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

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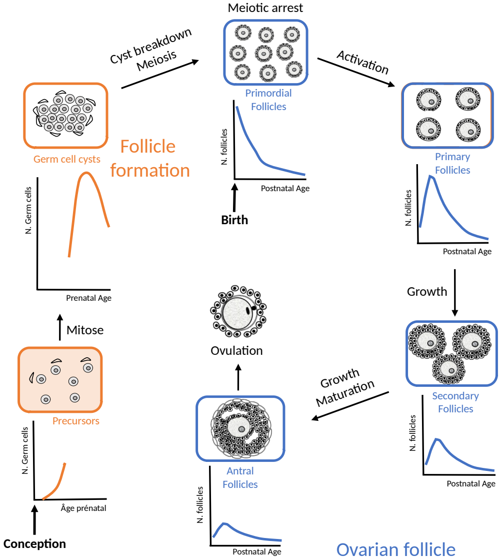
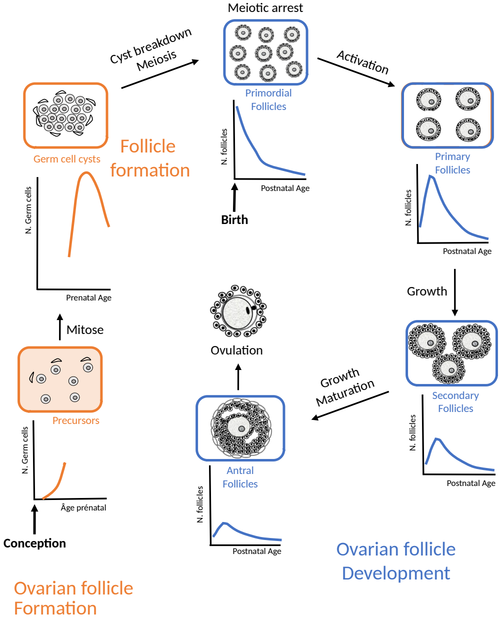


Ovarian follicle Development

Ovarian follicle Formation

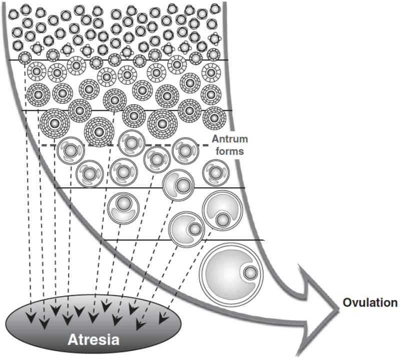


- Pool of Quiescent follicles
  static reserve (perinatal in most mammals)
  Slow activation
- Basal growth
  Dynamic reserve (starting at birth) Spanning over several ovarian cycles
- Terminal growth
  After puberty : ovulation within an ovarian cycle

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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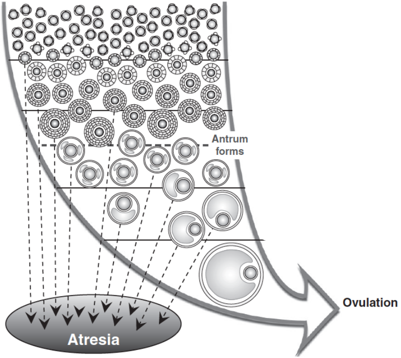
- Growing follicles

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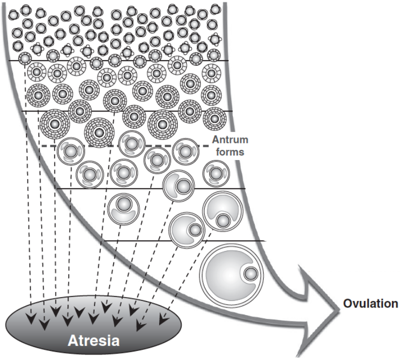
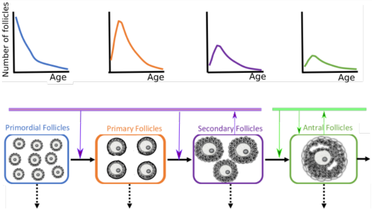
$>$**Only** 400 **follicles will ever reach the pre-ovulatory stage**

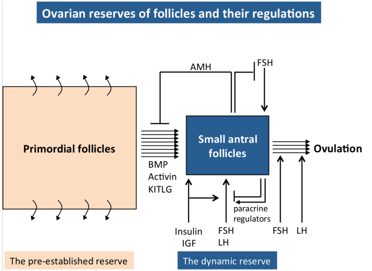


Scaramuzzi et al., Reprod.Fert. Dev. 2011

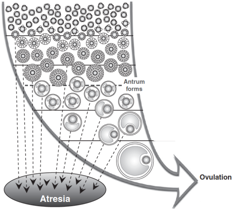
Population dynamics in female gametogenesis

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





Monniaux, Theriogenology 2016



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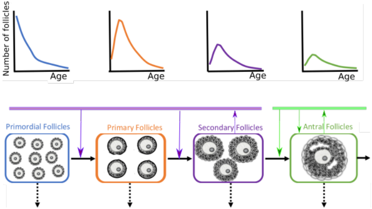
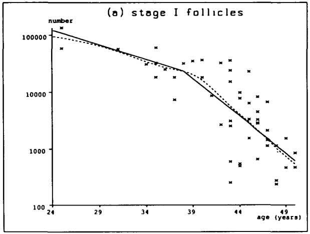
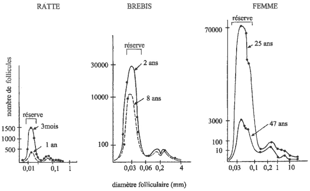


⇒ Irreversible (slow) decay of an initial pool of quiescent follicle

⇒ "Stable" repartition of growing follicle



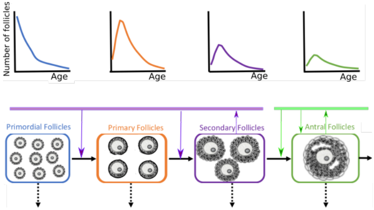
Faddy and Gosden 1995

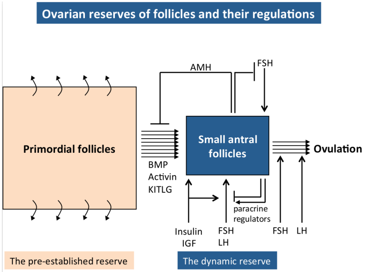


Thibault and Levasseur, 2001

Societal challenges : to preserve the reproductive ability

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



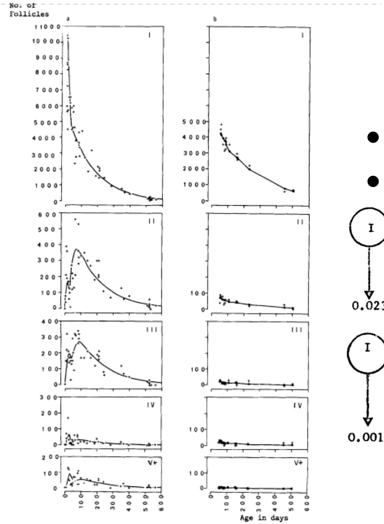


Monniaux, Theriogenology 2016

Economic and environmental challenges

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

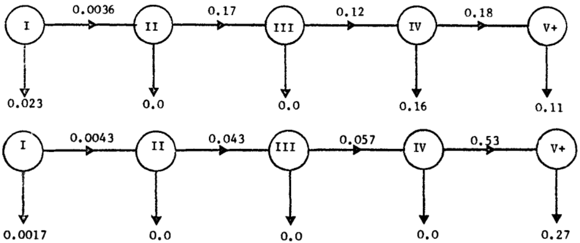
Aim : revisit compartmental model with nonlinear interaction and timescale analysis



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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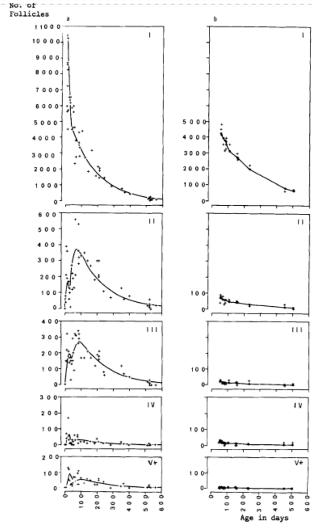

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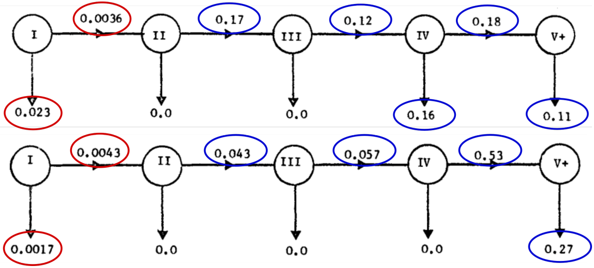
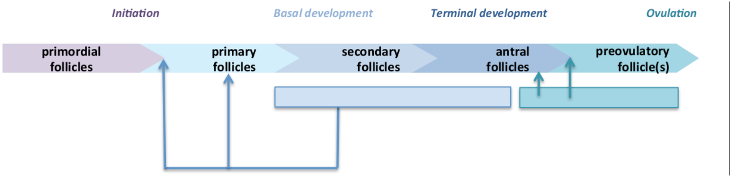


Lifespan follicle population model

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

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



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

Lifespan follicle population model

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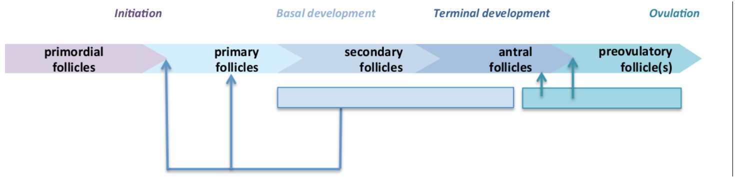
$$
\begin{array}{ccccccccc}
X & \overset{\lambda_0}{\rightarrow} & Y_1 & \overset{\lambda_1}{\rightarrow} & Y_2 & \overset{\lambda_2}{\rightarrow} & \cdots & & Y_d \\
\downarrow \mu_0 & & \downarrow \mu_1 & & \downarrow \mu_2 & & & & \downarrow \mu_d \\
\emptyset & & \emptyset & & \emptyset & & & & \emptyset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

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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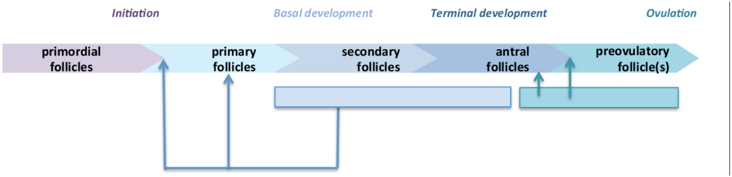
Lifespan follicle population model

- 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

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



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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 :

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

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

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

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*

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

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

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

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" :
  $M_f^{\varepsilon}(t) = f\Big(X^{\varepsilon}(t)\Big) - \int_0^t Af\Big(X^{\varepsilon}(s), Y^{\varepsilon}(s)\Big)ds + R_f^{\varepsilon}(t)$ 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
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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 :

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

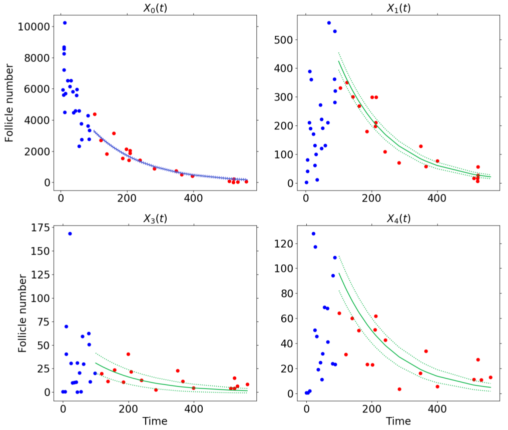
- Par couplage : $X \leq U$ et $\sum_{j=1}^{i} Y_j \leq \sum_{j=1}^{i} V_j$.
- Lyapounov $F(y) = \sum_{i=1}^{d} \left(\sum_{j=1}^{i} y_j \right)^{p_i}$ pour $p_i \searrow$.

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 $\mid f \mid \leq F$
  $\langle f, \pi_x - \pi_{x'} \rangle = (x - x') \langle (g_x(\cdot + 1) - g_x(\cdot)) \lambda_0, \pi_{x'} \rangle$
  où g_x est solution de l'équation de Poisson : $L_x g_x = \langle f, \pi_x \rangle - f$ et vérifie $\mid g_x \mid \leq F$

Does it works in practice ?

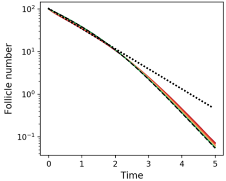


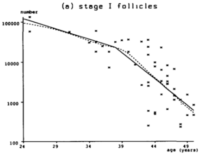
$$\begin{cases} x_0(t) & = X_0^{in} \exp\Big(-(\lambda_0+\mu_0)t \Big) \\ \pi_{x_0(t)}(y) & = \prod_{i=1}^{d} \frac{(x_0(t)\alpha_i)^{y_i}}{y_i!} e^{-x_0(t)\alpha_i} \end{cases}$$

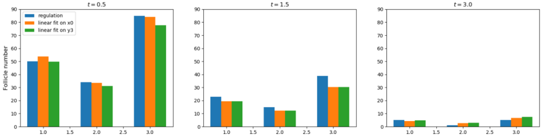
$$\alpha_i = \prod_{j=0}^{i-1} \frac{\lambda_j}{\lambda_{j+1}+\mu_{j+1}}$$

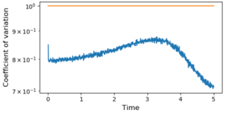
- Timescale separation is coherent with published data on follicle counts in mice at the lifespan time scale, *away from a transient period*.

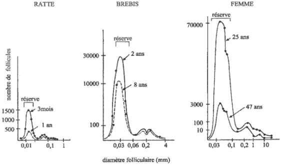
What is it useful for ?











- ✓ 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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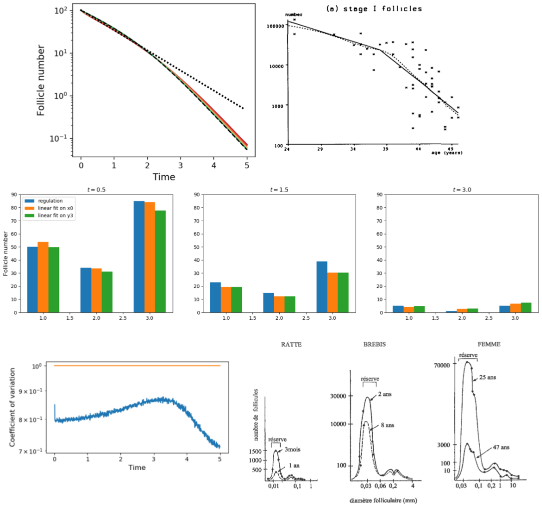


- ✓ acceleration of reserve decay with age : $\frac{dx}{dt} = -(a + \frac{b}{1+cx})x$ -> Mechanistic explanation of previously published statistical regression model (*Coxworth and Hawkes 2010*)
- ✓ "stable" evolution of growing follicles Y -> Antral Follicle Count for fertility test and primary ovarian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

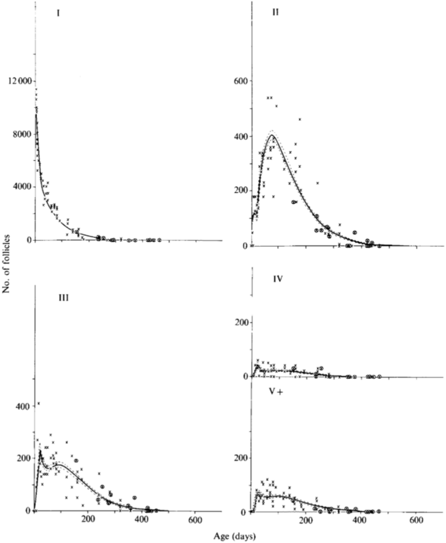
X=quiescent follicles ; Y=small growing follicles ; Z large terminal

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

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

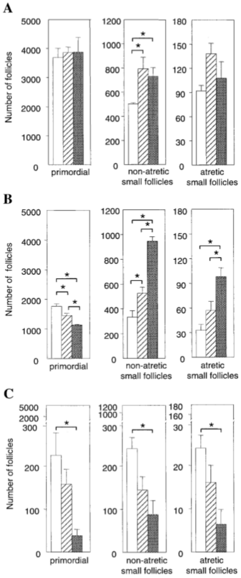
- Follicle count in mice from birth until 500 days.
- Reserve + 4 compartments (Faddy's classification)
- (Recovery of points by hand)



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

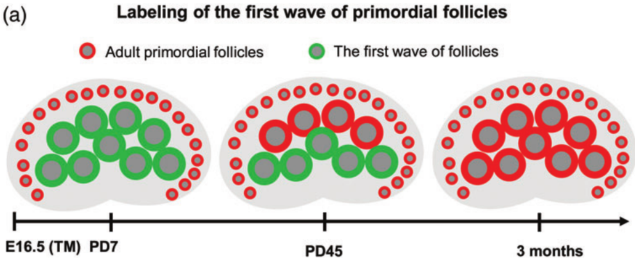
Perturbation data : KO AMH

- 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

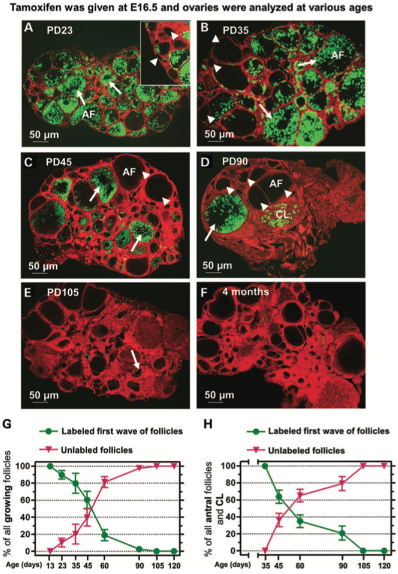


Zheng, Zhang and Liu, Hum. Mol. Reprod, 2014

Ovarian Reserve build-up

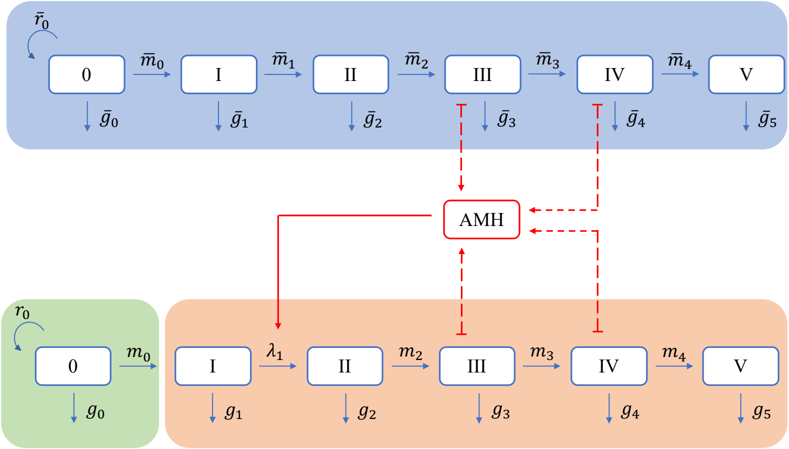
- Tracing follicles of the first wave of activated follicles.
- Proportion of first wave activated follicles among growing follicles.

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



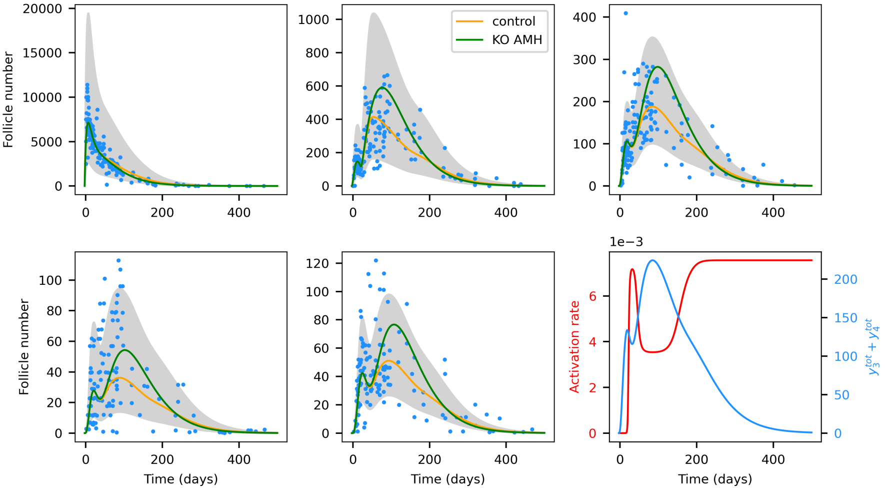
Zhang, Zhang and al., Hum. Mol. Gen. 2014

ODE model



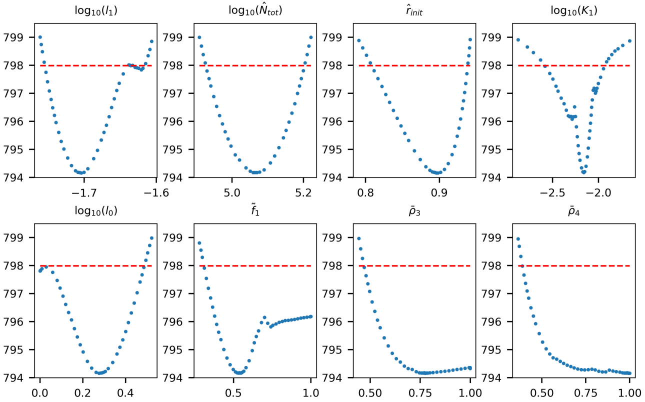
$\bar{r}_0$
0
$\bar{m}_0$
I
$\bar{m}_1$
II
$\bar{m}_2$
III
$\bar{m}_3$
IV
$\bar{m}_4$
V
$\bar{g}_0$
$\bar{g}_1$
$\bar{g}_2$
$\bar{g}_3$
$\bar{g}_4$
$\bar{g}_5$
AMH
r_0
0
m_0
I
λ_1
II
m_2
III
m_3
IV
m_4
V
g_0
g_1
g_2
g_3
g_4
g_5

Data fitting



Identifiability

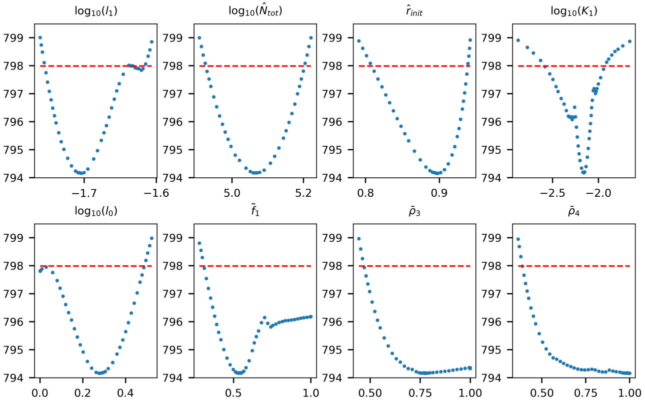
Theoretical *(Structural Identifiability Julia package)* and practical identifiability *(Data2Dynamics Matlab package)*



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

Identifiability

Theoretical *(Structural Identifiability Julia package)* and practical identifiability *(Data2Dynamics*



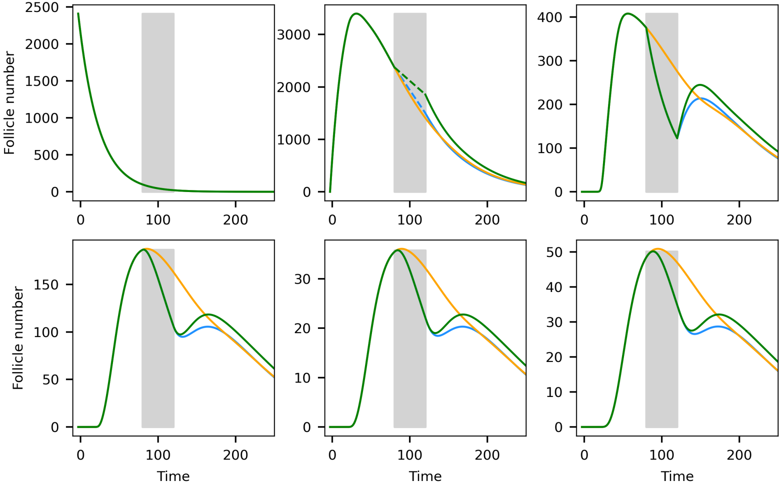
Matlab package)

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

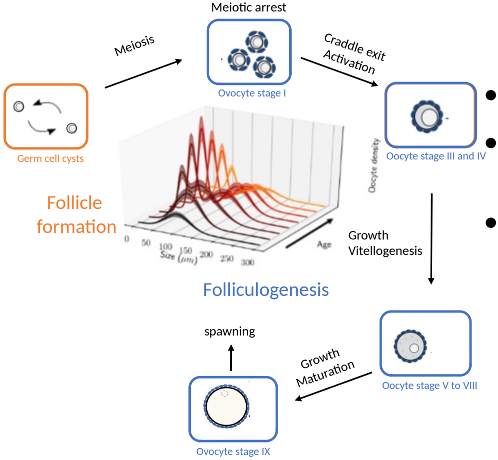
Parameter values interpretation

- 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



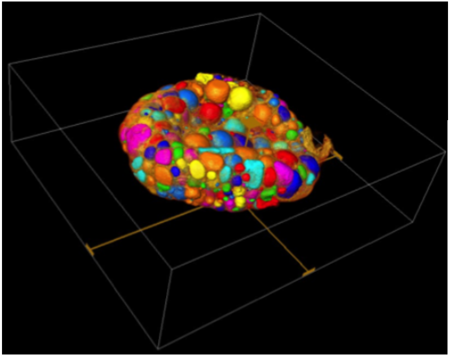
Comparison with fish oogenesis

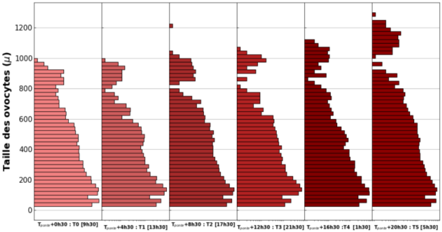


- Study of Medaka oogenesis
- Renewed asynchronous oogenesis
- Useful for Eco-Toxicology studies

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 ?

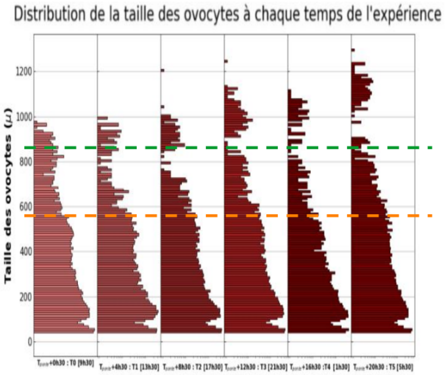
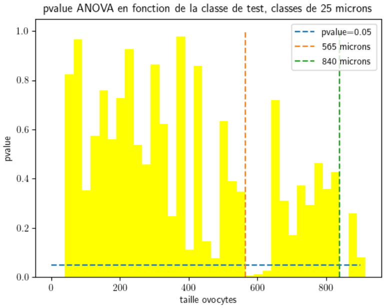


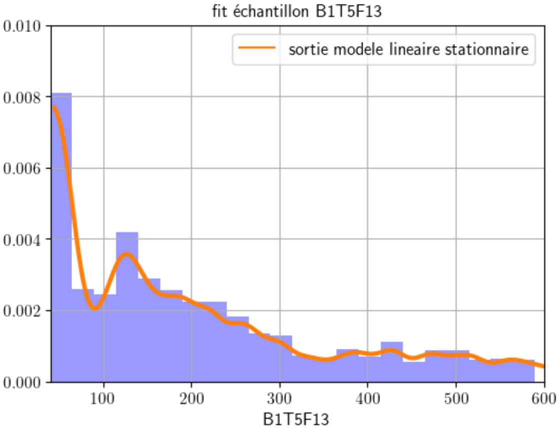
FIGURE A.1 – Présentation de l'évolution des distributions de la taille des ovocytes de 10 en 10 μm en échelle logarithmique



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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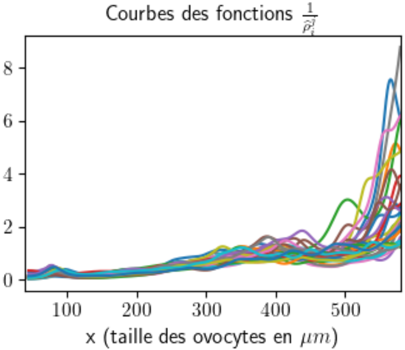
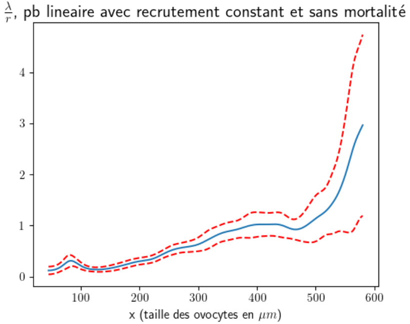
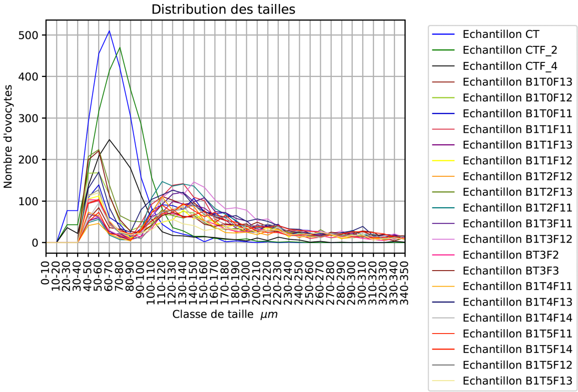
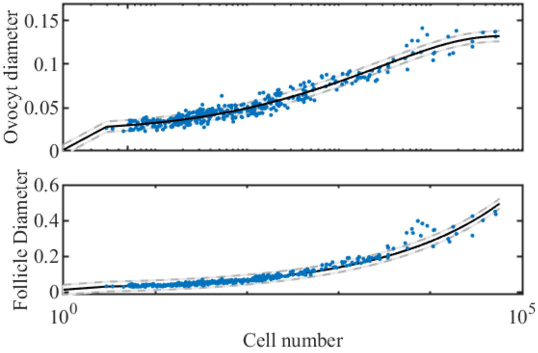


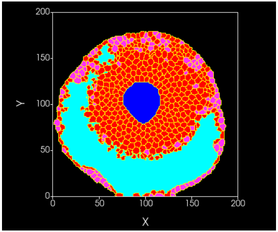


Transition Juvénile -> adulte



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 !

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- ⋆ INRAE LPGP (Violette Thermes)
- ⋆ INSERM - Paris Cité (Céline Guigon)
- ⋆ CEMRACS 2018 (Céline Bonnet, Keltoum Chahour)