\dfrac{d\rho_0(t)}{dt} & = & \Big(r_0(\rho(t,.)) - \lambda_0(\rho(t,.)) - \mu_0(\rho(t,.))\Big)\rho_0(t)\,, \\
\partial_t \rho(t,x) & = & -\partial_x(\lambda(\rho(t,.),x)\rho(t,x)) - \mu(\rho(t,.),x)\rho(t,x) \\
\lim_{x\to 0} \lambda(\rho(t,.),x)\rho(t,x) & = & \lambda_0(\rho(t,.))\rho_0(t)\,,
\end{cases}
$$

Dépendance du cycle ovarien ?

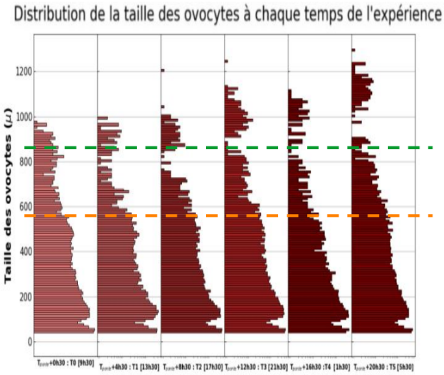
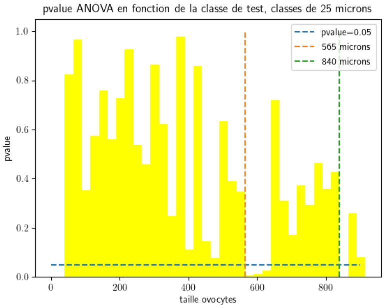


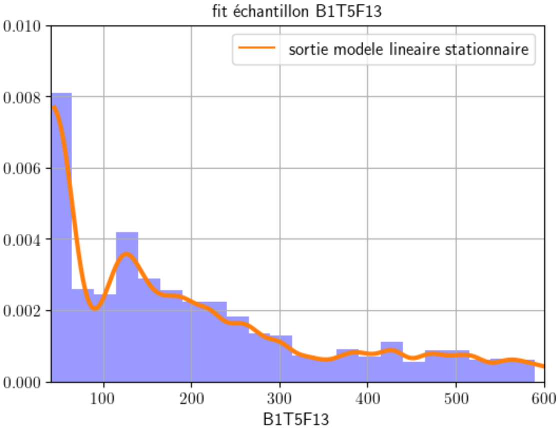
FIGURE A.1 – Présentation de l'évolution des distributions de la taille des ovocytes de 10 en 10 μm en échelle logarithmique



Problème stationnaire pour la partie indépendante du cycle

$$\begin{cases} 0 &= -\partial_x(\lambda(\rho,x)\rho(x)) - \mu(\rho,x)\rho(x)\,, \quad \text{for } x \in (0,1)\,, \\ r &= \lim_{x\to 0} \lambda(\rho,x)\rho(x)\,, \end{cases}$$

Résultat préliminaire de problème inverse (modèle linéaire, $\mu = 0$)



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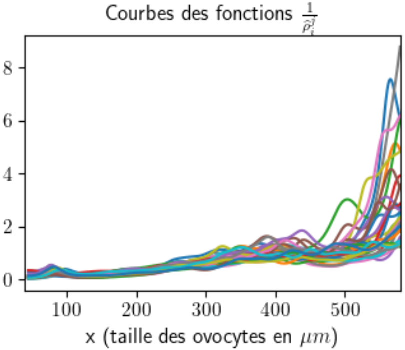
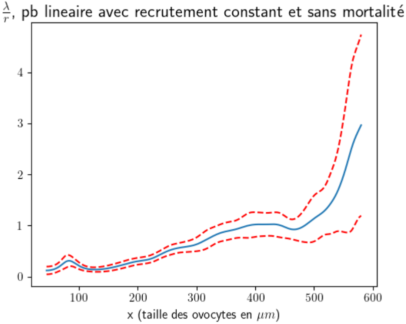
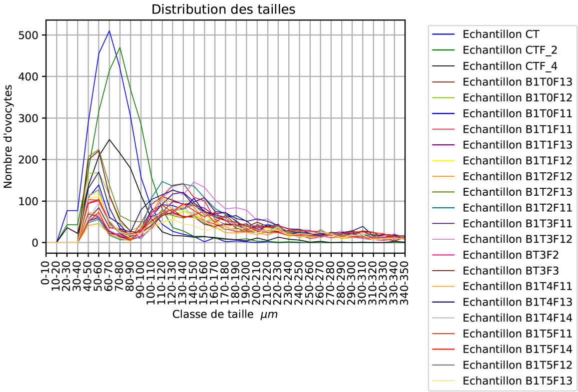
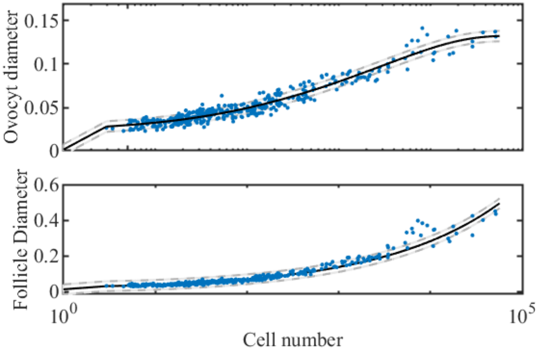


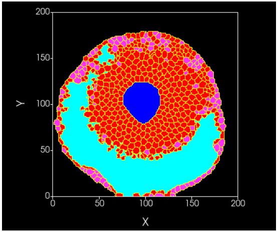


Transition Juvénile -> adulte



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-doc position avalaible in 2023 !

Thanks for your attention !

- ⋆ INRIA Saclay : Frédérique Clément, Louis Fostier, Guillaume Ballif, Frédérique Robin
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- ⋆ INRAE LPGP (Violette Thermes)
- ⋆ INSERM - Paris Cité (Céline Guigon)
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