Modeling (some aspects of) the female reproductive system

Romain Yvinec

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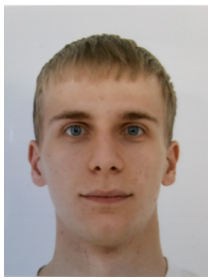
Equipe BIOS, Physiologie de la Reproduction et des Comportements, INRAE (Tours)
Equipe MUSCA, INRIA-INRAE-CNRS (Saclay)

Remerciement

- ⋆ 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), Kerloum Chahour (U. Côte d'Azur))



Problèmes scientifiques et sociétaux en reproduction

Compréhension d'un processus complexe de biologie du développement, survenant pendant toute la durée de vie

- De nombreux types de cellules impliqués et diverses interactions
- De nombreuses échelles spatiales et temporelles différentes
- Rétroaction hormonale (endocrinienne, paracrine, autocrine)
- Contrainte stérique et biophysique

Préserver la capacité de reproduction

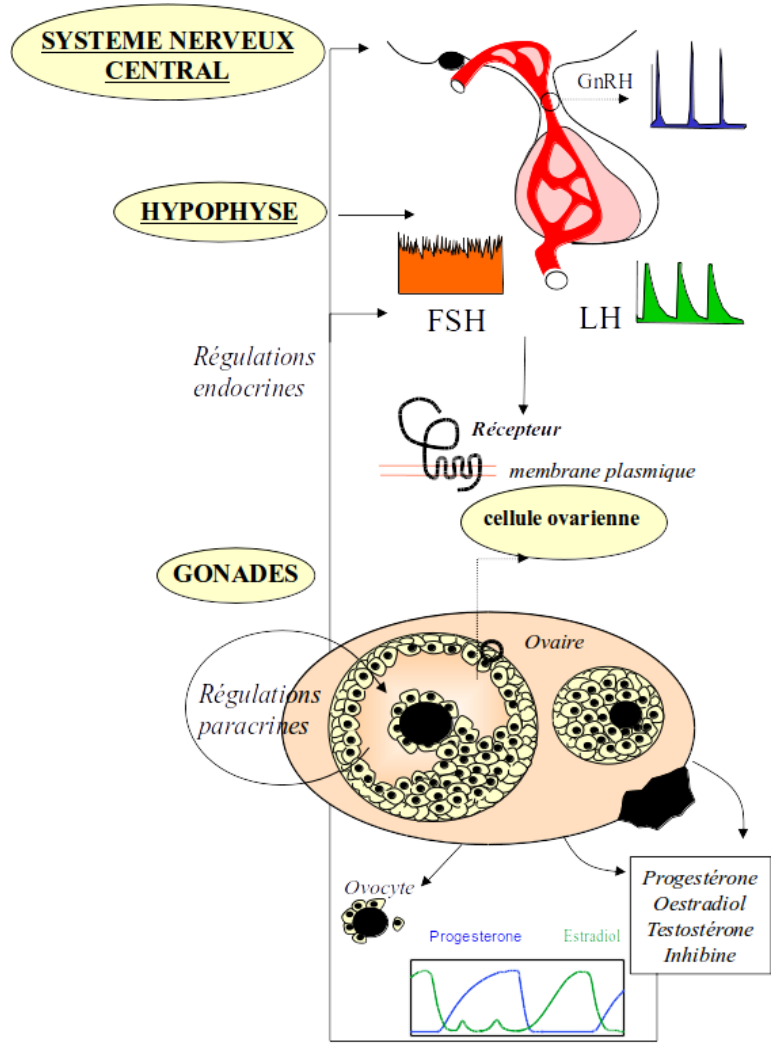
- Altérations iatrogènes ou physiologiques
- Sensibilité aux conditions environnementales
- Préservation de la biodiversité

Contrôle de la fonction de reproduction (chez l'Homme et l'animal)

- Biotechnologie de la reproduction (*in vivo*, *ex vivo*, *in vitro*)
- Enjeux clinique, économique et environnementaux

Le système reproducteur féminin des mammifères : un système multi-échelle complexe

- Signaux neuro-hormonaux
  Encodage et décodage
- Gamétogenèse
  Dynamique de population
- Croissance d'un follicule
  Morphodynamique de cellules
- Niveau intra-cellulaire
  réseaux de signalisation



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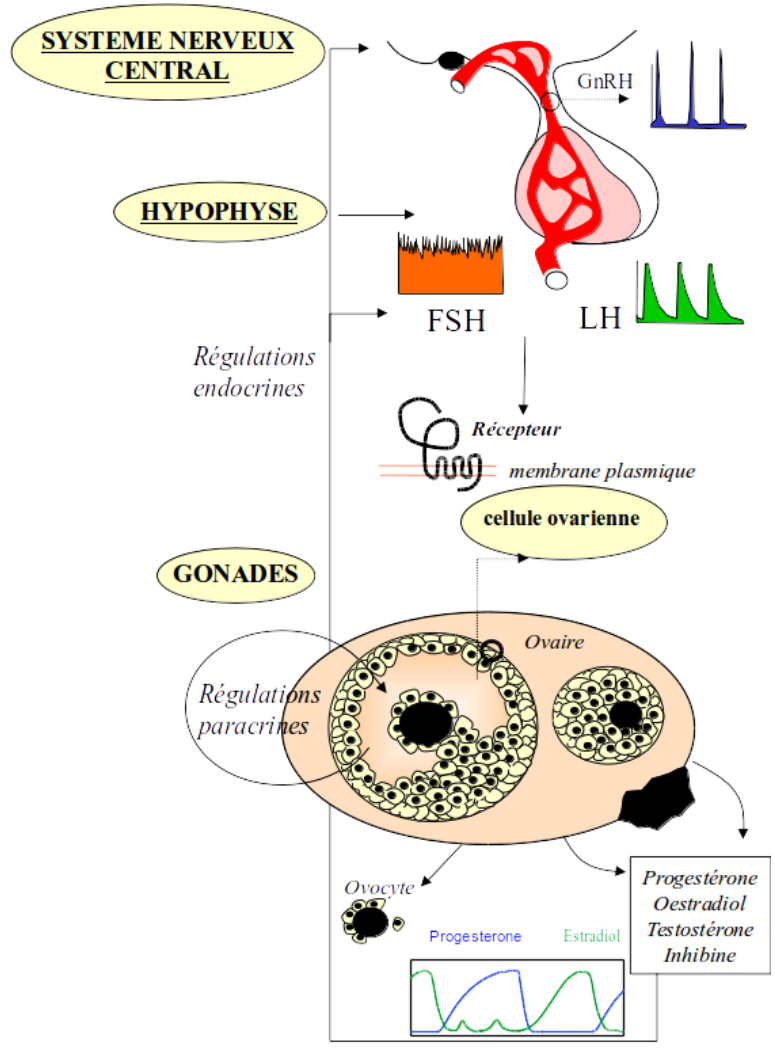

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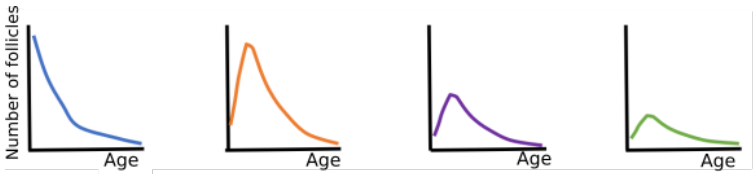
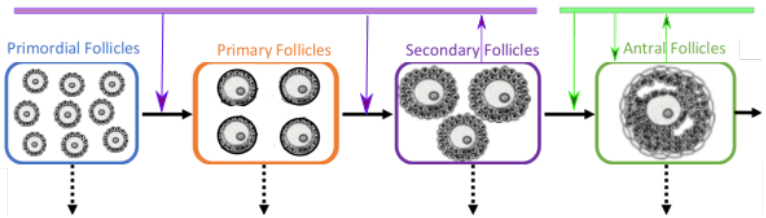
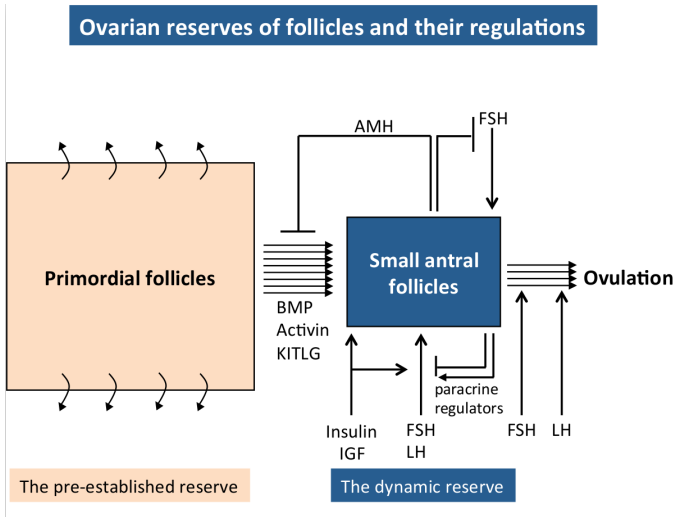
Le système reproducteur féminin des mammifères : un système multi-échelle complexe

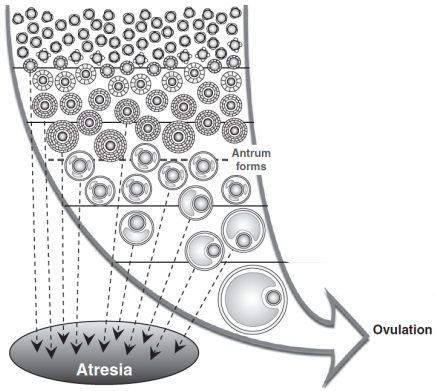
- Gamétogenèse
  Dynamique de population
  - Espace : niveau tissulaire
  - Temps : vie reproductive





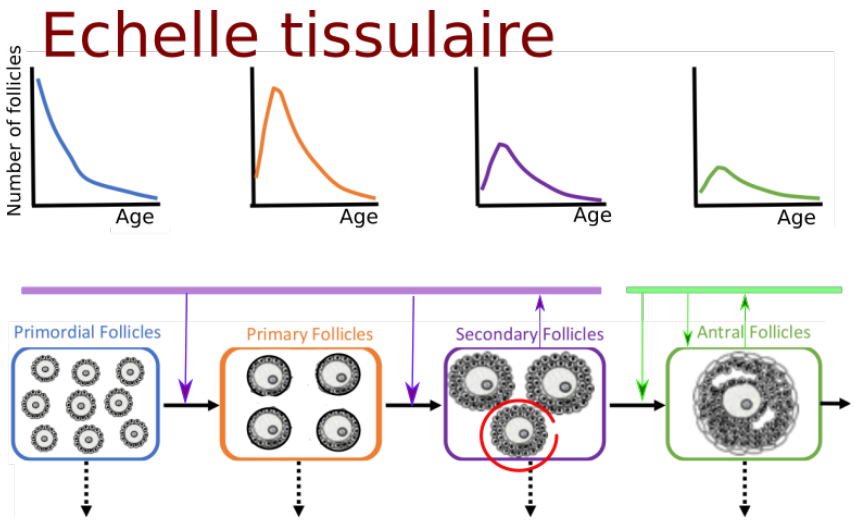


Monniaux, Theriogenology 2016



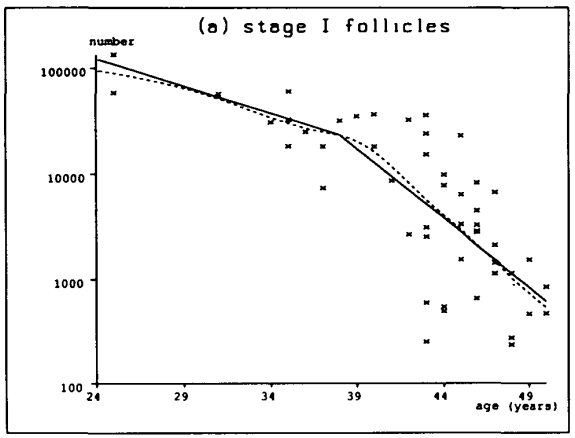
Scaramuzzi et al., Reprod.Fert. Dev. 2011

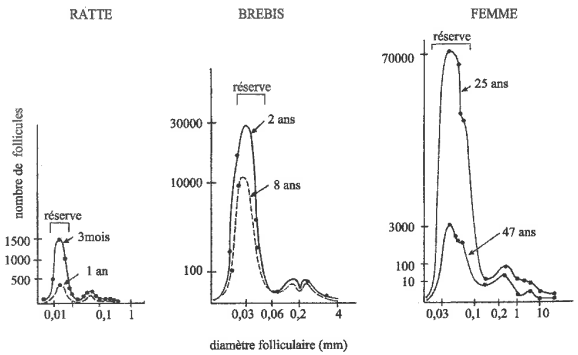
Modèles de population de follicules (vie reproductive)



⇒ Evolution irréversible d'un pool initial de follicule quiescent

⇒ Décroissance lente du nombre total de follicules et répartition "stable" dans l'espace de maturité (ou taille)





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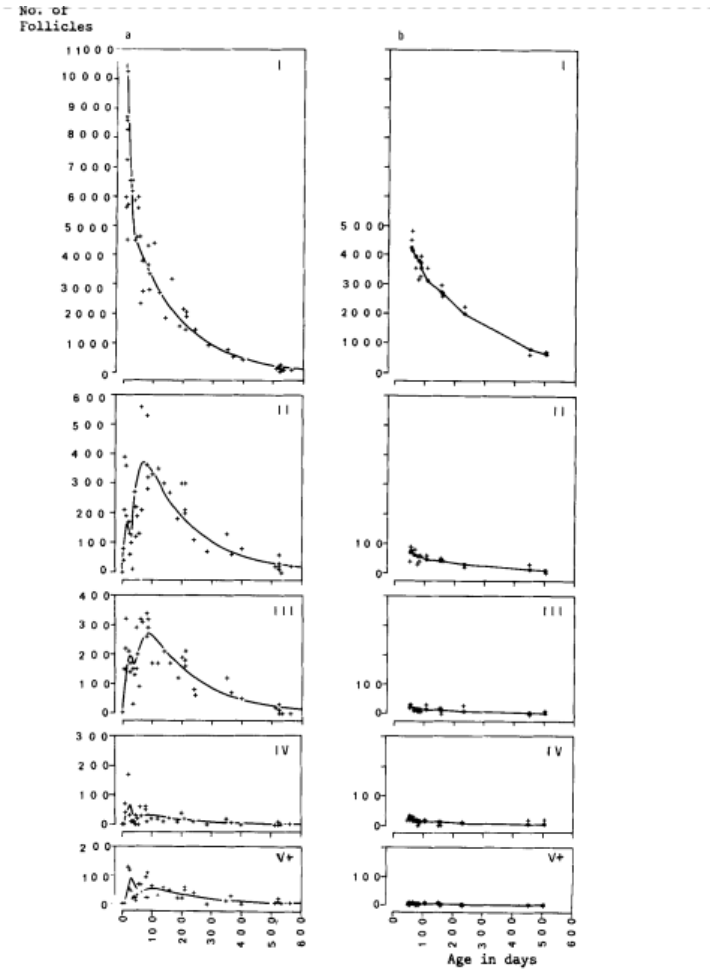
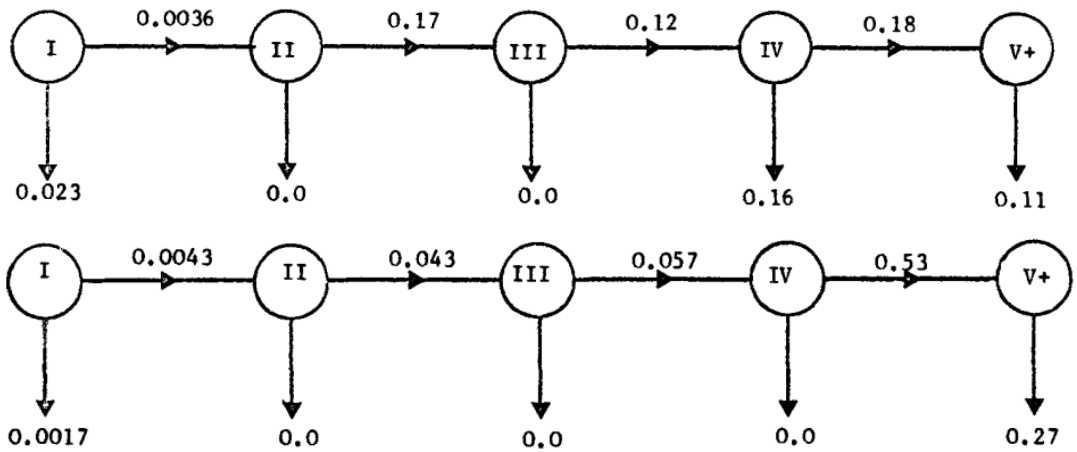


Faddy et al., J. Exp. Zool. 1976

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.*

- Modèle "migration-mort"
- Modèle linéaire inhomogène en temps



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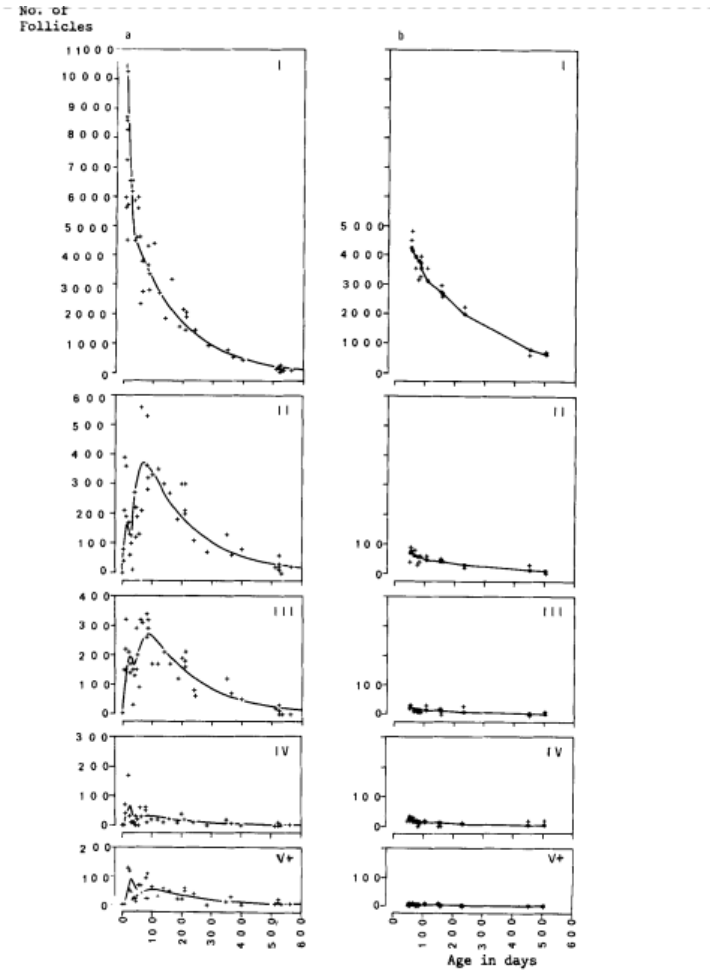

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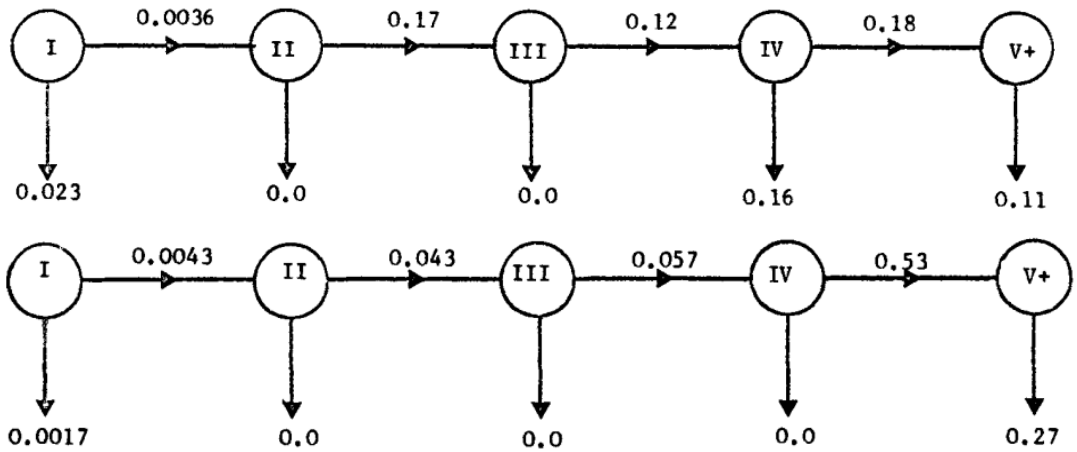

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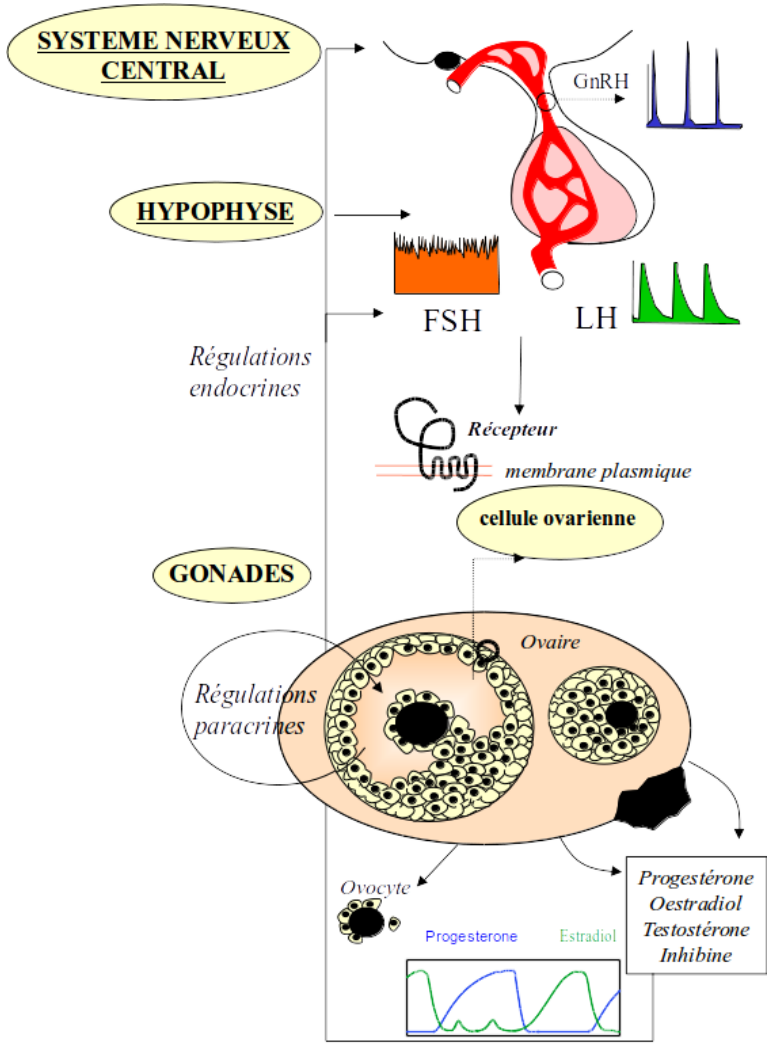

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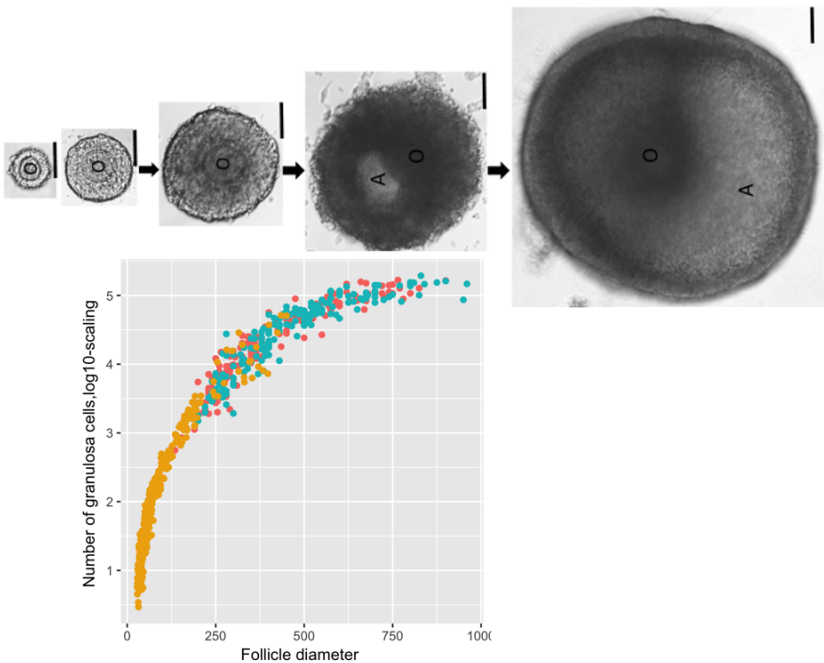
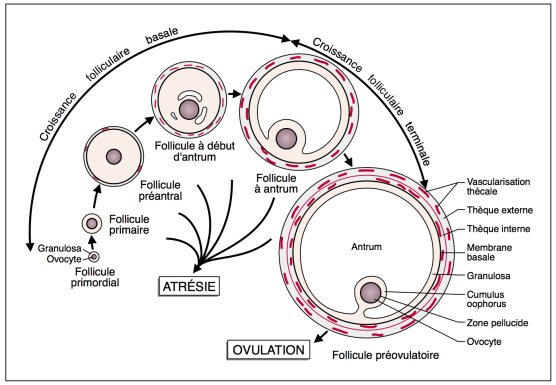
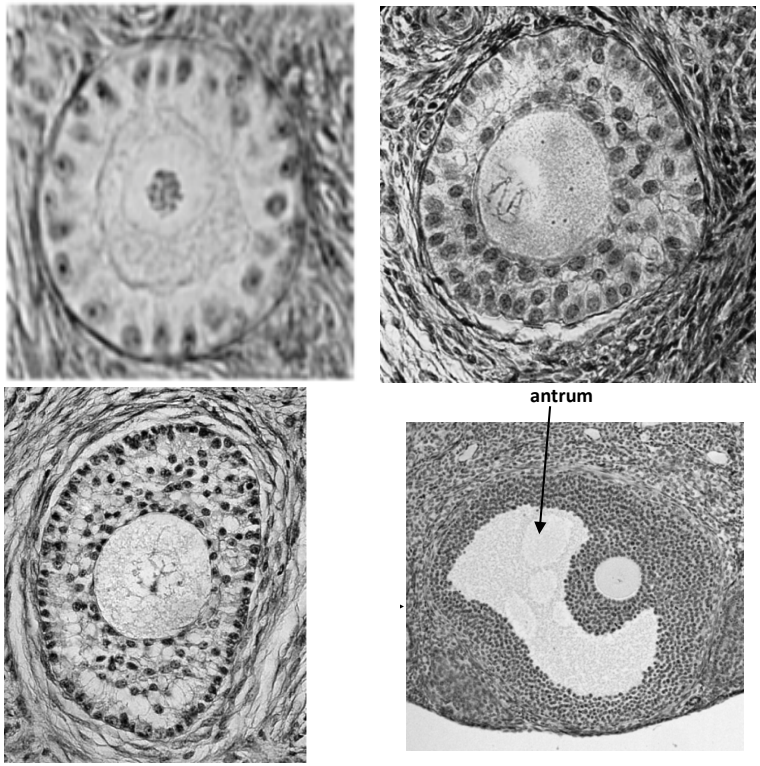
Le système reproducteur féminin des mammifères : un système multi-échelle complexe

- Croissance d'un follicule
  Morphodynamique de population
  - Espace : niveau cellulaire
  - Temps : Plusieurs cycles ovariens



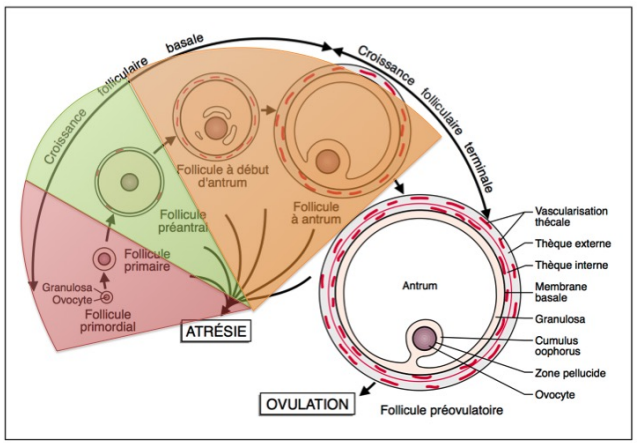




Courtesy of Danielle Monniaux.

Modélisation de la croissance d'un follicule

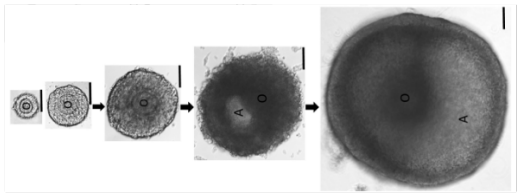
Croissance d'un follicule

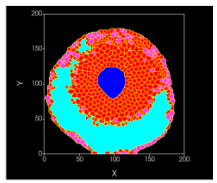


Monniaux et al., M/S. 1999

- Thèse de F. Robin, (co-supervisée. F. Clément)

Echelle cellulaire





Différentes phases de croissance

- Activation
  Transition / Prolifération cellulaire
- Croissance Basale
  Prolifération / superposition cellulaire
- Croissance Antrale
  Prolifération / Différentiation cellulaire et cavitation
- Phase Terminale
  Prolifération / Différentiation et dépendance aux gonadotropines

Gametogenesis : Ovarian folliculogenesis

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

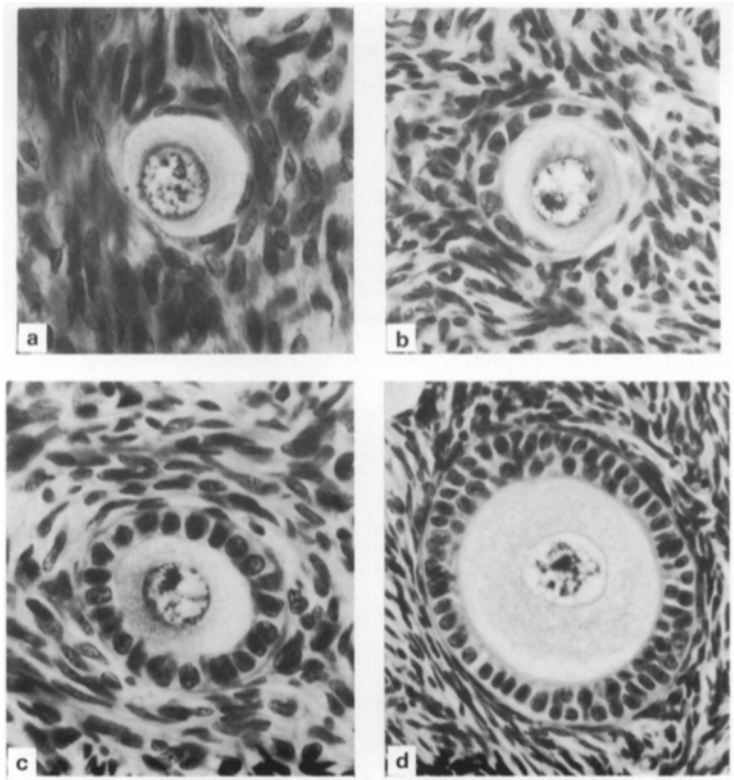
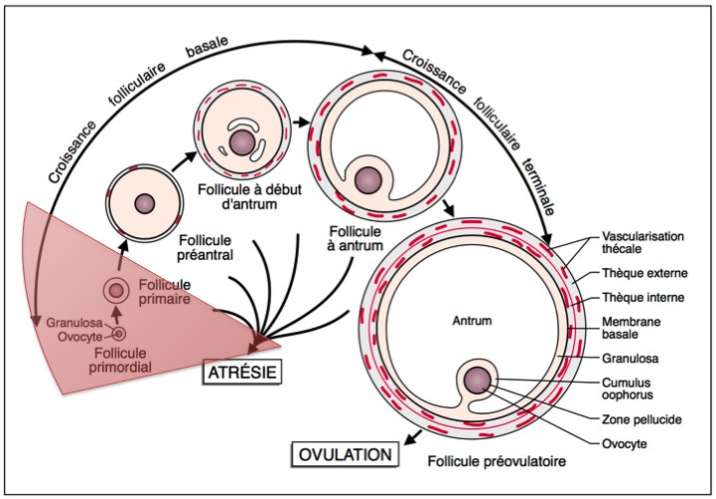


Fig. 1. Illustrations of follicle types: (a) Type B, × 570; (b) Type B/C, × 570; (c) Type C, × 570; (d) Type D, × 410.

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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- Morphogenesis and maturation of ovarian follicles
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- Basal growth
  Dynamic reserve (starting at birth)
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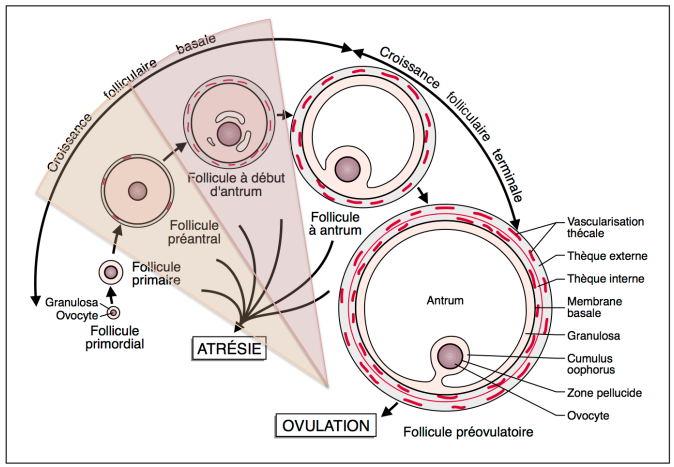

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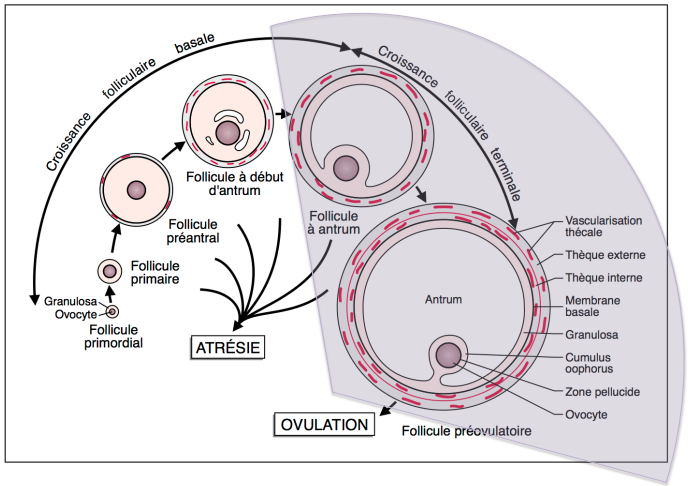

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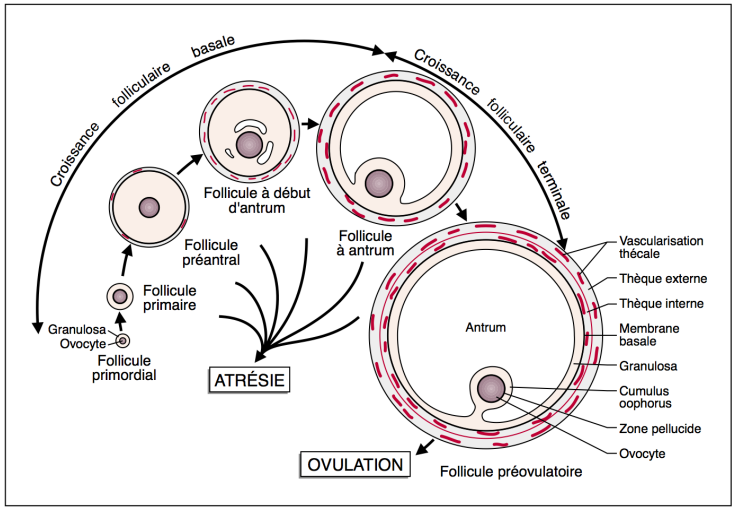
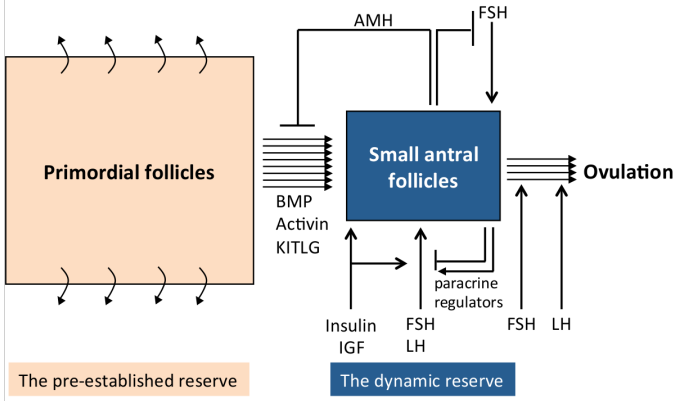
  After puberty : ovulation within an ovarian cycle
- Interactions between all follicles via complex (neuro-) hormonal signals



Ovarian reserves of follicles and their regulations



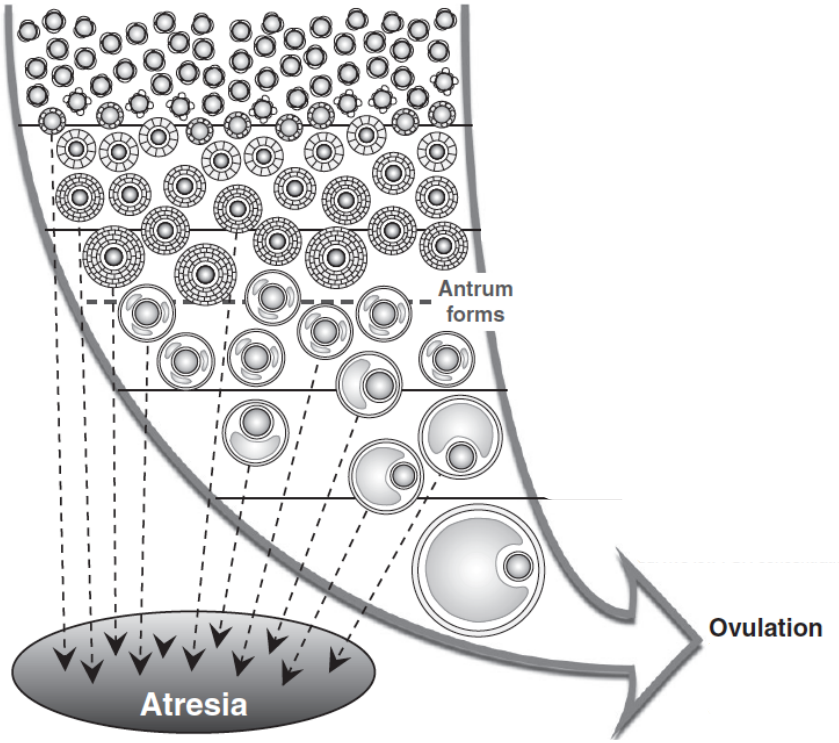
Monniaux, Theriogenology 2016

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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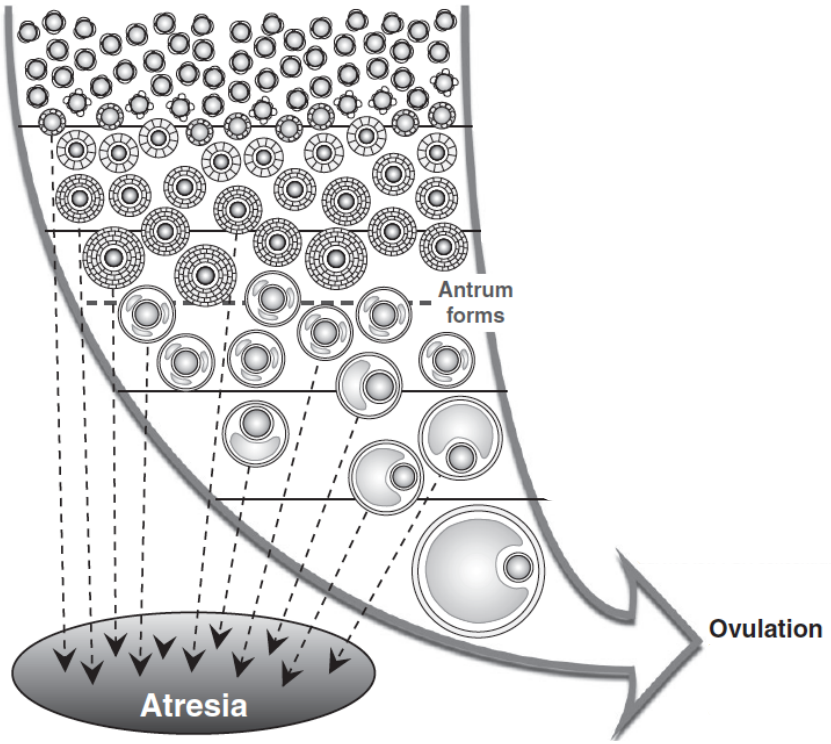
  - At birth $\approx 1 \cdot 10^6$
  - At puberty $10^4 - 10^6$
  - At menopause $< 10^3$
  - Activation rate "A few per days"
- Growing follicles
  - Maturation time $120 - 180j$
  - Basal follicles $10^3 - 10^4$
  - Terminal follicles 10^2
  - Pre-Ovulatory follicles a few
  - Atresia Most of them !



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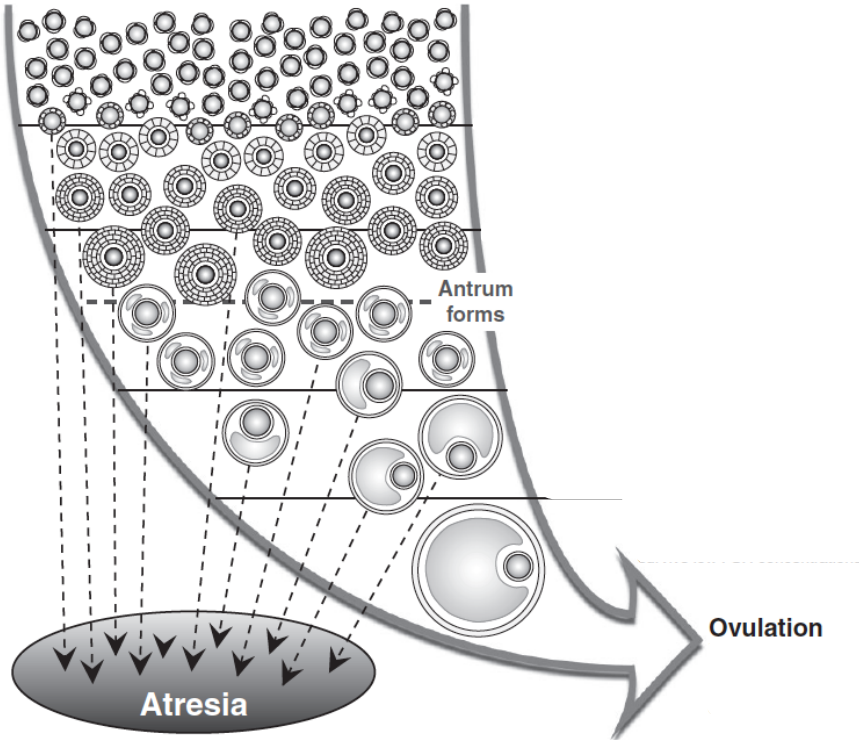
-> **Only** 400 **follicles will ever reach the pre-ovulatory stage**

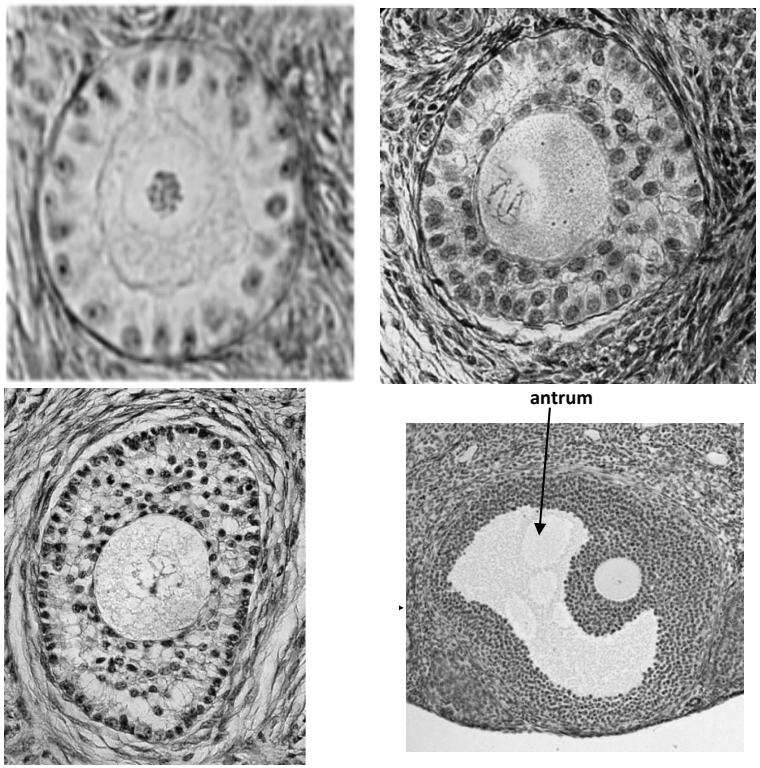


Scaramuzzi et al., Reprod.Fert. Dev. 2011

Order of magnitude

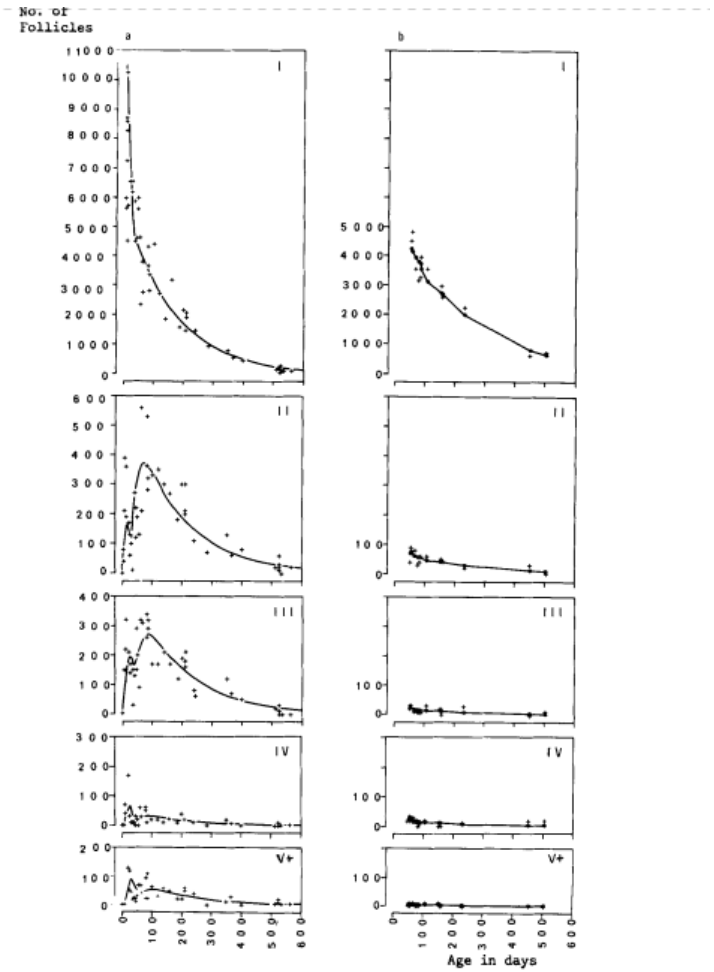
- **a single follicle (in women)**
  at different maturation stages

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



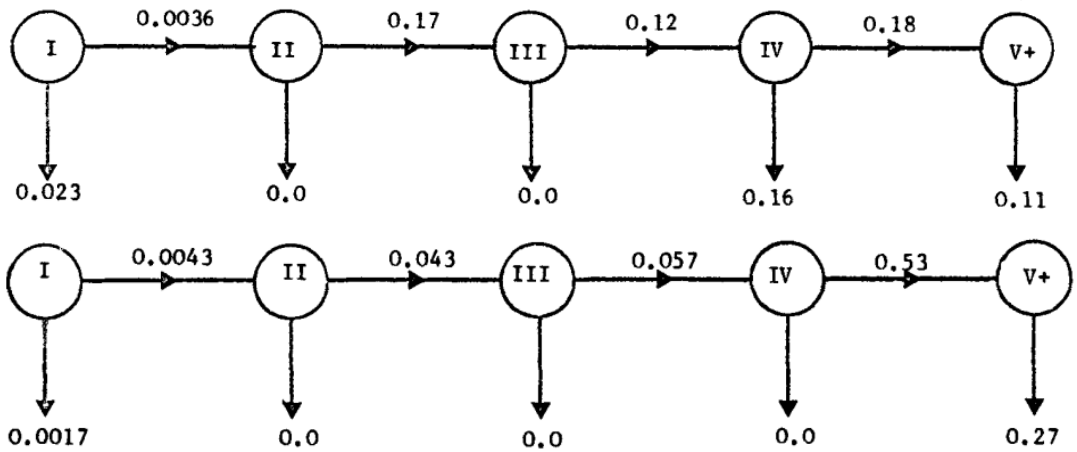
Courtesy of Danielle Monniaux.

Modèles de population de follicules (vie reproductive)



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

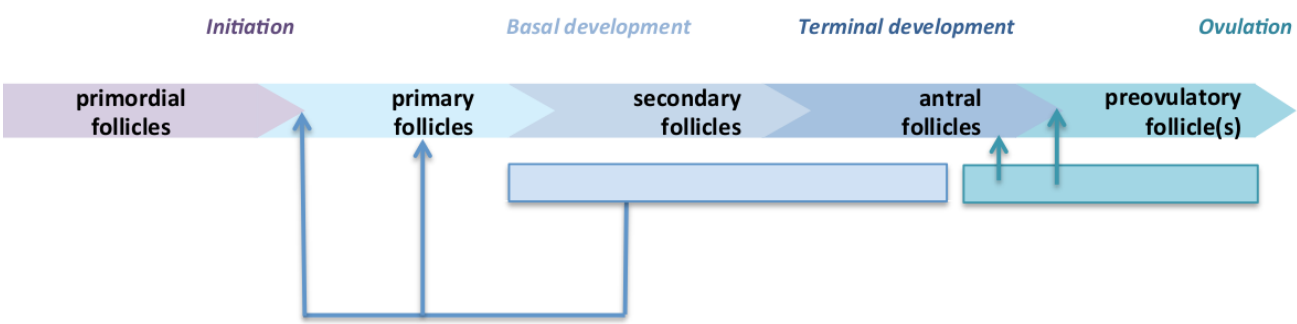
- **Peut-on expliquer ces dynamiques avec des interactions non linéaire ? Comment les analyser sur l'échelle de temps de vie d'une individu ?**
- Quels paramètres peut-on inférer à partir de ces observations ?



Modèles de population de follicules (vie reproductive)

- Population structurée en compartiments
- Interaction non linéaire entre les populations de follicules via $\lambda's$ et $\mu's$.

$$\begin{array}{ccccccccc} & & \lambda_0(\cdot) & & \lambda_1(\cdot) & & \lambda_2(\cdot) & & \\ X_0 & & \rightarrow & X_1 & \rightarrow & X_2 & \rightarrow & \cdots & X_d \\ \downarrow \mu_0(\cdot) & & & \downarrow \mu_1(\cdot) & & \downarrow \mu_2(\cdot) & & & \downarrow \mu_d(\cdot) \\ \emptyset & & & \emptyset & & \emptyset & & & \emptyset \end{array}$$



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

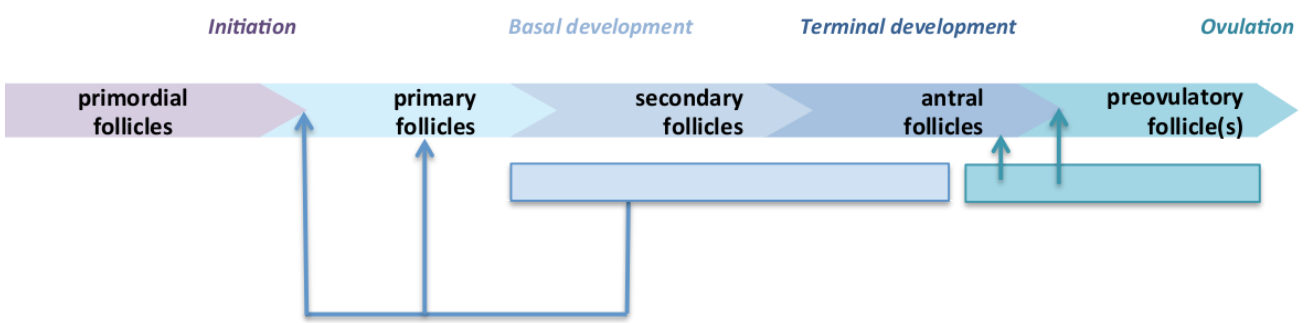
Modèles de population de follicules (vie reproductive)

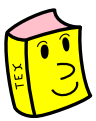
un choix possible

- Population structurée en compartiments
- Interaction non linéaire entre les populations de follicules via $\lambda's$ et $\mu's$.

$$\begin{array}{ccccccc} & & \lambda_0 & & \lambda_1 & & \lambda_2 \\ X_0 & & \rightarrow & X_1 & \rightarrow & X_2 & \rightarrow \quad \cdots \\ \downarrow \mu_0 & & & \downarrow \mu_1 & & \downarrow \mu_2 & \\ \emptyset & & & \emptyset & & \emptyset & \end{array} \qquad \begin{array}{ccc} X_d & & \\ \downarrow \mu_d & \mu_i(X) & = \quad g_i\left(1 + K_{2,i}\sum_{j=0}^{d}\omega_{2,j}X_j\right) \\ \emptyset & & \end{array}$$

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





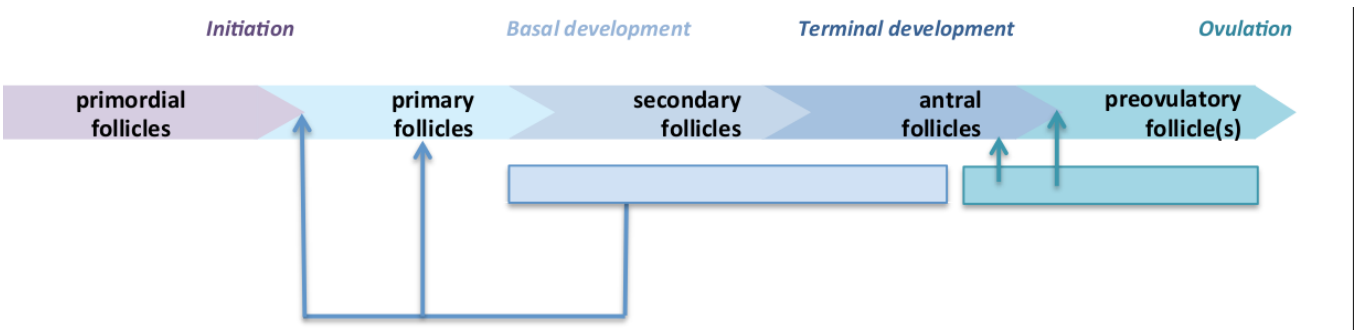
Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, ESAIM : PROCEEDINGS AND SURVEYS, 2020.

Modèles de population de follicules (vie reproductive)

- Population structurée en compartiments
- Interaction non linéaire entre les populations de follicules via $\lambda's$ et $\mu's$.
- Deux échelles de temps/nombres

- Pool quiescent $\gg$ Follicules en croissance
- Activation lente $\ll$ croissance rapide

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



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

Chaîne de Markov en temps continu, remise à l'échelle :
$(X^\varepsilon(t) = \varepsilon X_0(t/\varepsilon),\ Y^\varepsilon(t) = (X_1(t/\varepsilon), \cdots, X_d(t/\varepsilon)))$:

	événements	Intensité
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 :	$(X, Y) \to (X, Y - e_i)$,	$\frac{1}{\varepsilon} \mu_i(Y) Y_i$, $i = 1..d$,

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

Theorem (G. Ballif, F. Clément, R.Y. *en révision*)

(...) $(X^\varepsilon, Y^\varepsilon)$ *converge dans* $\mathcal{D}_{\mathbb{R}}[0,\infty[\times \mathcal{L}_m(\mathbb{N}^d)$ *vers l'unique solution de*

$$\begin{cases} \frac{dx}{dt}(t) &= \Lambda_0\big(x(t)\big)x(t)\,, & x(0) = x^{\text{in}}\,, \\ \Lambda_0\big(x(t)\big) &= \sum_{y\in\mathbb{N}^d} \Big(r_0(y) - \lambda_0(y) - \mu_0(y)\Big)\pi_{x(t)}(y)\,, & \text{où} \end{cases}$$

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

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

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

Éléments de preuves

- 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" :
  $M_f^{\varepsilon}(t) = f\Big(X^{\varepsilon}(t)\Big) - \int_0^t Af\Big(X^{\varepsilon}(s), Y^{\varepsilon}(s)\Big) \mathrm{s} + R_f^{\varepsilon}(t)$ où
  $Af(x,y) = \Big(r_0(y) - \lambda_0(y) - \mu_0(y)\Big) x f'(x)$
- Identification de la martingale "rapide" :
  $M_g^{\varepsilon}(t) := \varepsilon\Big[g\big(Y^{\varepsilon}(t)\big) - g\big(Y^{\varepsilon}(0)\big)\Big] - \int_0^t \int_{\mathbb{N}^d} L_{X^{\varepsilon}(s)} g\big(Y^{\varepsilon}(s)\big) ds$

	événements	Intensité
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 :	$(X,Y) \to (X, Y-e_i)$,	$\frac{1}{\varepsilon} \mu_i(Y)Y_i$, $i = 1..d$,

Hypothèses

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

Éléments de preuves

- Processus majorant linéaire :

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

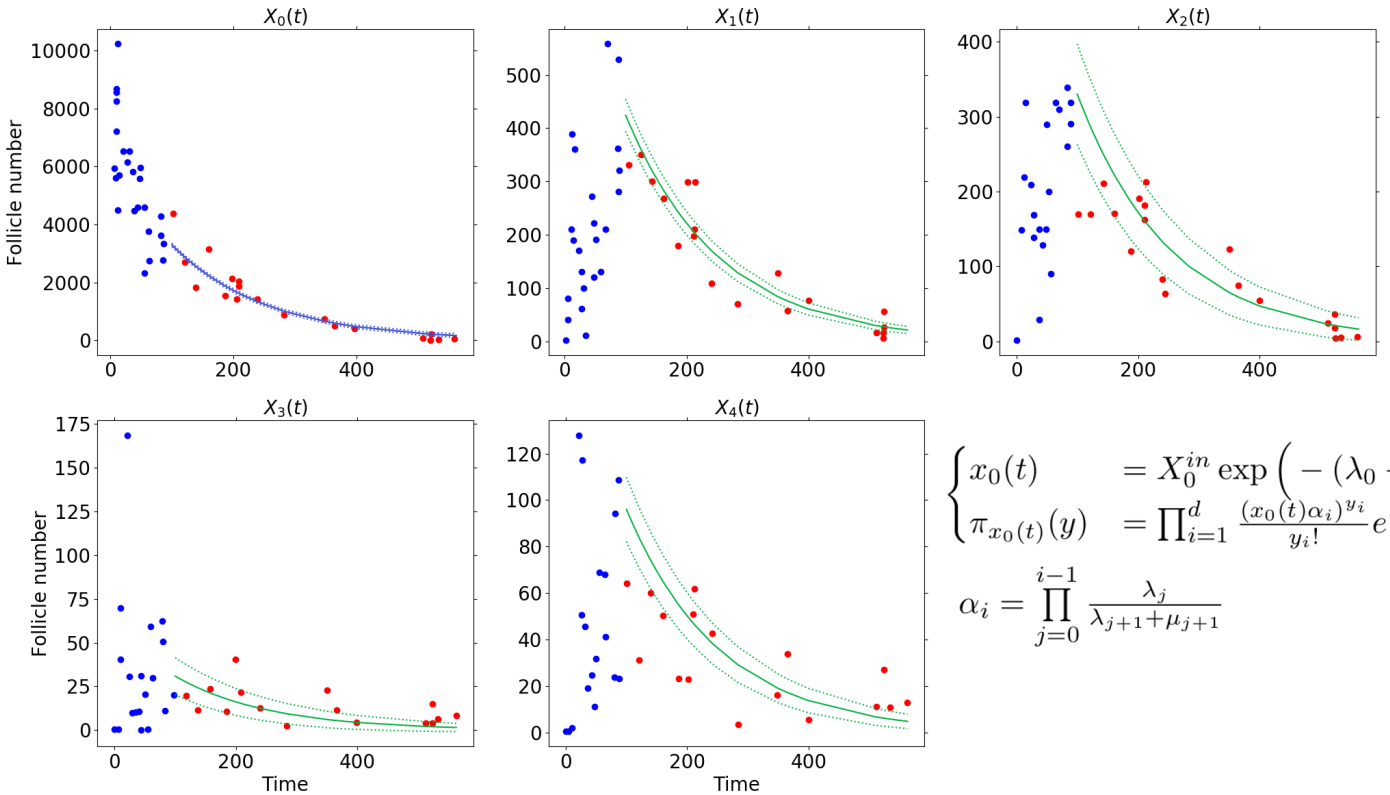
- Par couplage : $X \leq U$ et $\sum_{j=1}^{i} Y_j \leq \sum_{j=1}^{i} V_j$.
- Lyapounov $F(y) = \sum_{i=1}^{d} \left(\sum_{j=1}^{i} y_j \right)^{p_i}$ pour $p_i \searrow$.

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 $\mid g_x \mid \leq F$

Modèle limite

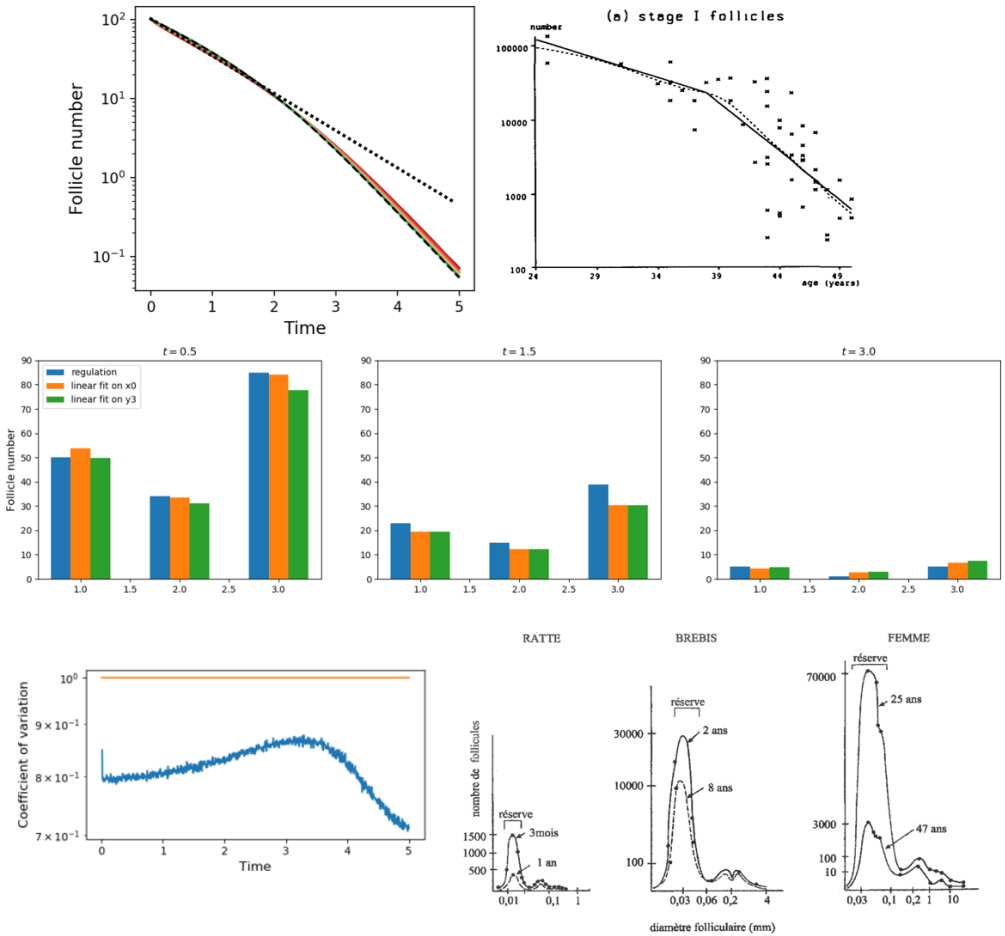


$$\begin{cases} x_0(t) & = X_0^{in} \exp\Big(-(\lambda_0 + \mu_0)t \Big) \\ \pi_{x_0(t)}(y) & = \prod_{i=1}^{d} \frac{(x_0(t)\alpha_i)^{y_i}}{y_i!} e^{-x_0(t)\alpha_i} \end{cases}$$

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

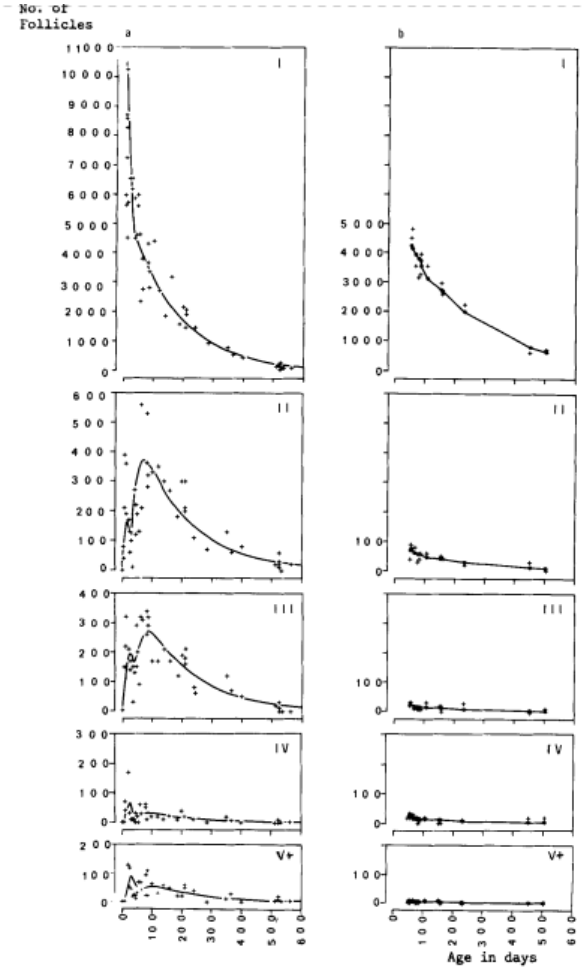
- La séparation de l'échelle de temps est cohérente avec les connaissances biologiques et les données de comptage des follicules.

Modèle limite



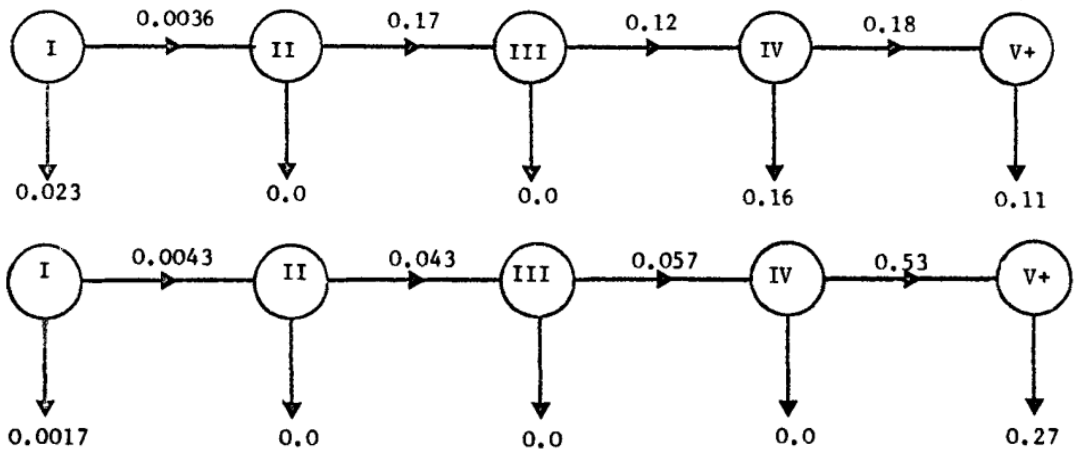
- ✓ accélération de la décroissance de la réserve : $\frac{dx}{dt} = -(a + \frac{b}{1+cx})x$
- ✓ forme "stable" de π_x pour l'évolution de la répartition des follicules en croissance

Modèles de population de follicules (vie reproductive)



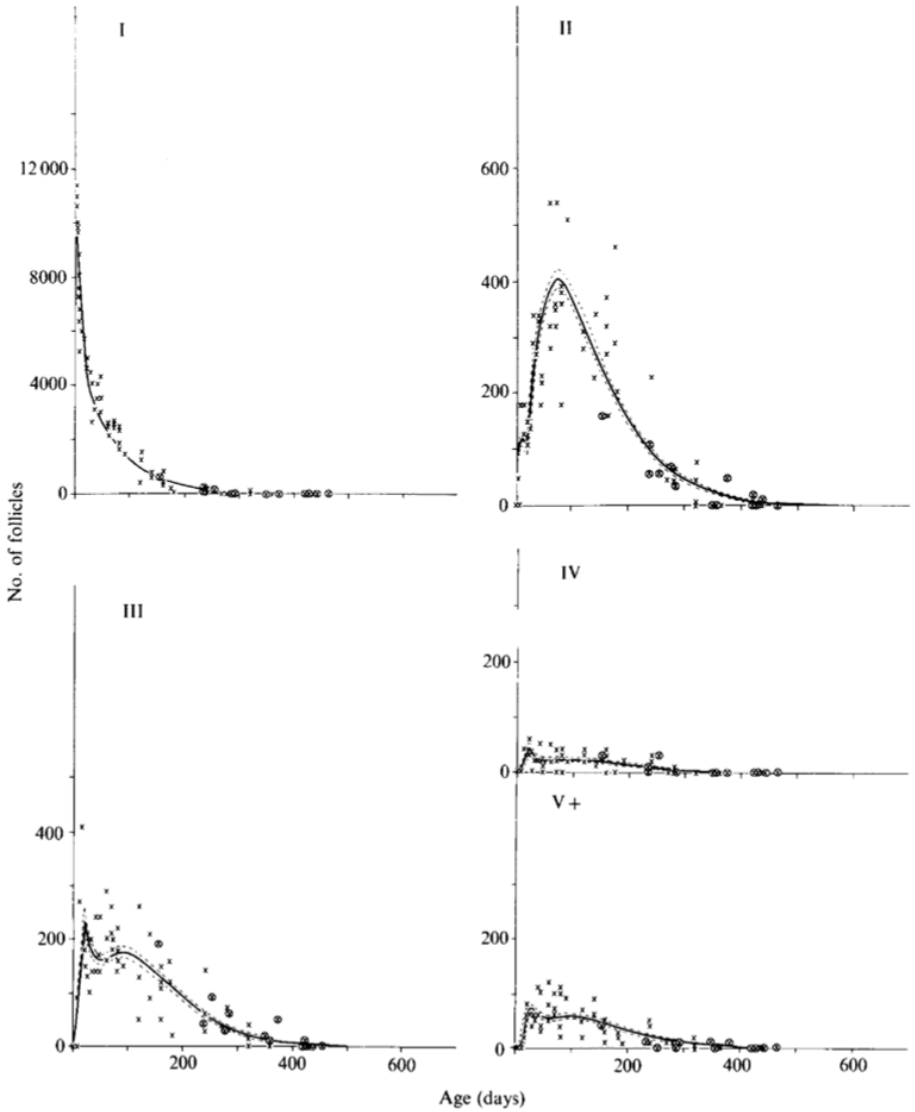
Faddy et al., J. Exp. Zool. 1976

- Peut-on expliquer ces dynamiques avec des interactions non linéaire ?
  Comment les analyser sur l'échelle de temps de vie d'une individu ?
- **Quels paramètres peut-on inférer à partir de ces observations ?**
  (Preliminary results)



"Time" course

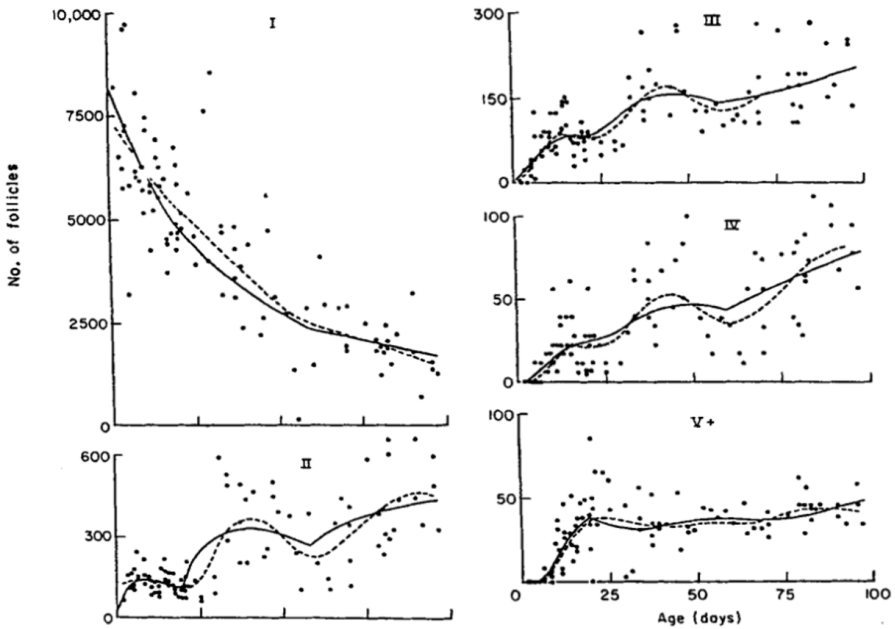
- Follicle count in mice of strain CBA from birth until 500 days.
- Reserve + 4 compartments (classification of Faddy)
- (Recovery of points by hand)



Faddy, Gosden and Edwards, J. Endo., 1983

"Time" course

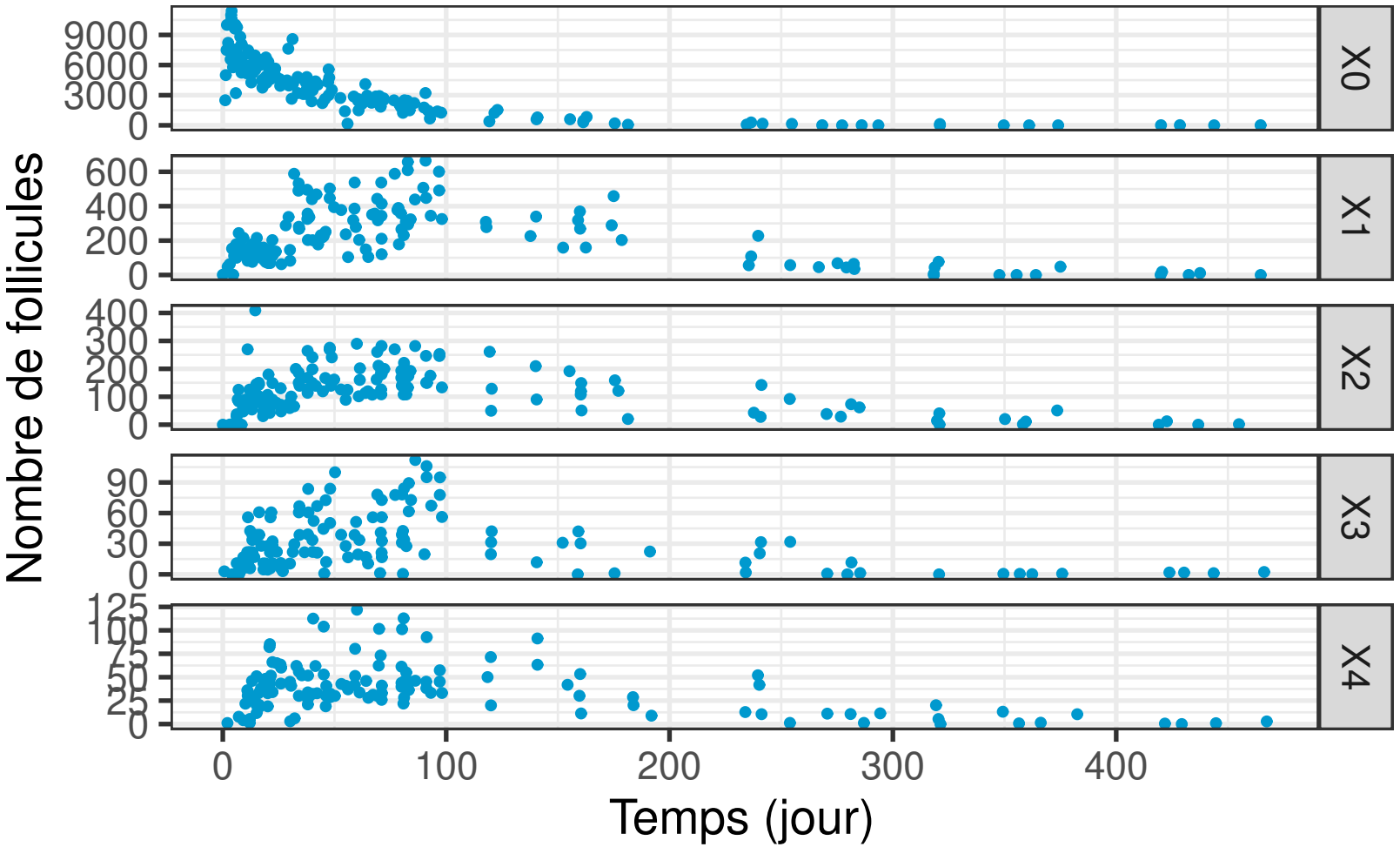
- Follicle count in mice of strain CBA/CA from birth until 100 days.
- Reserve + 4 compartments (classification of Faddy)
- (Recovery of points by hand)



Faddy, Telfer and Gosden, Cell Proliferation, 1987

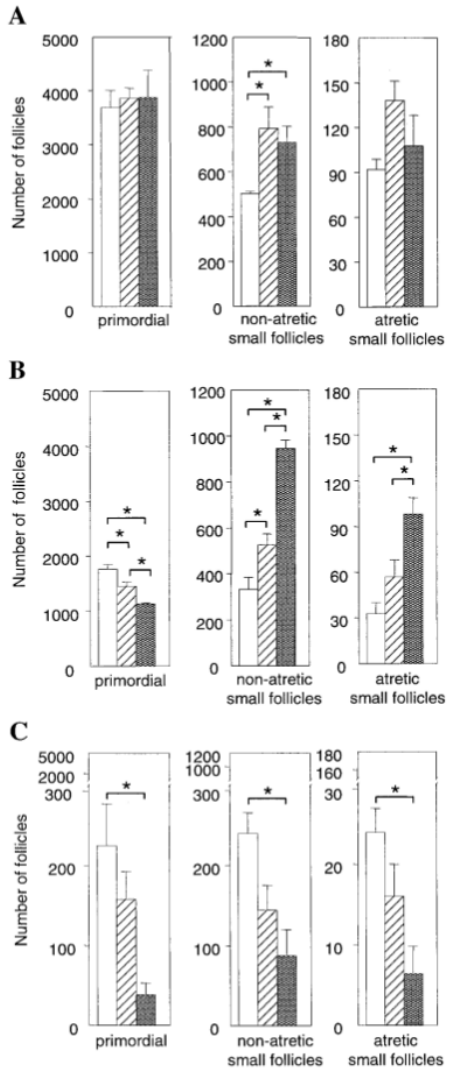
Faddy, Telfer and Gosden, Cell Proliferation, 1987

"Time" course


Nombre de follicules
Temps (jour)
X0
X1
X2
X3
X4
9000
6000
3000
0
600
400
200
0
400
300
200
100
0
90
60
30
0
125
100
75
50
25
0
0
100
200
300
400

Perturbation data : KO AMH

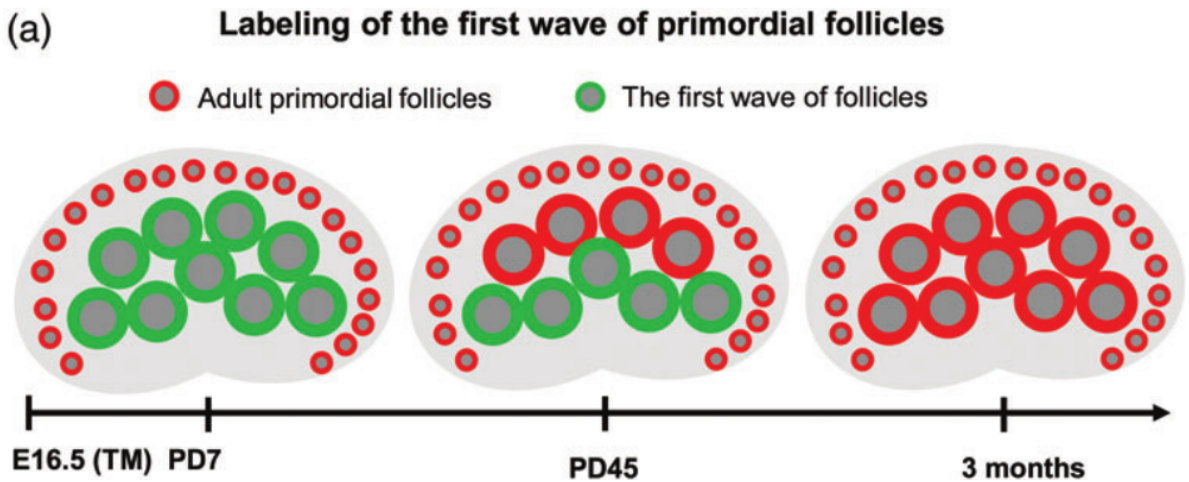
- AMH Inhibition in vivo on mice of strain C57B6.
- 3 genotypes : control group (+/+), heterozygous mice KO AMH (+/-) homozygous mice KO AMH (-/-).
- Follicle counts at 3 ages :
  - 25 days (A)
  - 120 days (B)
  - 390 days (C)



Durlinger and al, Endocrinology, 1999

Refinement on "initial" condition

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

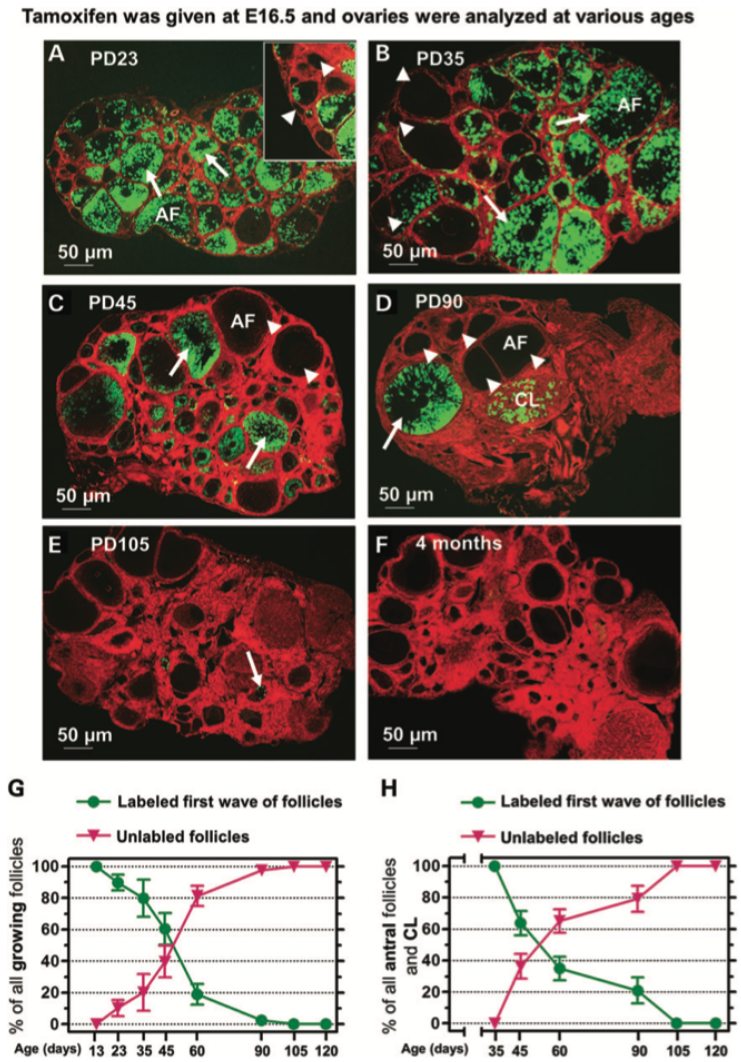


Zheng, Zhang and Liu, Hum. Mol. Reprod, 2014

Refinement on "initial" condition

- Tracing follicles of the first wave of activated follicles (in green).
- Proportion $p(t)$ of first wave activated follicles among growing follicles.

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



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

EDO model

O = germ cell before entering in follicle (pre/peri-natal)
X_i = Follicle in maturity stage i

$$
\begin{array}{ccccccccccc}
O+O & & & & & & & & & & \\
\uparrow r_O & & & & & & & & & & \\
O & \xrightarrow{m_O} & X_0 & \xrightarrow{m_0+\frac{f_0}{1+K_0(x_2+x_3)}} & X_1 & \xrightarrow{m_1} & X_2 & \xrightarrow{m_2} & X_3 & \xrightarrow{m_3} & X_4 \\
g_O \downarrow & & g_0 \downarrow & & g_1 \downarrow & & g_2 \downarrow & & g_3 \downarrow & & \downarrow g_4 \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

EDO model

2 populations $(0, X_i)$ and $(0', X_i')$:

$$
\begin{array}{ccccccccccc}
O + O & & & & & & & & & & \\
\uparrow r_O & & & & & & & & & & \\
O & \xrightarrow{m_O} & X_0 & \xrightarrow{m_0 + \frac{f_0}{1+K_0(x_2+x_3+x_2'+x_3')}} & X_1 & \xrightarrow{m_1} & X_2 & \xrightarrow{m_2} & X_3 & \xrightarrow{m_3} & X \\
g_O \downarrow & & g_0 \downarrow & & g_1 \downarrow & & g_2 \downarrow & & g_3 \downarrow & & \downarrow \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

$$
\begin{array}{ccccccccccc}
O' + O' & & & & & & & & & & \\
\uparrow r_{O'} & & & & & & & & & & \\
O' & \xrightarrow{m_O'} & X_0' & \xrightarrow{m_0'} & X_1' & \xrightarrow{m_1'} & X_2' & \xrightarrow{m_2'} & X_3' & \xrightarrow{m_3'} & X_4' \\
g_O' \downarrow & & g_0' \downarrow & & g_1' \downarrow & & g_2' \downarrow & & g_3' \downarrow & & \downarrow g_4' \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

EDO model

2 populations $(0, X_i)$ and $(0', X_i')$:

$$
\begin{array}{ccccccccccc}
O + O & & & & & & & & & & \\
\uparrow r_O & & & & & & & & & & \\
O & \xrightarrow{m_O} & X_0 & \xrightarrow{m_0 + \frac{f_0}{1+K_0(x_2+x_3+x_2'+x_3')}} & X_1 & \xrightarrow{m_1} & X_2 & \xrightarrow{m_2} & X_3 & \xrightarrow{m_3} & X \\
g_O \downarrow & & g_0 \downarrow & & g_1 \downarrow & & g_2 \downarrow & & g_3 \downarrow & & \downarrow \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

$$
\begin{array}{ccccccccccc}
O' + O' & & & & & & & & & & \\
\uparrow r_{O'} & & & & & & & & & & \\
O' & \xrightarrow{m_O'} & X_0' & \xrightarrow{m_0'} & X_1' & \xrightarrow{m_1'} & X_2' & \xrightarrow{m_2'} & X_3' & \xrightarrow{m_3'} & X_4' \\
g_O' \downarrow & & g_0' \downarrow & & g_1' \downarrow & & g_2' \downarrow & & g_3' \downarrow & & \downarrow g_4' \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

K0 AMH : $K_0 = 0$

EDO model

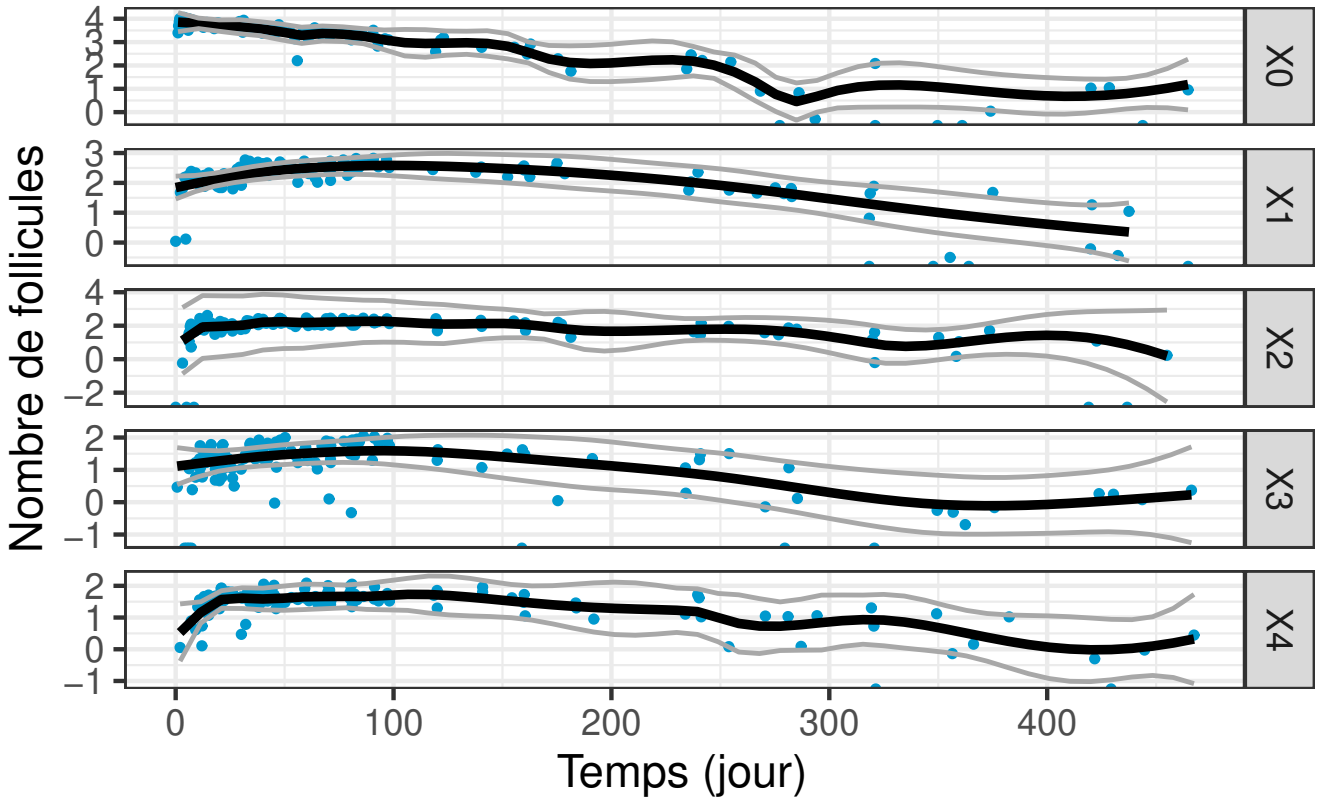
2 populations $(0, X_i)$ and $(0', X_i')$:

$$
\begin{array}{ccccccccccc}
O + O & & & & & & & & & & \\
\uparrow r_O & & & & & & & & & & \\
O & \xrightarrow{m_O} & X_0 & \xrightarrow{m_0 + \frac{f_0}{1+K_0(x_2+x_3+x_2'+x_3')}} & X_1 & \xrightarrow{m_1} & X_2 & \xrightarrow{m_2} & X_3 & \xrightarrow{m_3} & X \\
g_O \downarrow & & g_0 \downarrow & & g_1 \downarrow & & g_2 \downarrow & & g_3 \downarrow & & \downarrow \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

$$
\begin{array}{ccccccccccc}
O' + O' & & & & & & & & & & \\
\uparrow r_{O'} & & & & & & & & & & \\
O' & \xrightarrow{m_O'} & X_0' & \xrightarrow{m_0'} & X_1' & \xrightarrow{m_1'} & X_2' & \xrightarrow{m_2'} & X_3' & \xrightarrow{m_3'} & X_4' \\
g_O' \downarrow & & g_0' \downarrow & & g_1' \downarrow & & g_2' \downarrow & & g_3' \downarrow & & \downarrow g_4' \\
\emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset & & \emptyset
\end{array}
$$

27 paramètres...

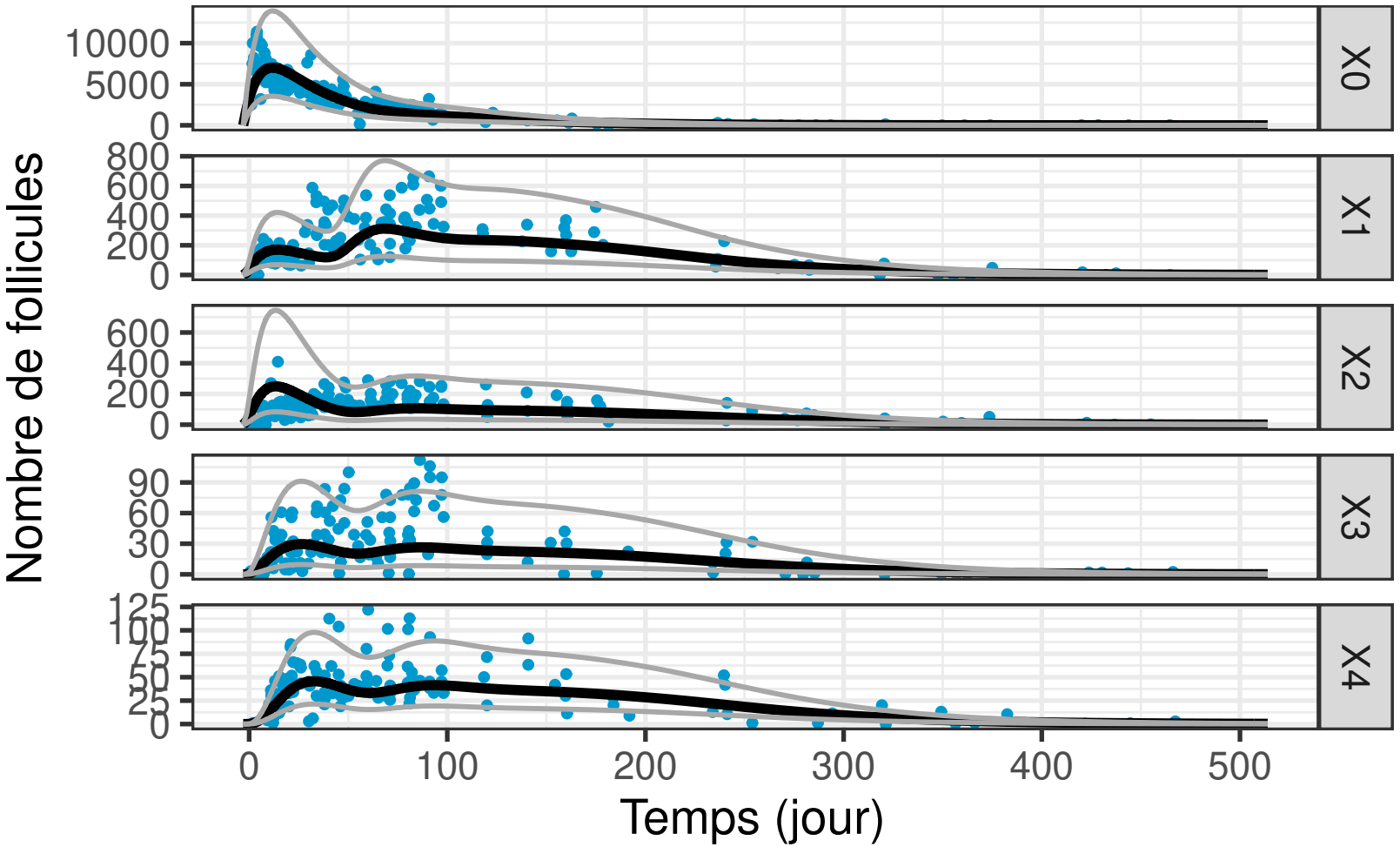
Cost function



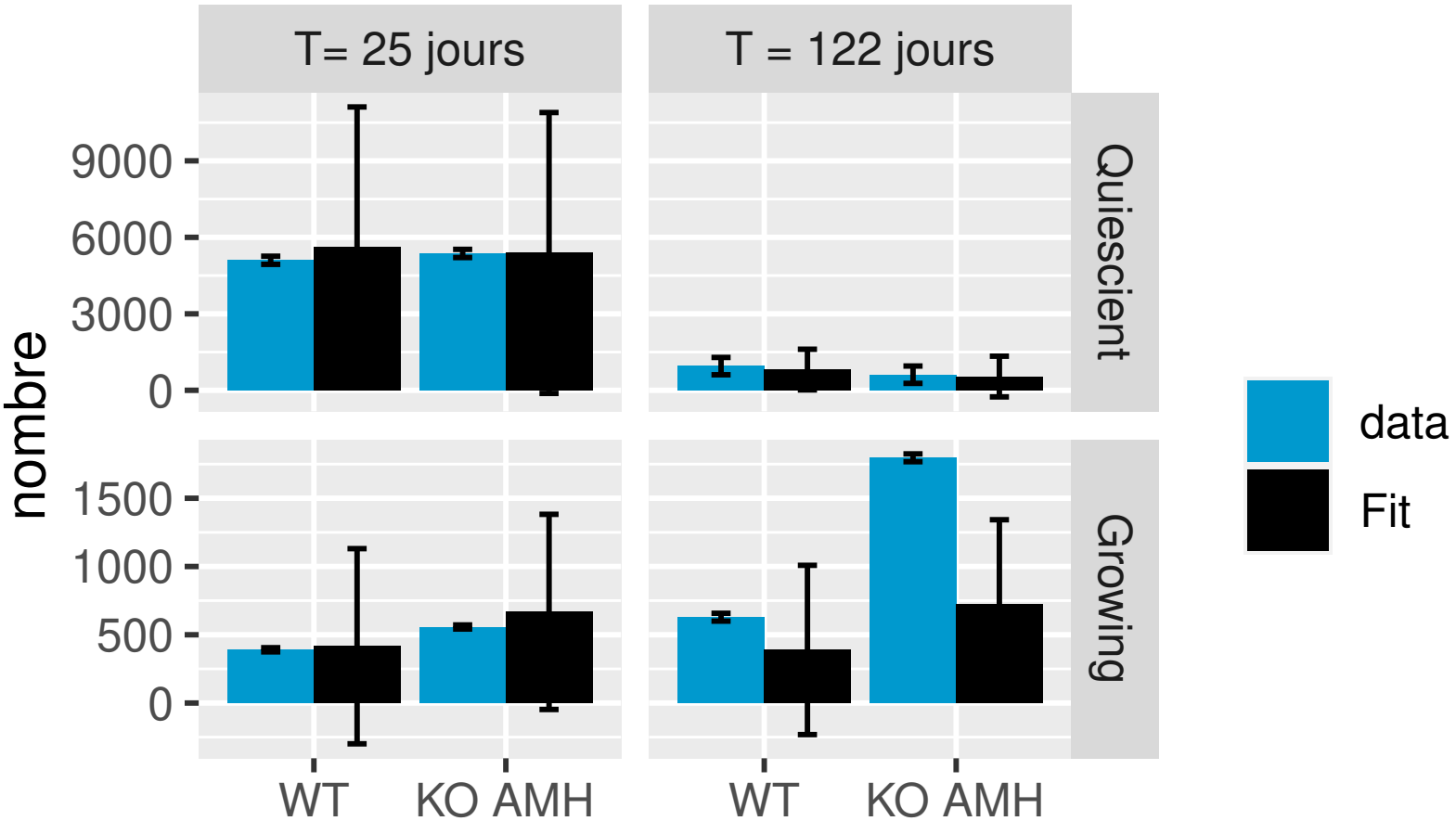
Multiplicative lognormal statistical model :

$$J_{faddy}(\theta) = \sum_{j=0}^{4} \left[\frac{1}{M_j} \sum_{i=1}^{M_j} \left(\frac{\log(x_0^\theta(t_i^0)) - \log(x_i^0)}{\sigma_j} \right)^2 + \log(\sigma_j) \right]$$

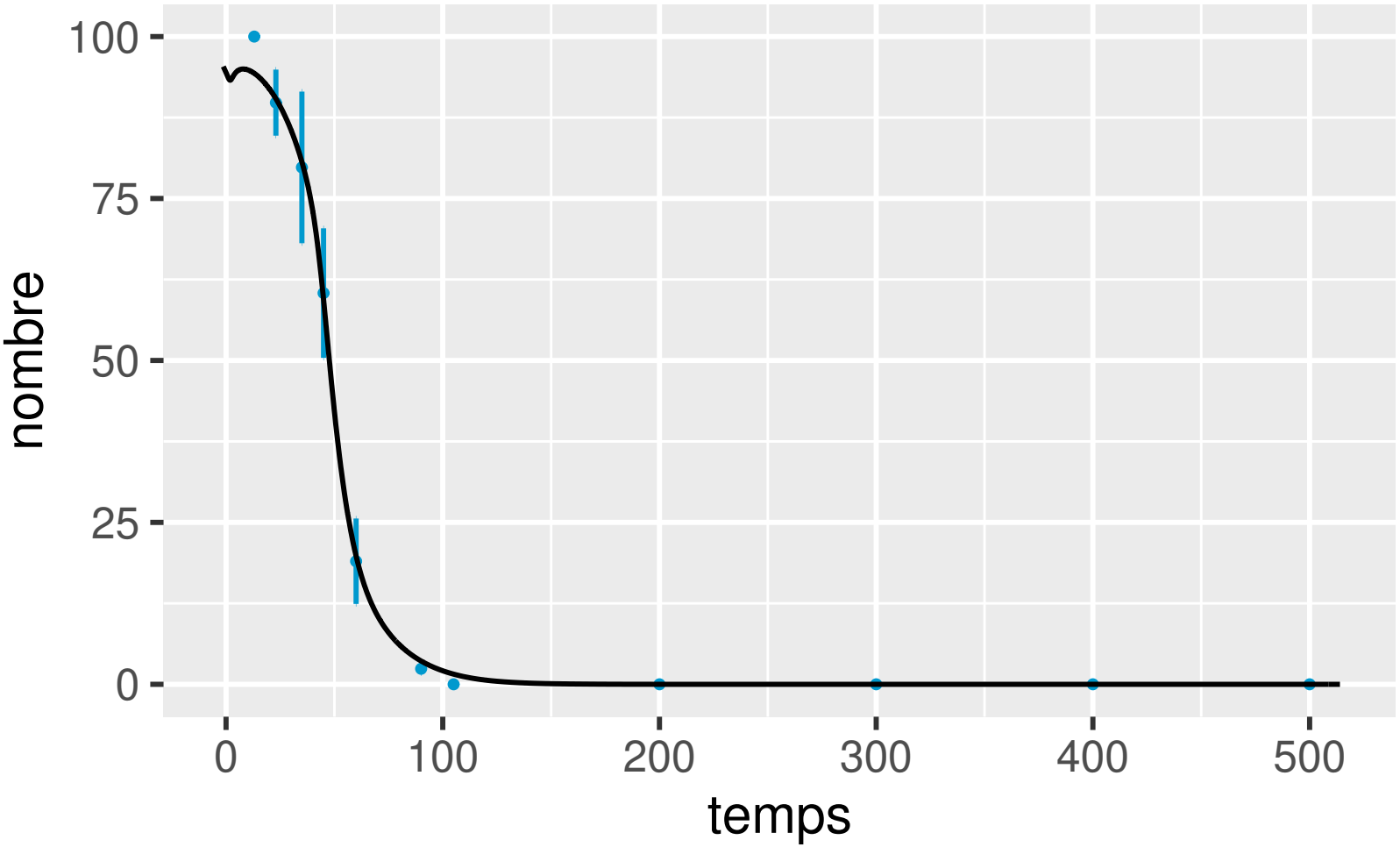
Data fitting



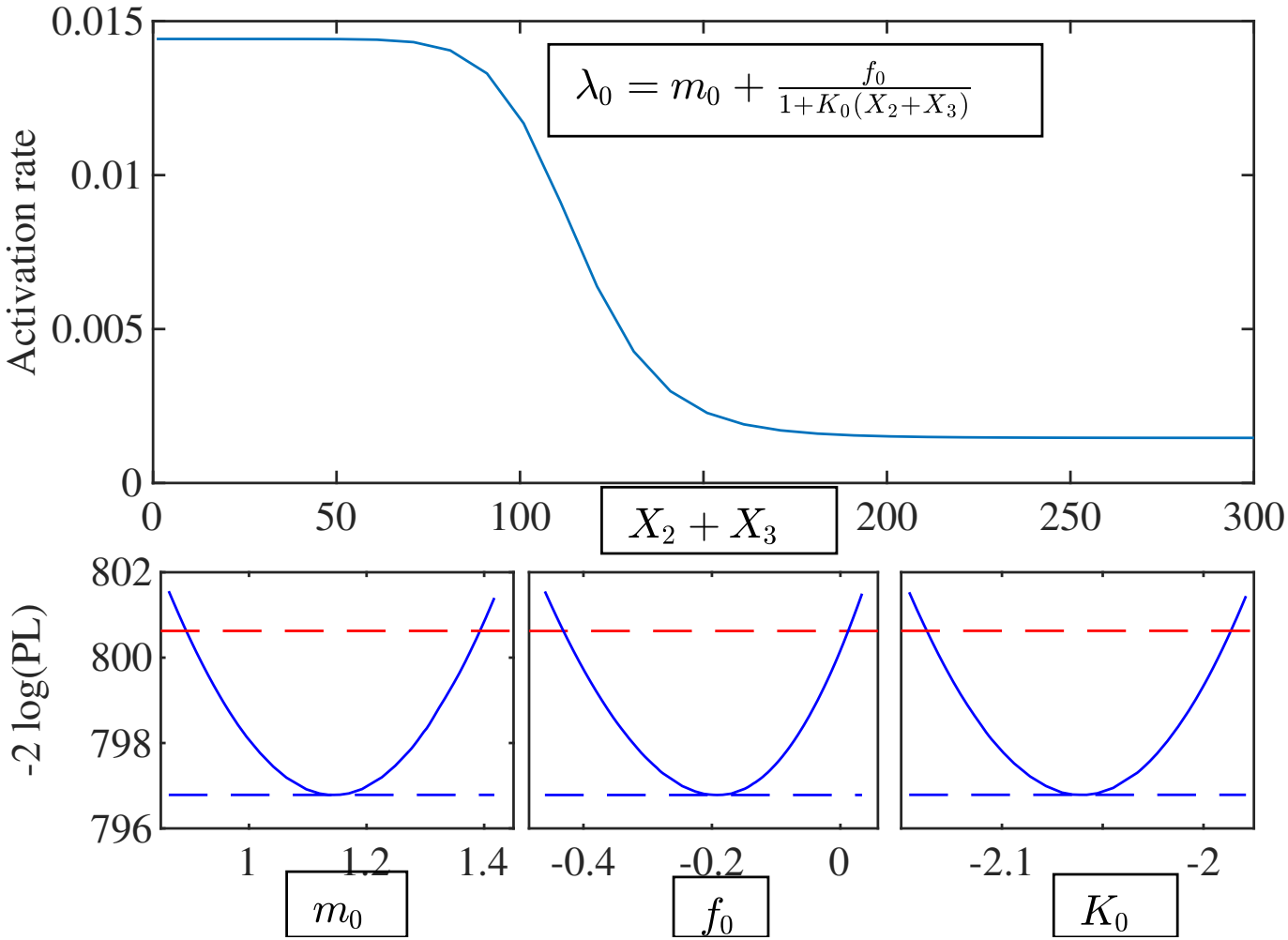
Data fitting



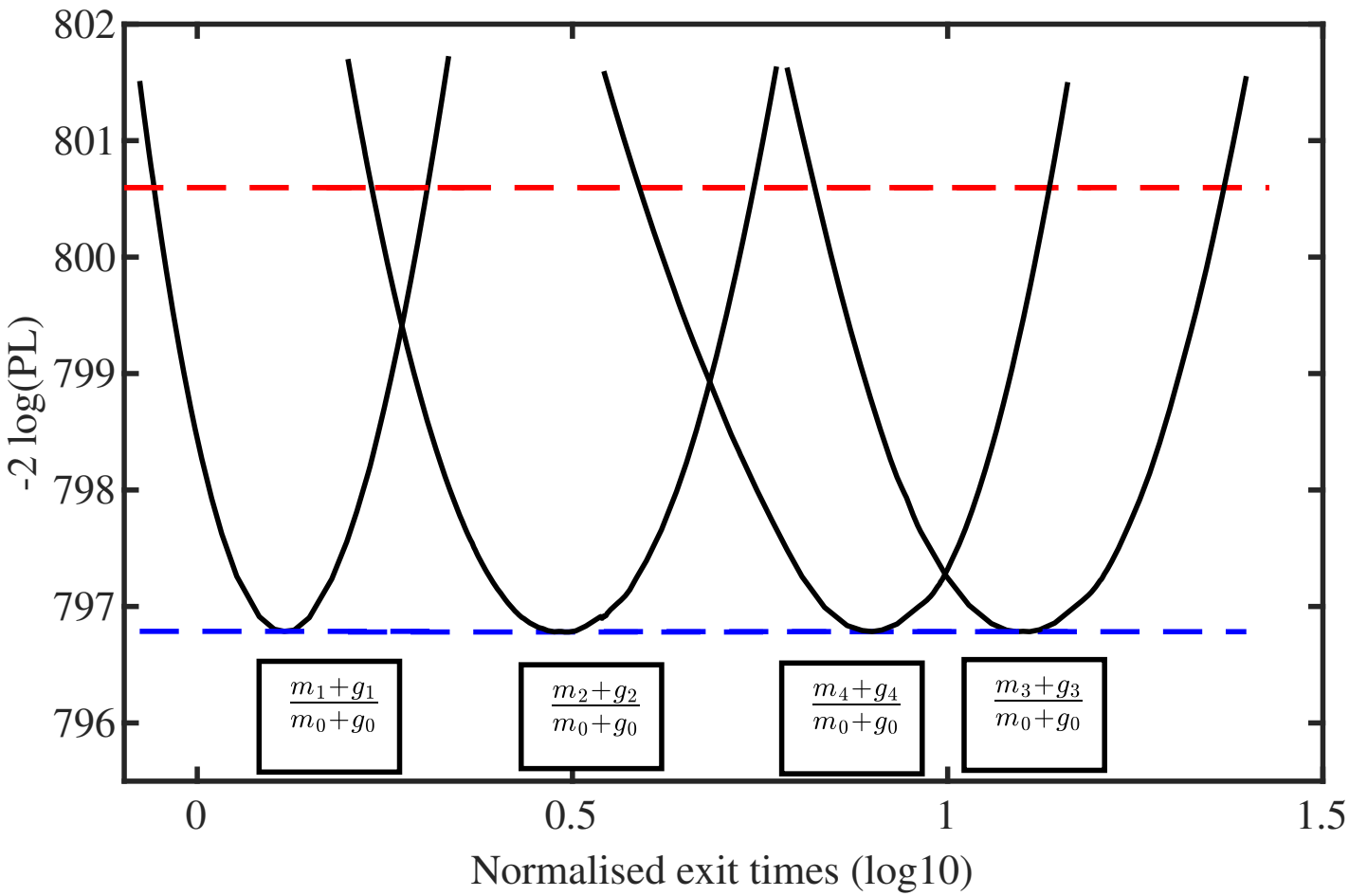
Data fitting



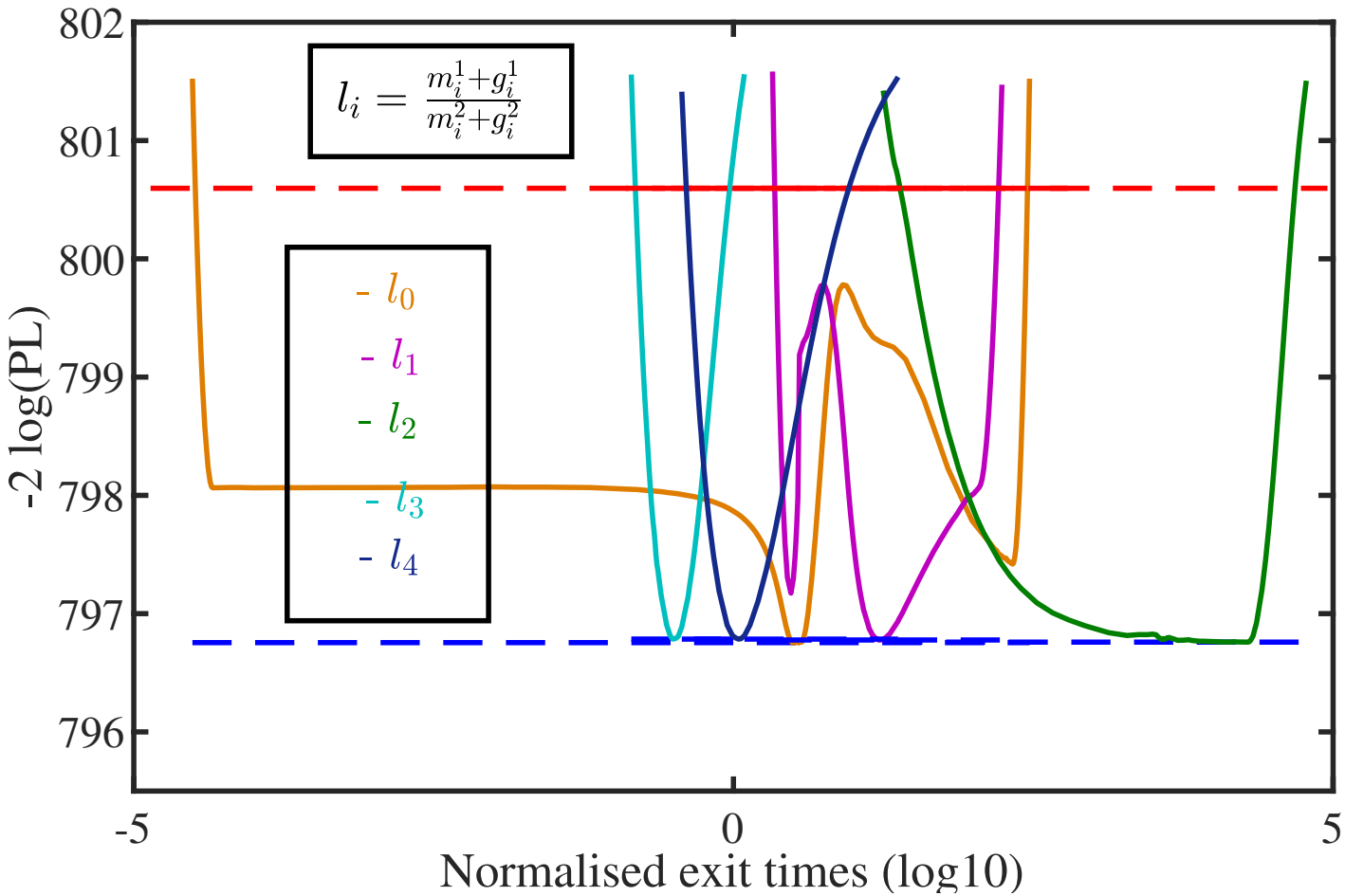
Taux d'activation



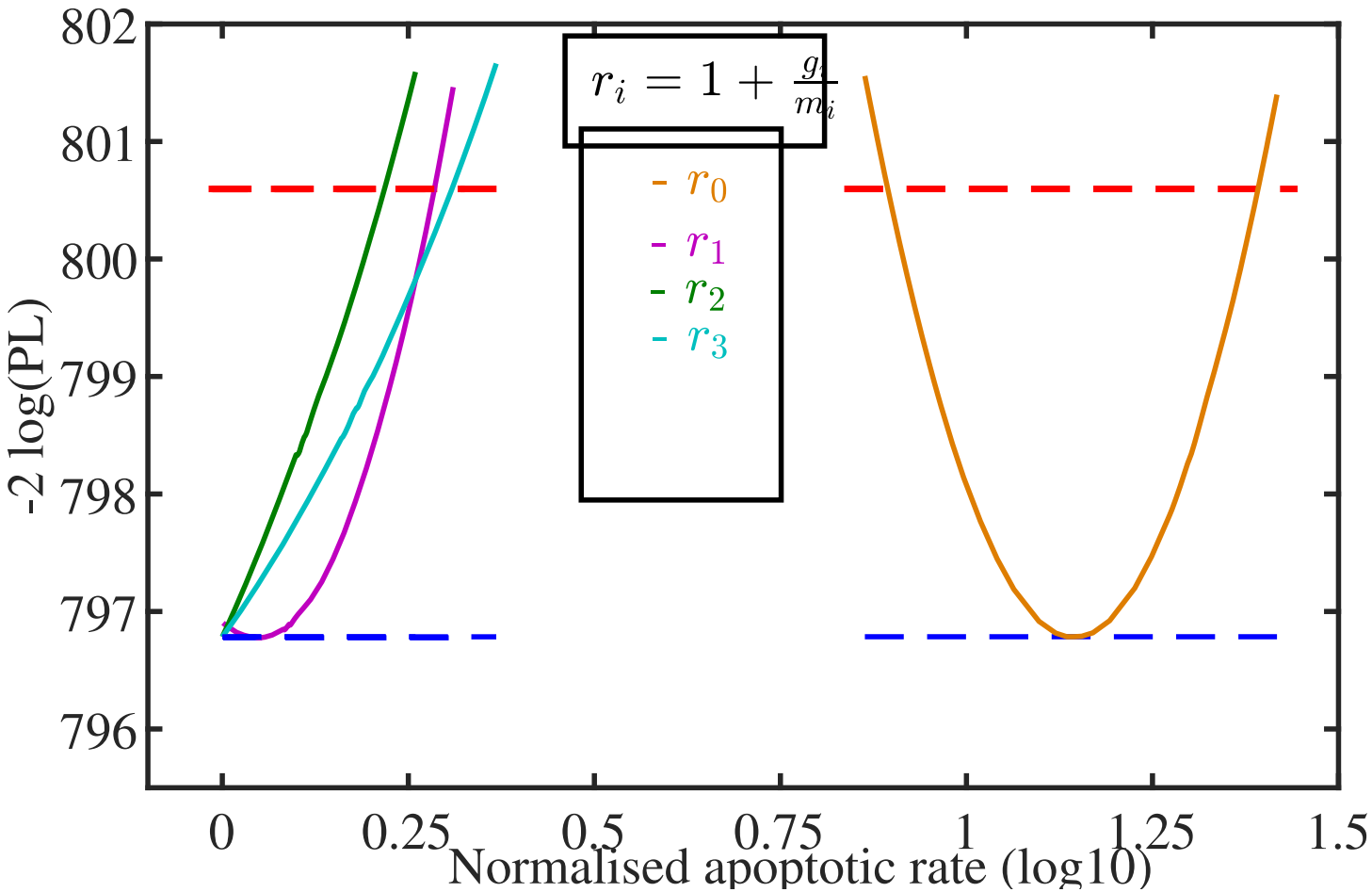
Vitesse d'évolution follicules en croissance / quiescent



Comparaison 1er/2e vague

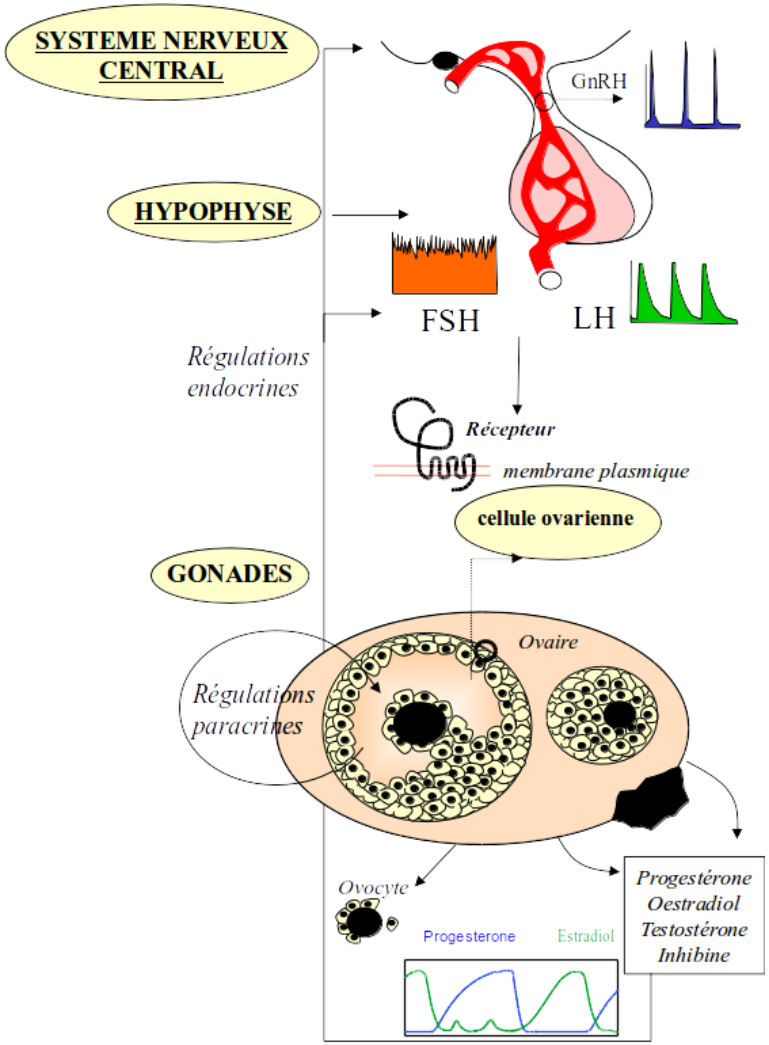


Taux d'atrésie



Le système reproducteur féminin des mammifères : un système multi-échelle complexe

- Signaux neuro-hormonaux
  Encodage et décodage
- Gamétogenèse
  Dynamique de population
- **Croissance d'un follicule**
  Morphodynamique de cellules
- Niveau intra-cellulaire
  réseaux de signalisation

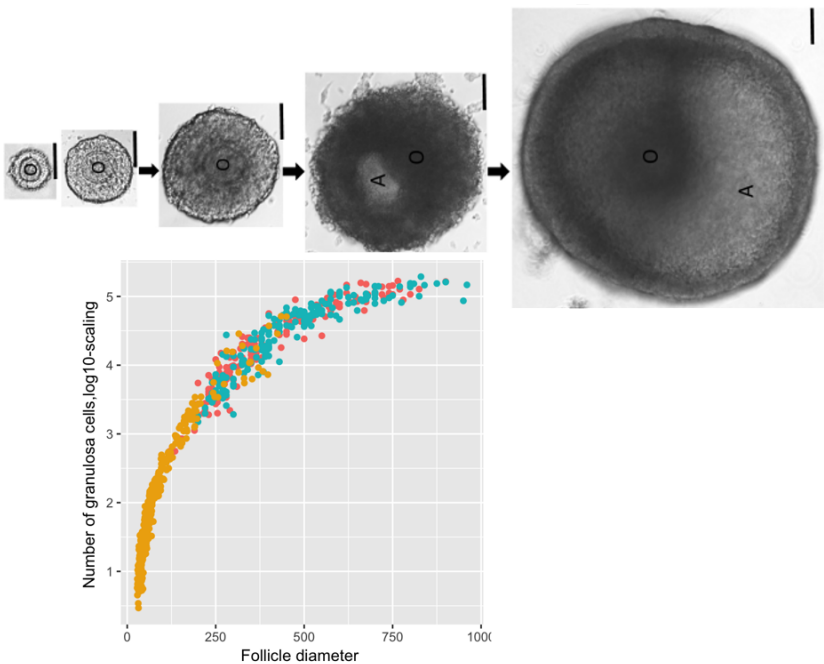


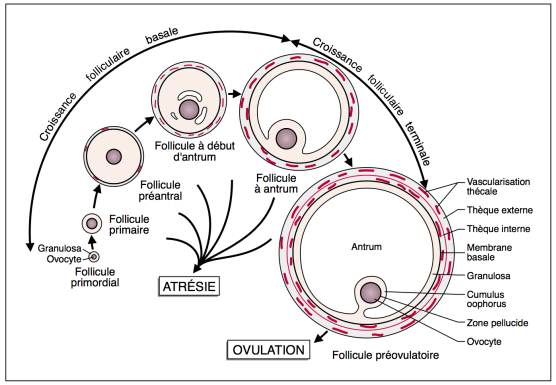
R.Y., P. Crépieux, E. Reiter, A. Poupon, F. Clément, *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.

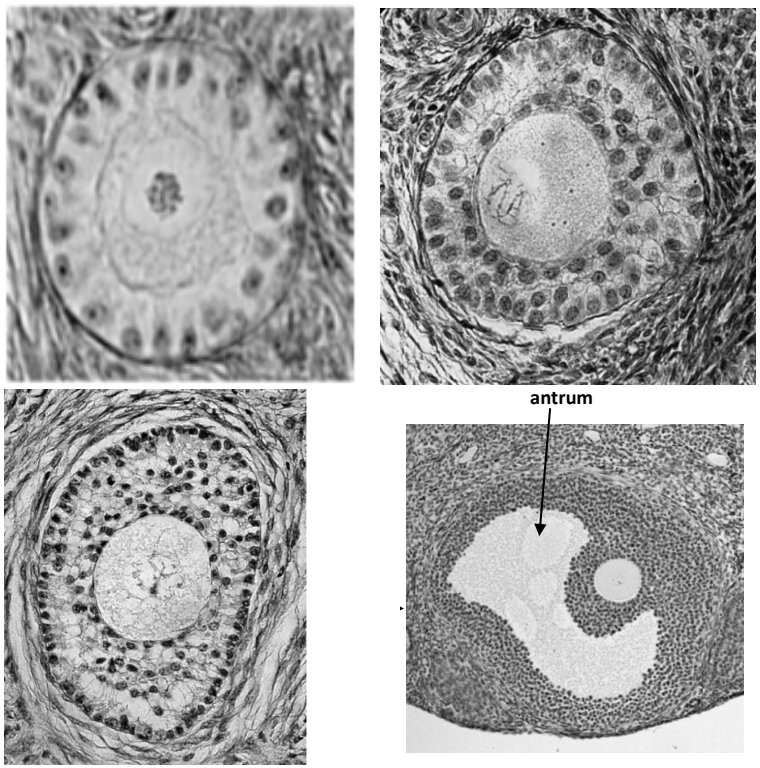
F. Clément, P. Crépieux, R. Y., and D. Monniaux. Mathematical modeling approaches of cellular endocrinology within the hypothalamo-pituitary-gonadal axis. Mol. Cell. Endocrinol., 2020.

Le système reproducteur féminin des mammifères : un système multi-échelle complexe

- Croissance d'un follicule
  Morphodynamique de population
  - Espace : niveau cellulaire
  - Temps : Plusieurs cycles ovariens







Courtesy of Danielle Monniaux.

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**

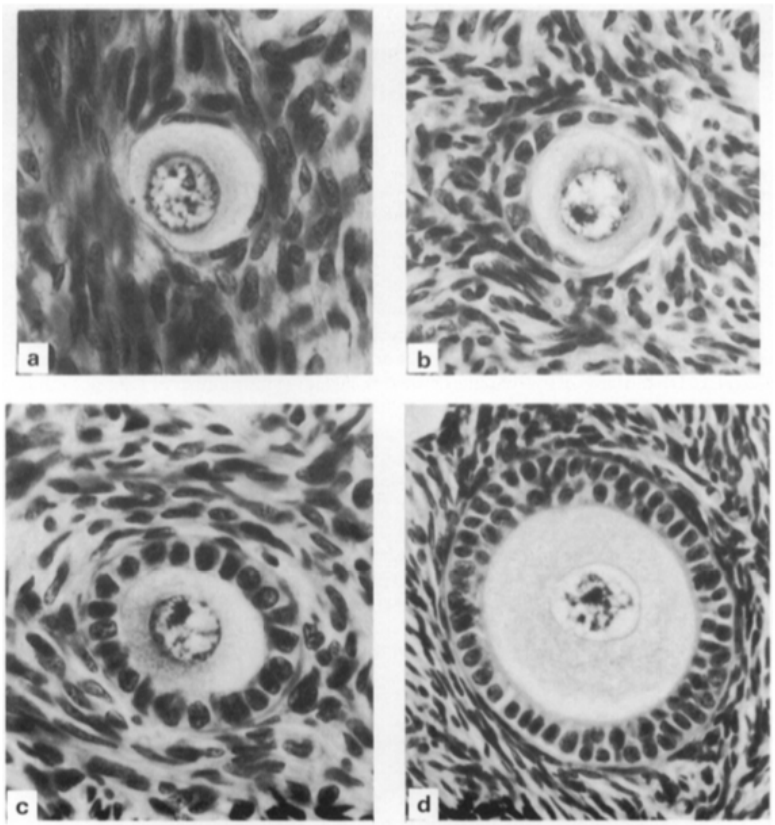
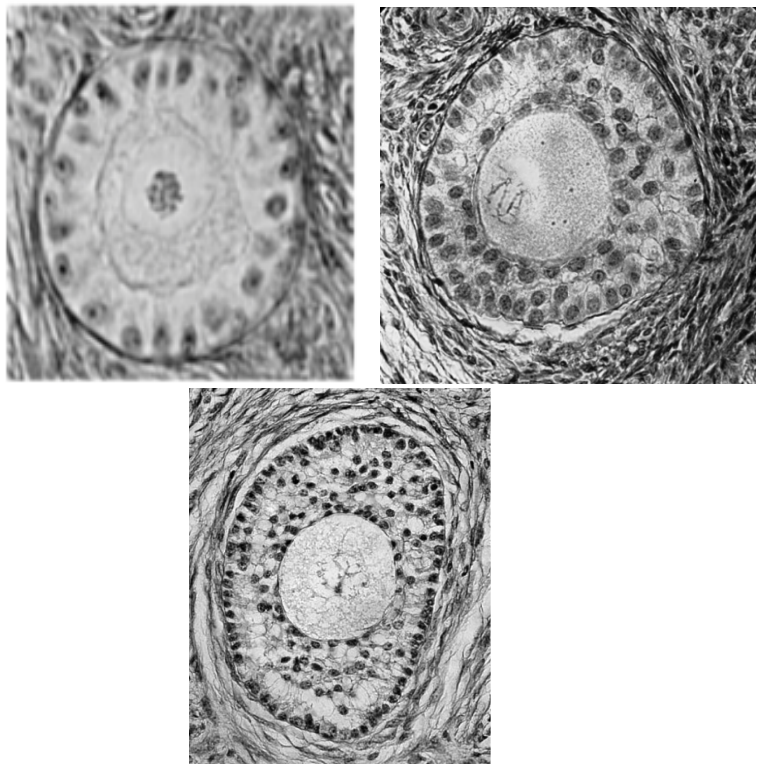


Fig. 1. Illustrations of follicle types: (a) Type B, ×570; (b) Type B/C, ×570; (c) Type C, ×570; (d) Type D, ×410.

Gougeon & Chainy, J. Reprod. Fert. 1987

Key features of follicle basal growth

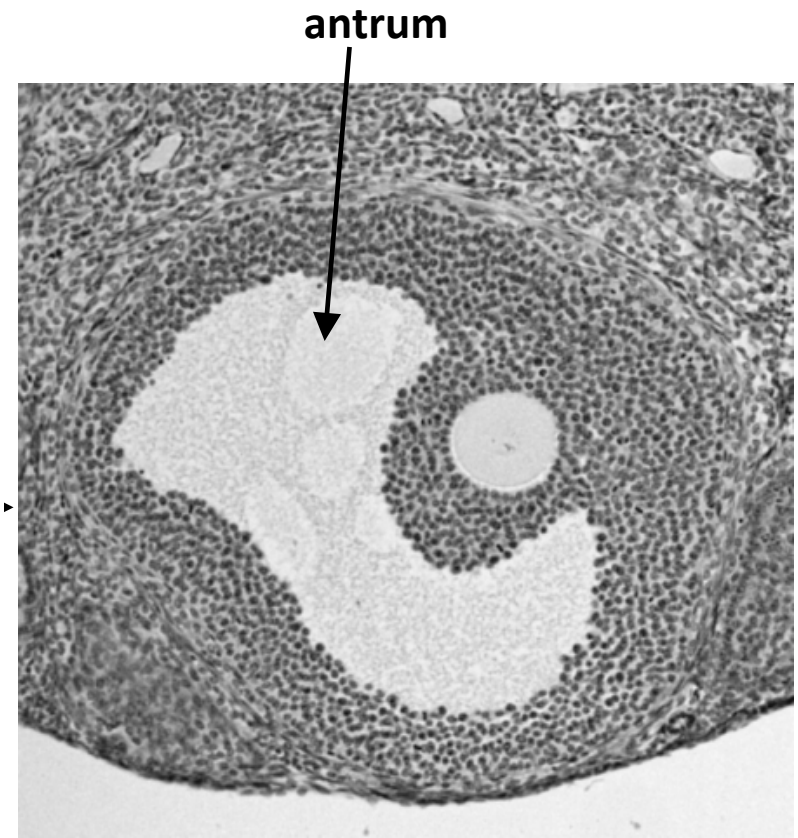
- Growth of a small follicle after initiation
- Spherical Symmetry
- Spatial structure of somatic cells in concentric layers
- Joint dynamic
  - ⋆ Ovocyte growth
  - ⋆ Somatic cells Proliferation
- Growth signals from the Ovocyte to somatic cells and *vice-versa*.



Courtesy of Danielle Monniaux.

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

EDO model

Q = Quiescent cells
P = Proliferative cells
D = Differentiated cells
d_O, d_A = germ cell and antrum diameters

$$\begin{array}{ccccc} & & P+P & & \\ & & \uparrow \gamma(d_0, d_A) & & \\ Q & \xrightarrow{\alpha+\beta(P)} & P & \xrightarrow{\delta(d_0,d_A)} & D \end{array}$$

$$\begin{aligned} \frac{d}{dt} d_0 &= f(d_0, P) \\ \frac{d}{dt} d_A &= g(d_A, P, Q) \end{aligned}$$

EDO model

Q = Quiescent cells
P = Proliferative cells
D = Differentiated cells
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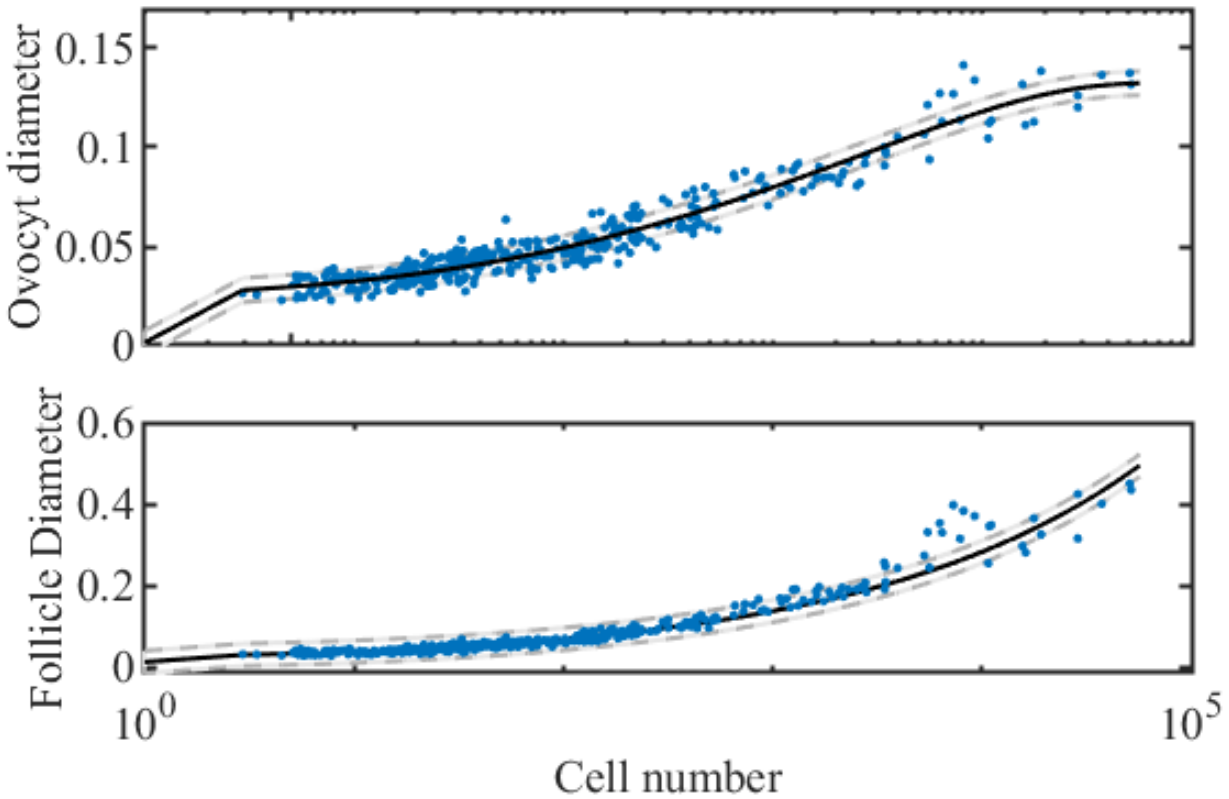
$$\begin{array}{ccccc} & & P+P & & \\ & & \uparrow \gamma(d_0, d_A) & & \\ Q & \xrightarrow{\alpha+\beta(P)} & P & \xrightarrow{\delta(d_0,d_A)} & D \end{array}$$

$$\begin{aligned} \frac{d}{dt} d_0 &= f(d_0, P) \\ \frac{d}{dt} d_A &= g(d_A, P, Q) \end{aligned}$$

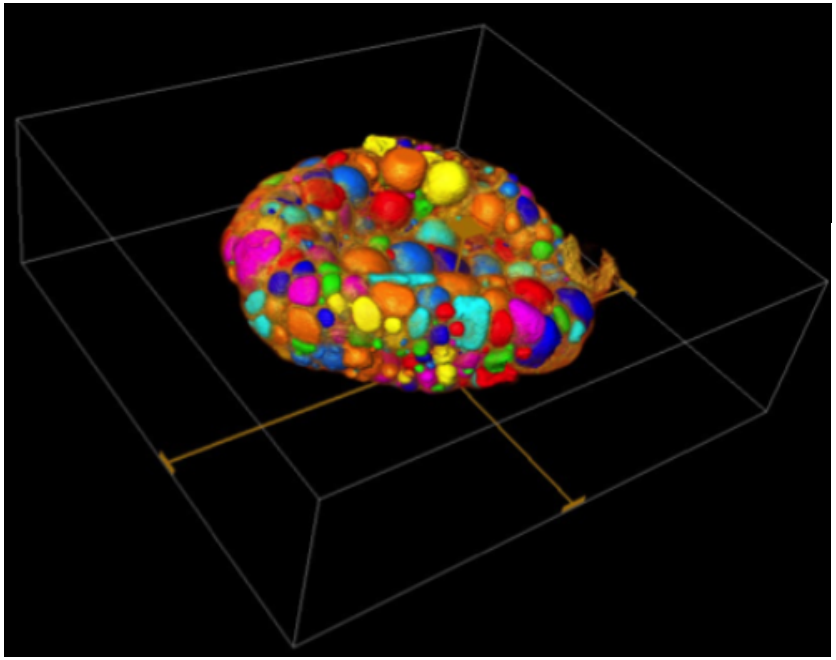
β, γ, δ, f and g depends on various functional hypotheses of molecular dialogue inside a follicle.

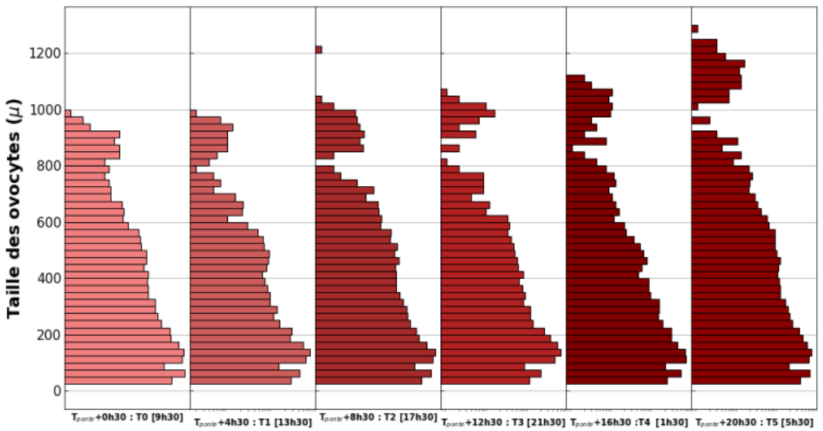
Data fitting



✓ data fitting shows (or confirms) positive feedbak loop for Quiescent cells activation (through Proliferative cells), germ cell growth (through Proliferative cells) and antrum growth (through Proliferative/Differentiative cells)

3D imaging data : Follicle count and morphometric measurement

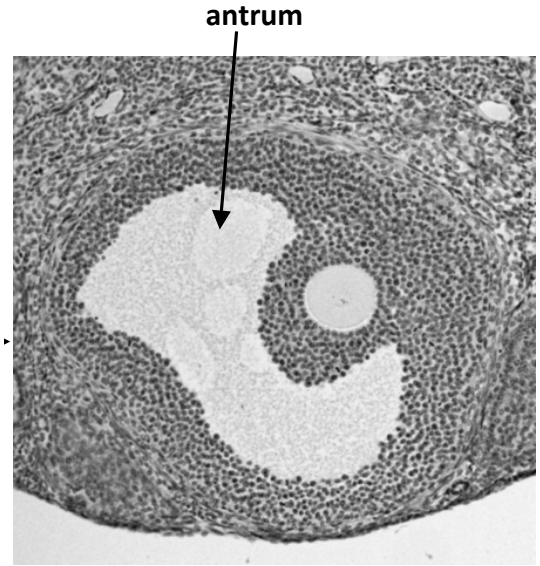


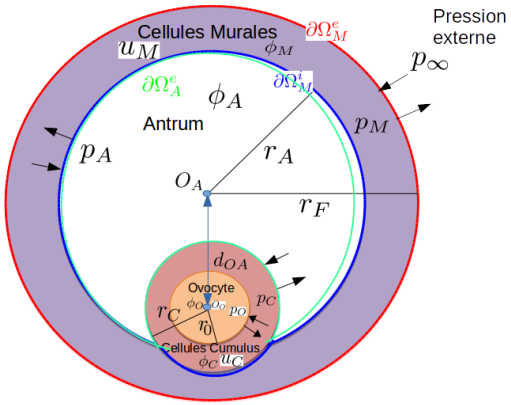


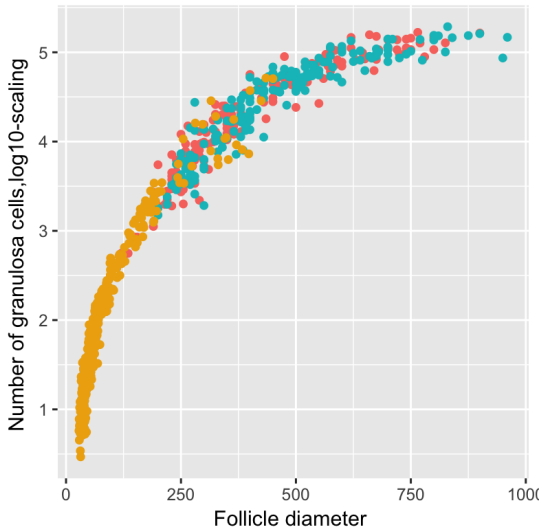
-> structuring the population based on morphologic variable.

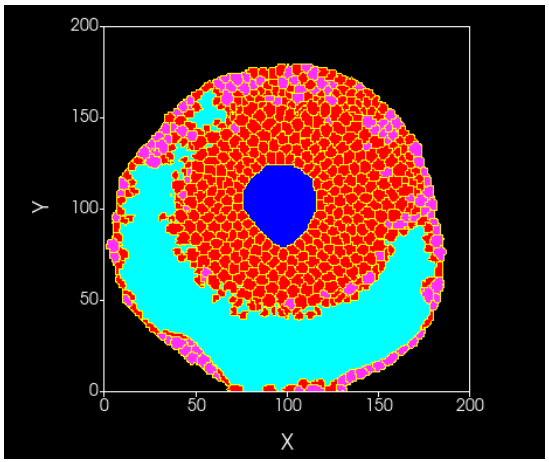
$$\begin{cases} \dfrac{d\rho_0(t)}{dt} & = & -(\lambda_0(\rho(t,.)) + \mu_0(\rho(t,.)))\rho_0(t)\,, \\ \varepsilon\partial_t\rho(t,x) & = & -\partial_x(\lambda(\rho(t,.),x)\rho(t,x)) - \mu(\rho(t,.),x)\rho(t,x)\,, \\ \lim\limits_{x\to 0}\lambda(\rho(t,.),x)\rho(t,x) & = & \lambda_0(\rho(t,.))\rho_0(t)\,,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

Vers des modèles plus réalistes ? Croissance antrale









work in progress...

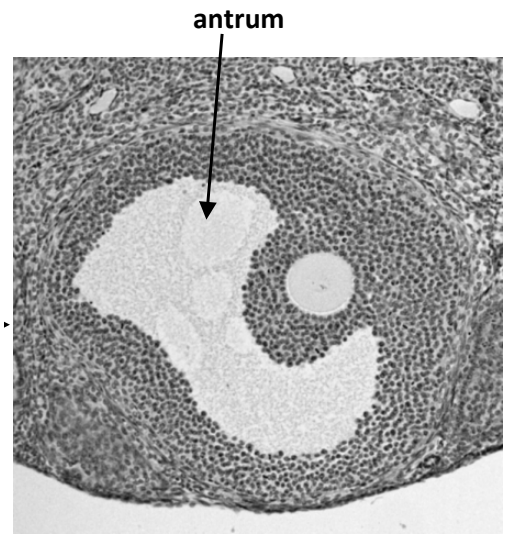
Antrum growth model

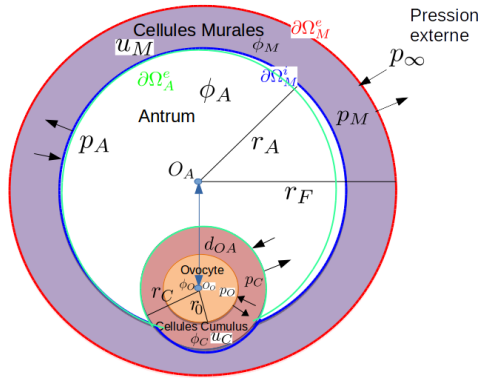
- Multiphasic advection-diffusion-reaction PDE

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

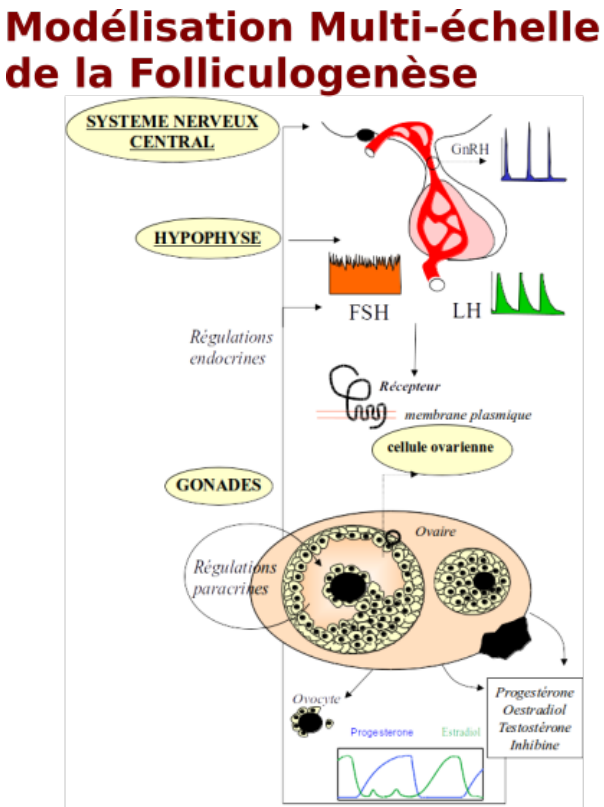
+ Boundary conditions and constitutive laws

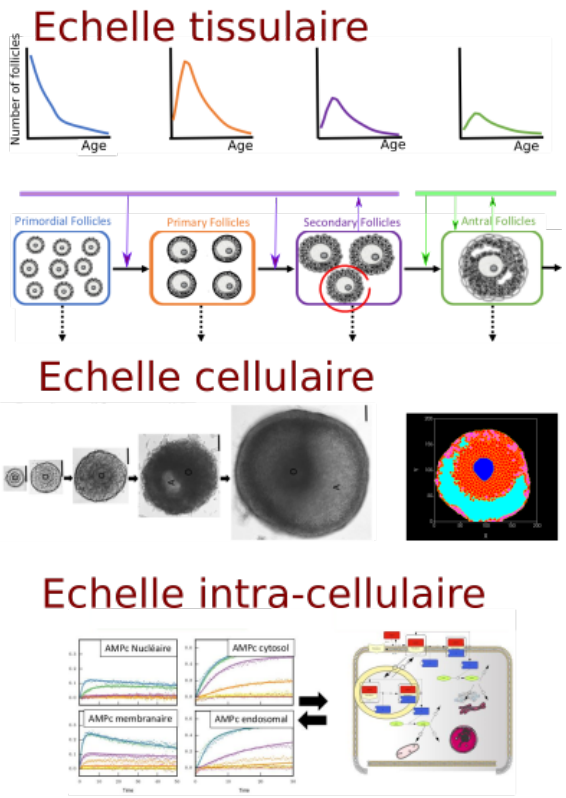
work in progress with Erwan Hingant...





Merci de votre attention !

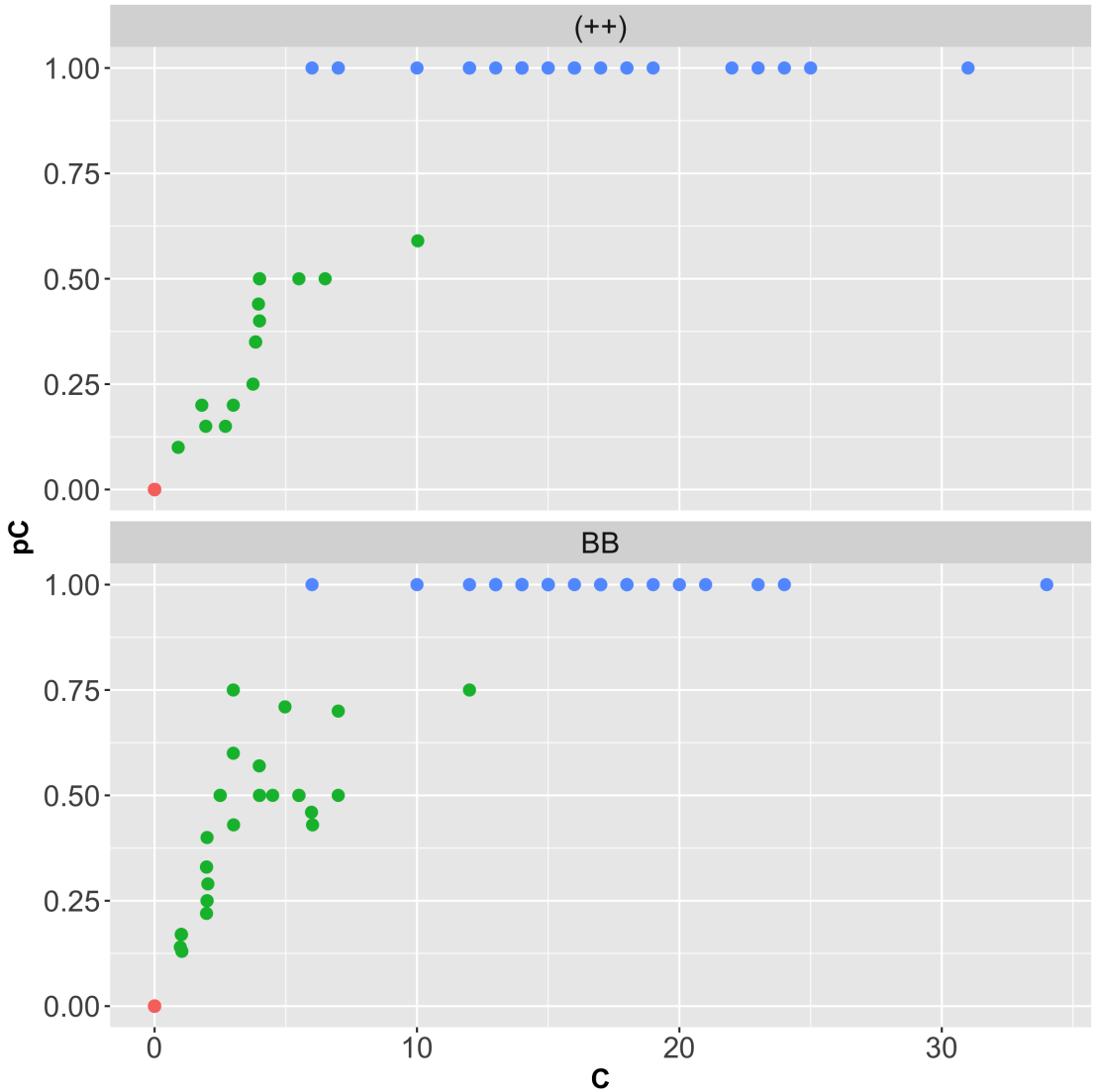




Inria INRAE

- ⋆ 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, Keltoum Chahour)

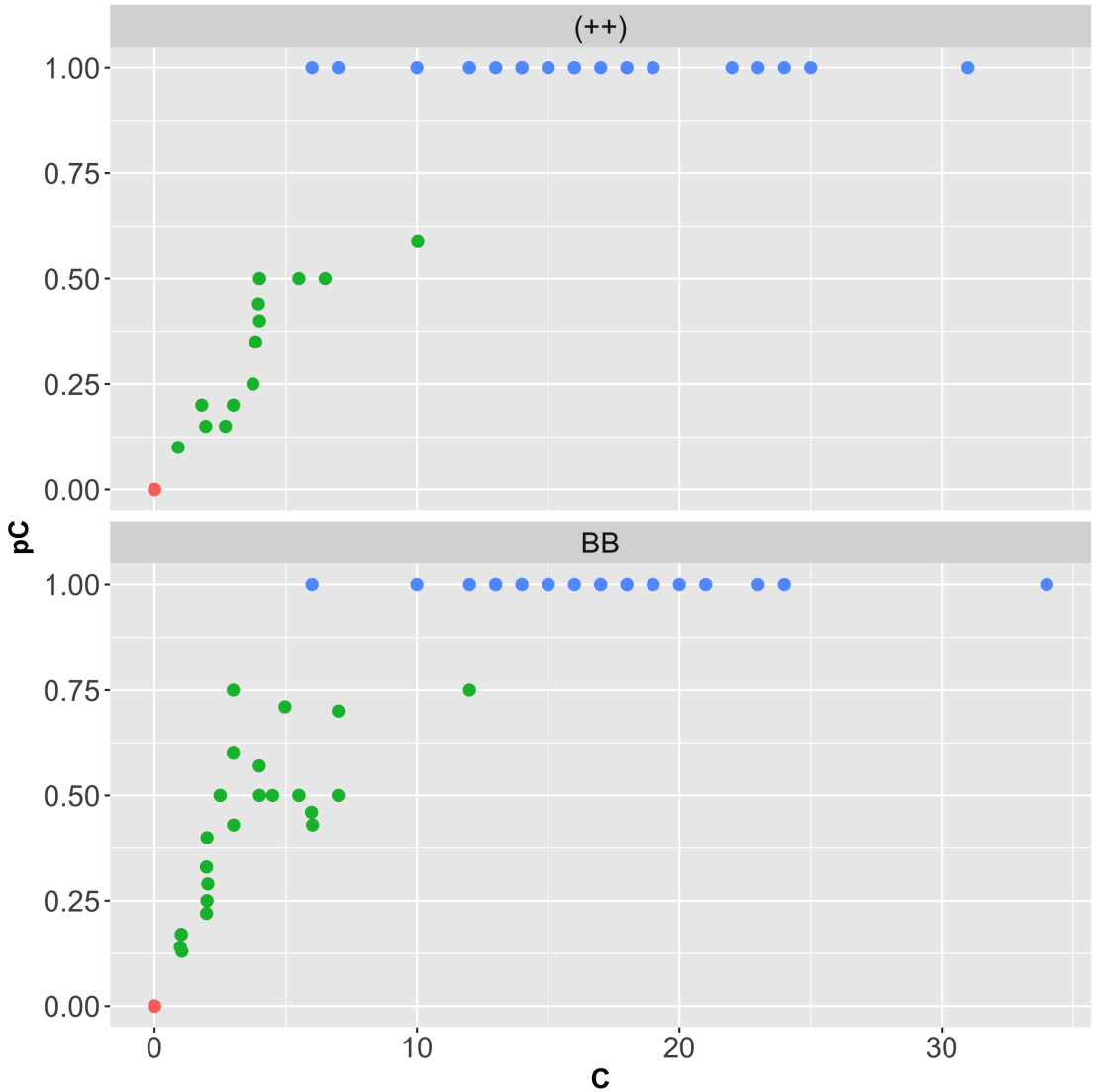
Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus (Courtesy of K. McNatty) : WT (++) vs Mutant (BB)

$\Rightarrow$ **Proportion of cuboid cells** $p_C = C/(F + C)$ **vs number of cuboid cells** C

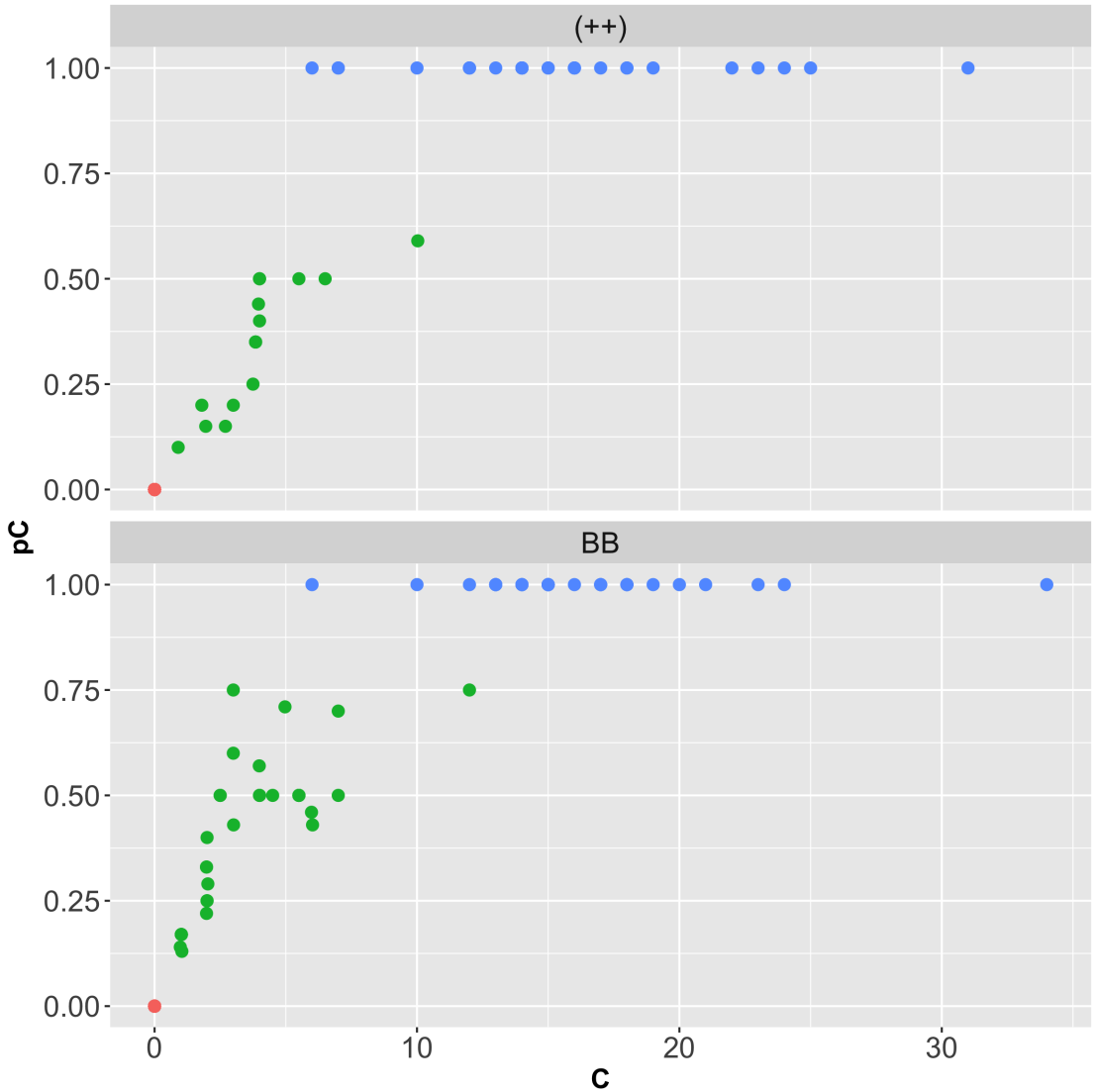
Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Once activated, follicles have "fast" cell proliferation

$\Rightarrow$ **Are both differentiation et de proliferation process concomitant or successive ?**

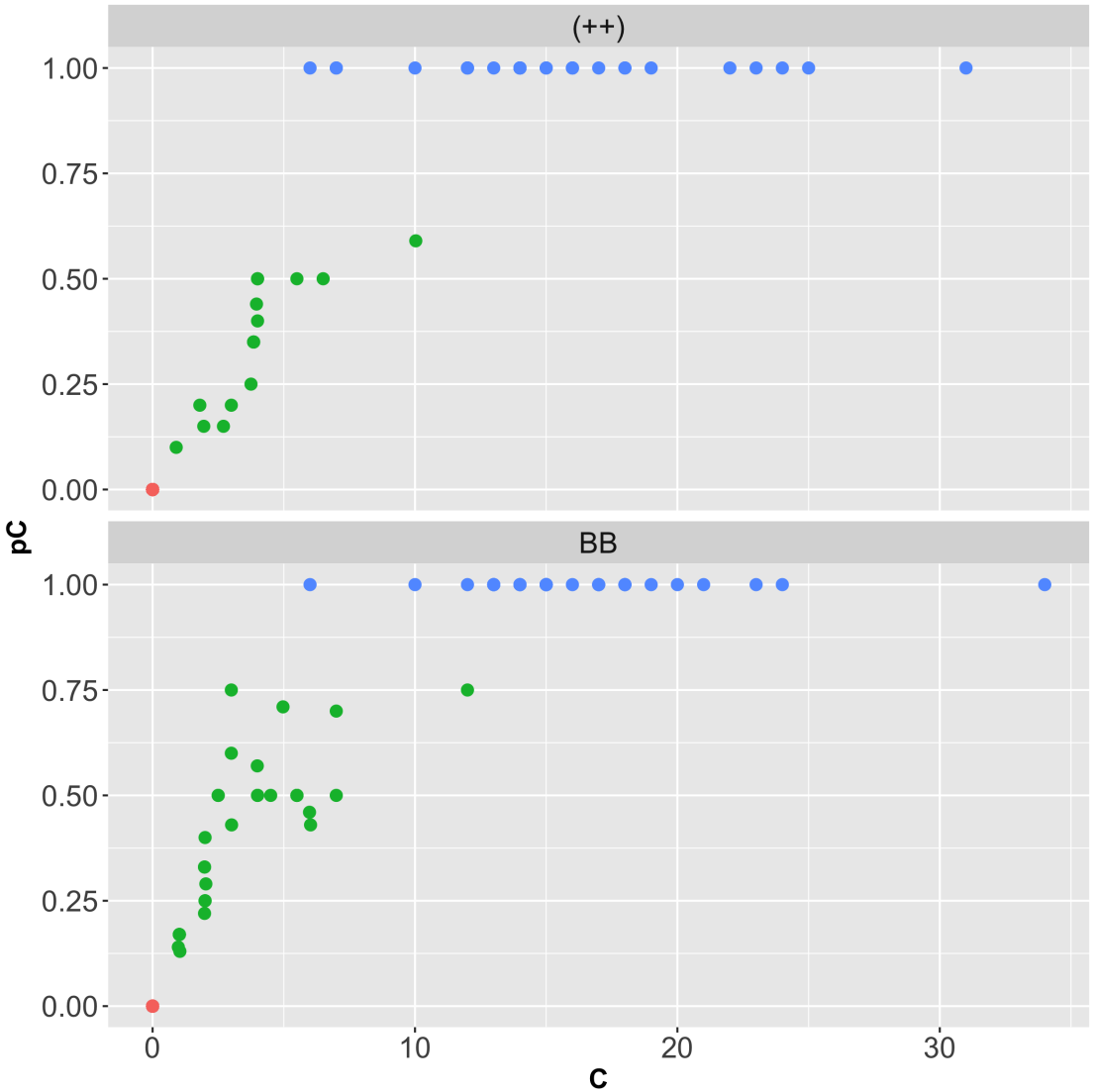
Ex vivo data (snapshot data)



- 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.

$\Rightarrow$ **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.

$\Rightarrow$ **Is the transition of cell differentiation abrupt or more progressive ?**

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

↪ Two cell populations : F (flattened) and C (cuboid)

↪ Small number of cells

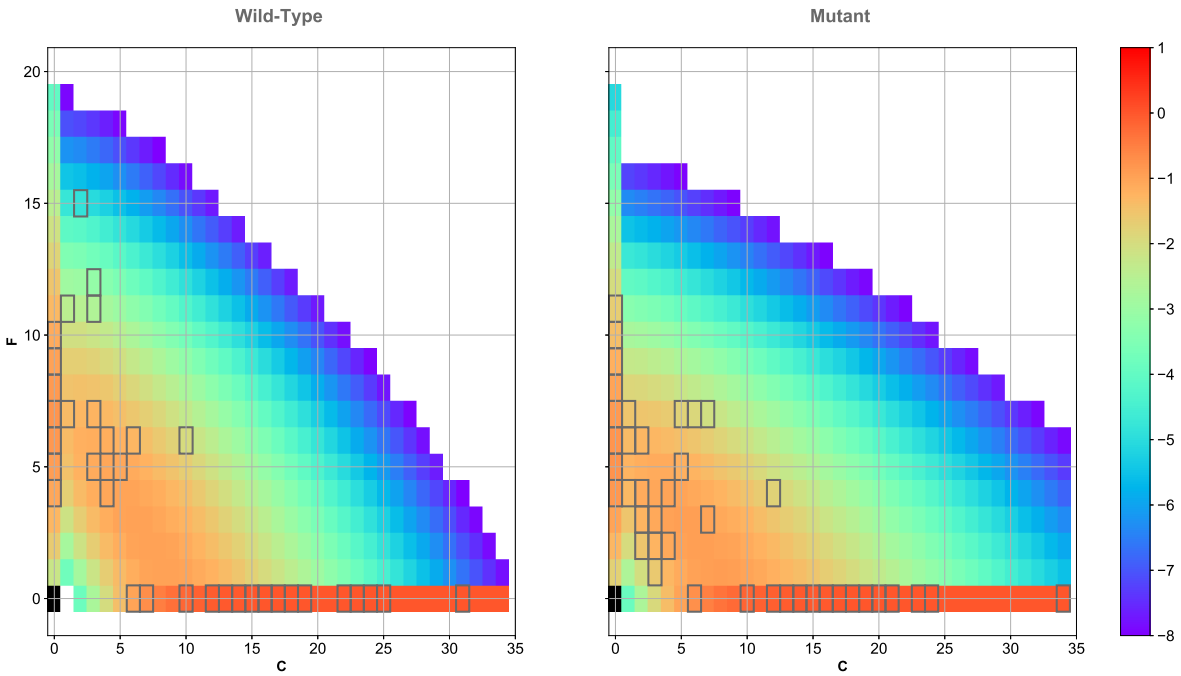
↪ Retro-action of cuboid cells on the differentiation rate : is it relevant ?

↪ From $(F_0, 0)$ to $(0, C_\tau)$

- Theoretical study
  - $\Rightarrow$ Statistics of the "transition" time τ to reach $F = 0$.
  - $\Rightarrow$ Variability of final cuboid cells ($\mathbb{E}\left[C_\tau\right] < \infty$ if $\gamma < \alpha + \beta$)
  - $\Rightarrow$ Impact of parameters e.g. on qualitative dynamics (progressive vs abrupt)
- Parameter calibration : lack of identifiability. Either $\gamma << 1$ and β unconstrained, or $\gamma > 1$ and $\beta/\gamma >> 1$

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

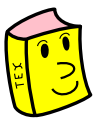
Agreement to data



⇒ The model can capture both data sets

⇒ Lack of identifiability (non-conclusive on retro-action)

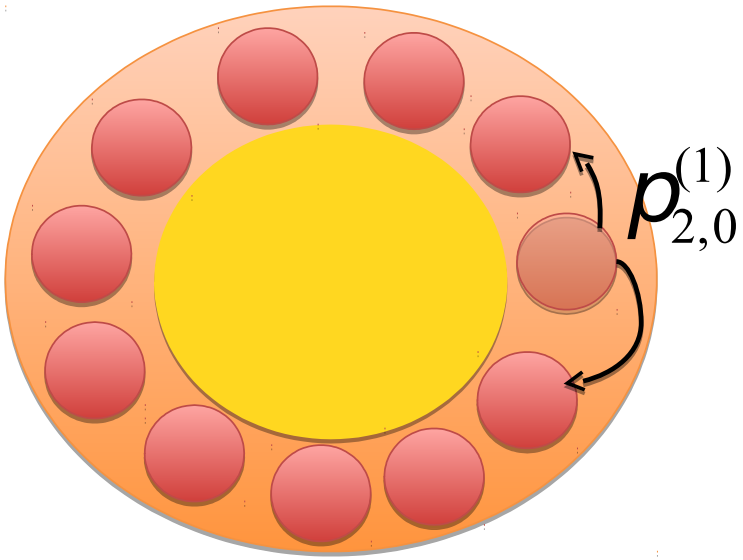
⇒ First differentiation, then proliferation (sligtly more concomitant in mutant case)



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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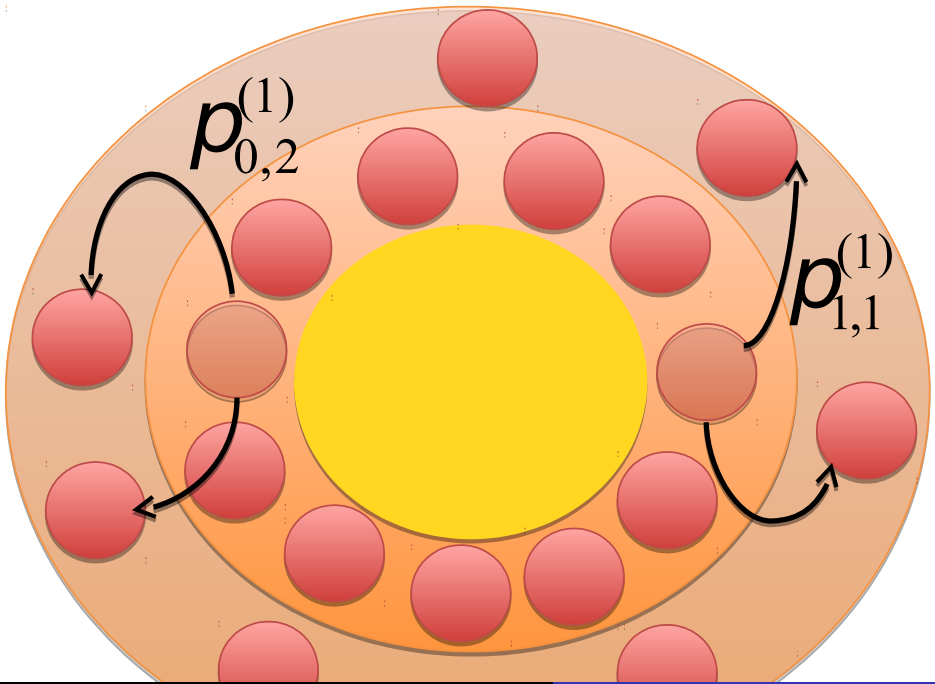

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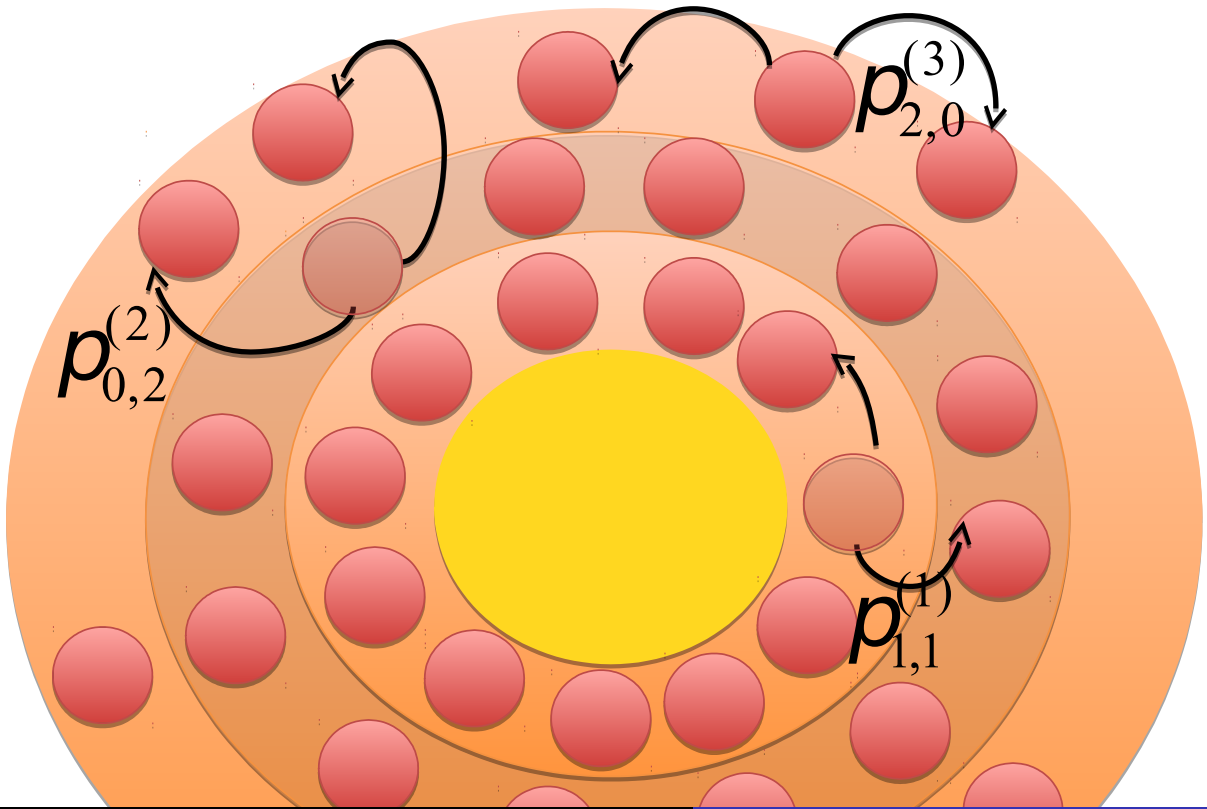

Data

- 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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$\Rightarrow$ Can we explain proliferation in concentric layers by a simple model of "division-migration"? Or do physical constraint play important role ?

Data

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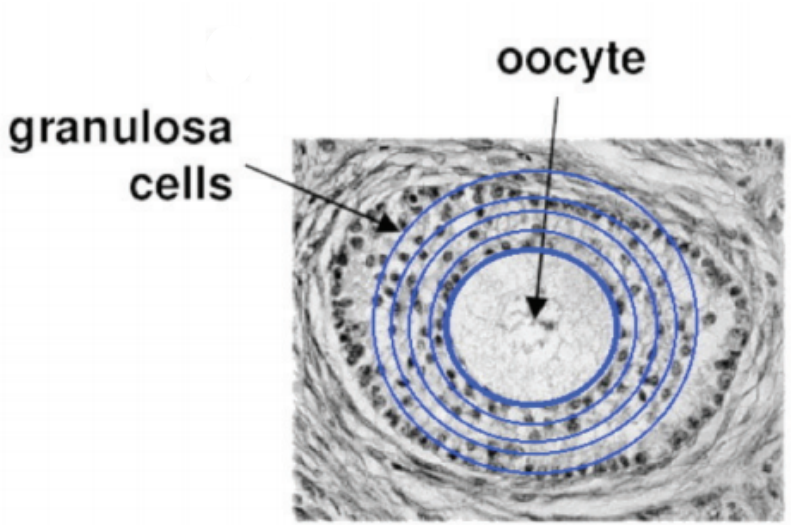
$\Rightarrow$ Can we characterize the growth rate of a follicle and spatial repartition of somatic cells ?

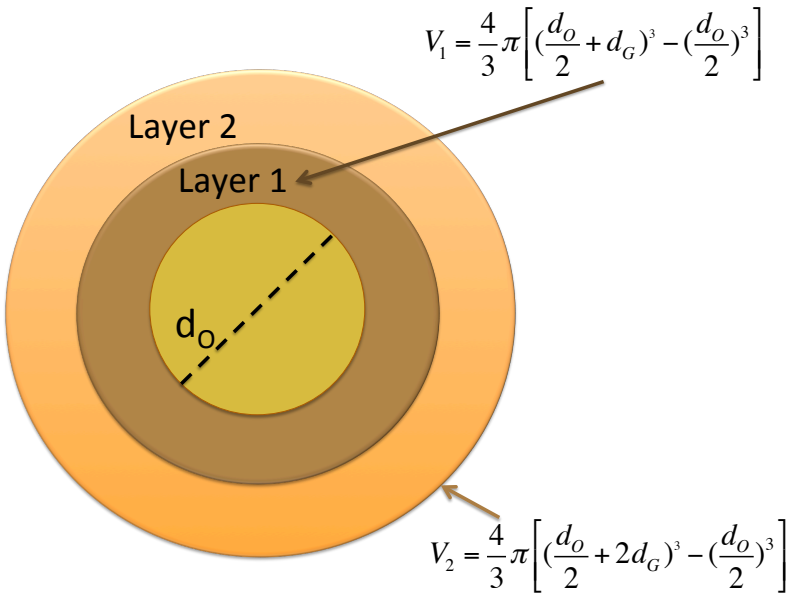
$\Rightarrow$ What is the impact of spatial position of a somatic cell on its division rate ?

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

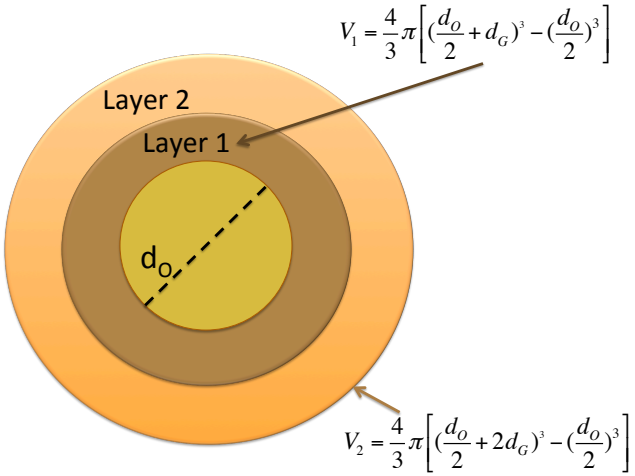
Somatic cells divide and migrate to successive layers.

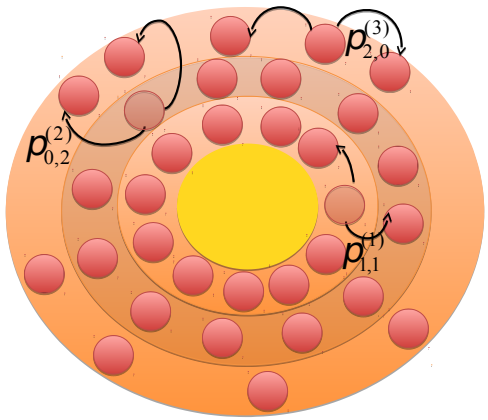




- The geometrical model allows a simple spatial description
- The model is linear and decomposable : exponential growth, with a stable asymptotic spatial profile : there exists a unique $\lambda > 0$ such that the process Z_t verifies

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



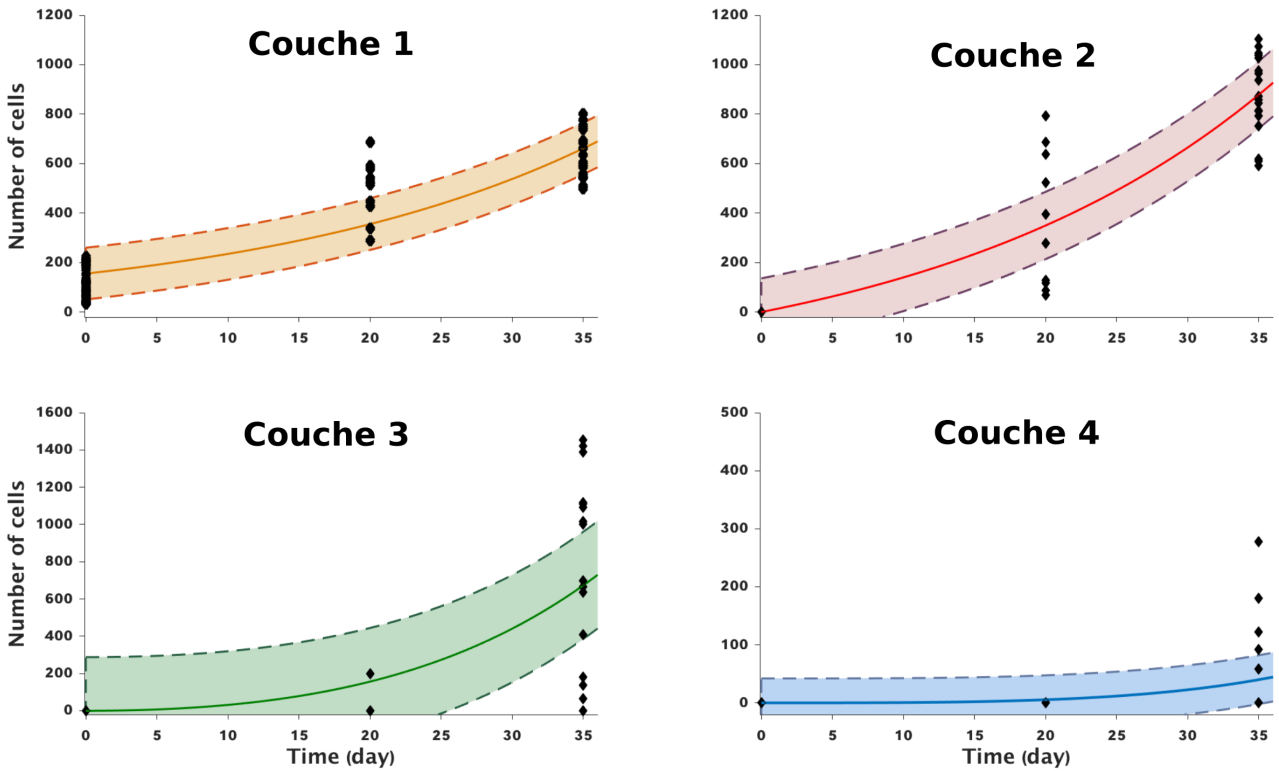


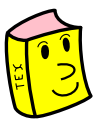
Clément et al. *Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion : Application to the Morphogenesis of Ovarian Follicles*, SIAM App. math, 2019

Fitting results

⇒ **Exponential** growth dominated by the first cell layer

⇒ Parameter identifiability and doubling time quantification (≈ 16 days) : Cell-cycle time ↗ with ovocyte distance





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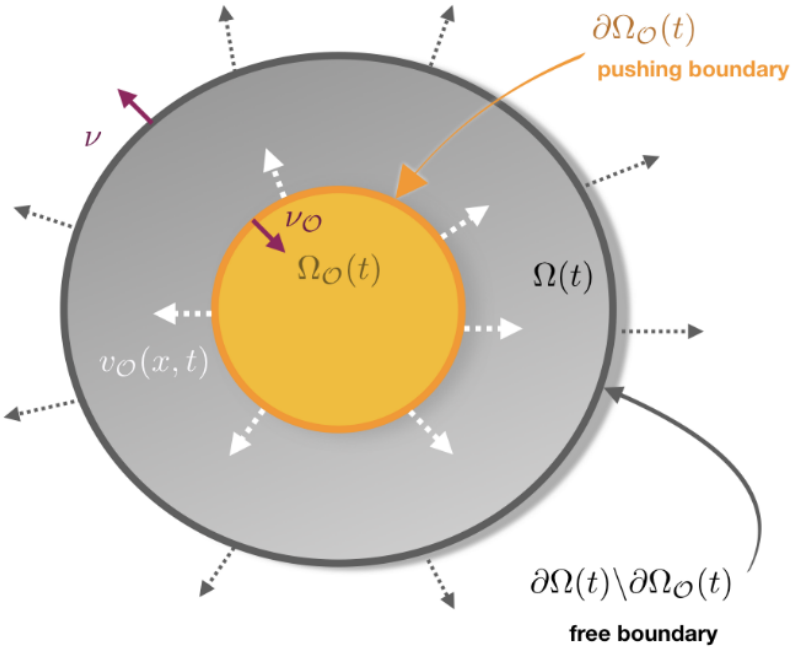
More realistic model ?

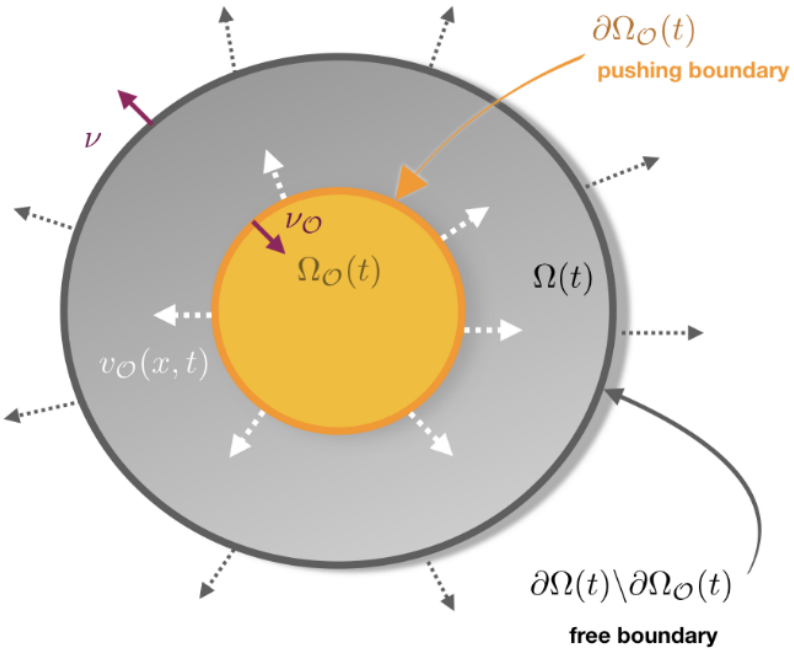


$\frac{\partial u}{\partial t} + div\left(\overrightarrow{v}u\right) = b(x)u(t,x)$
for $x \in \Omega(t)$ and with $\overrightarrow{v}$ linked to the negative gradient of the pressure, and the pressure related to the density...
Under locally constant density and spherical geometry, one have :

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

work in progress...

Vers des modèles plus réalistes ?



- Advection-reaction PDE

$$\frac{\partial u}{\partial t} + div\left(\overrightarrow{v}u\right) = b(x)u(t,x)$$
$$\overrightarrow{v} \sim \nabla u$$

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

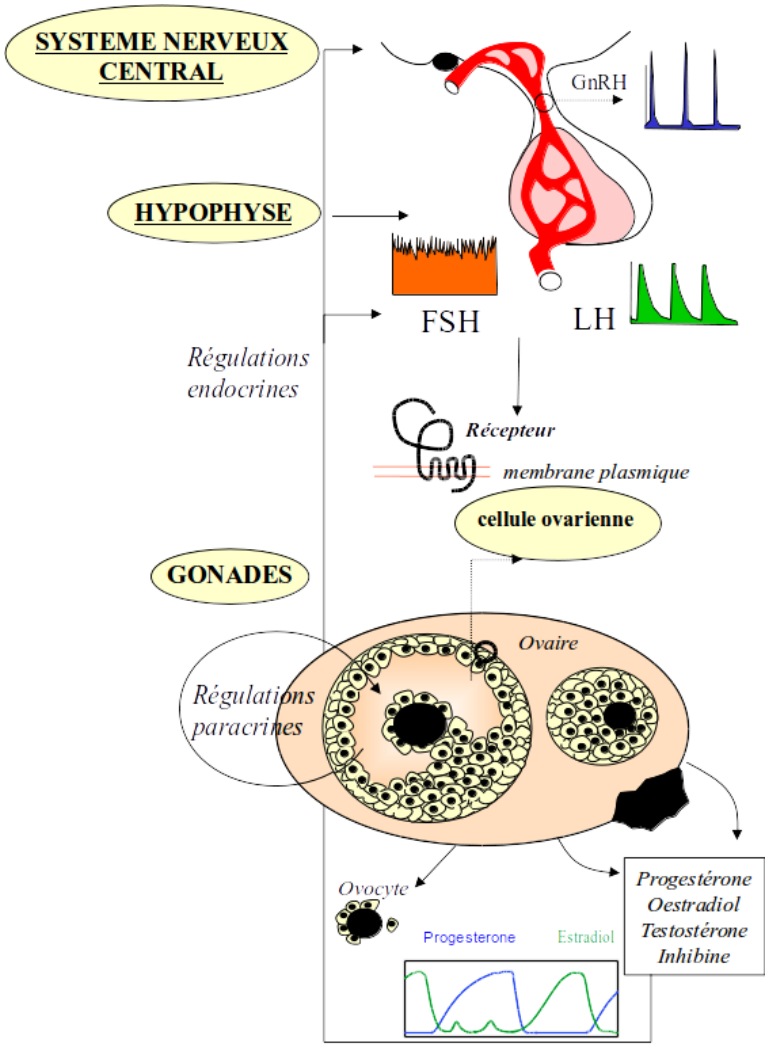
work in progress...

The Mammalian female reproductive system : a complex multiscale system

Encoding and decoding neuro-hormonal signals

Population dynamics : gametogenesis

Intra-cellular level : signaling networks



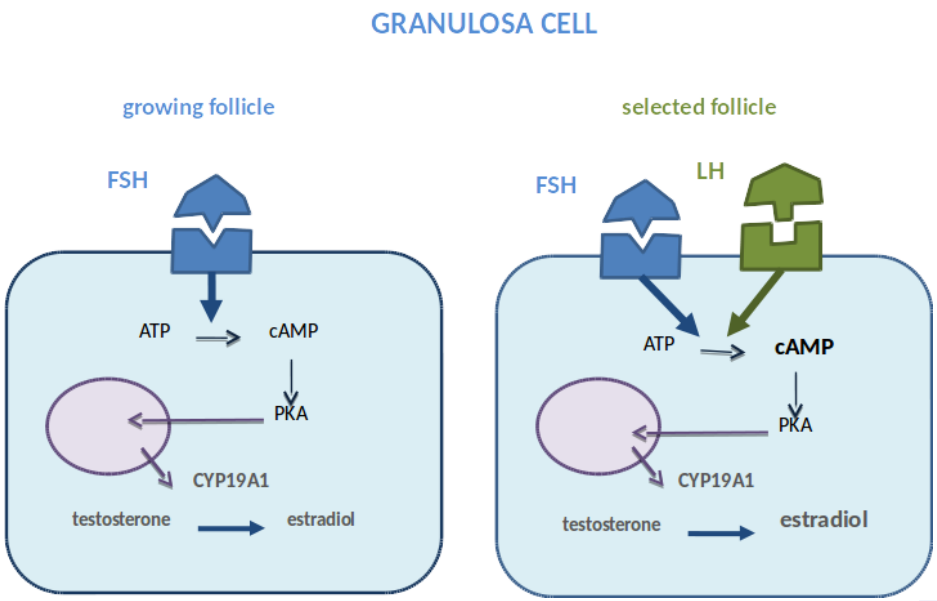
Yvinec et al., *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.

cAMP-induced FSH and its regulation at the cellular level

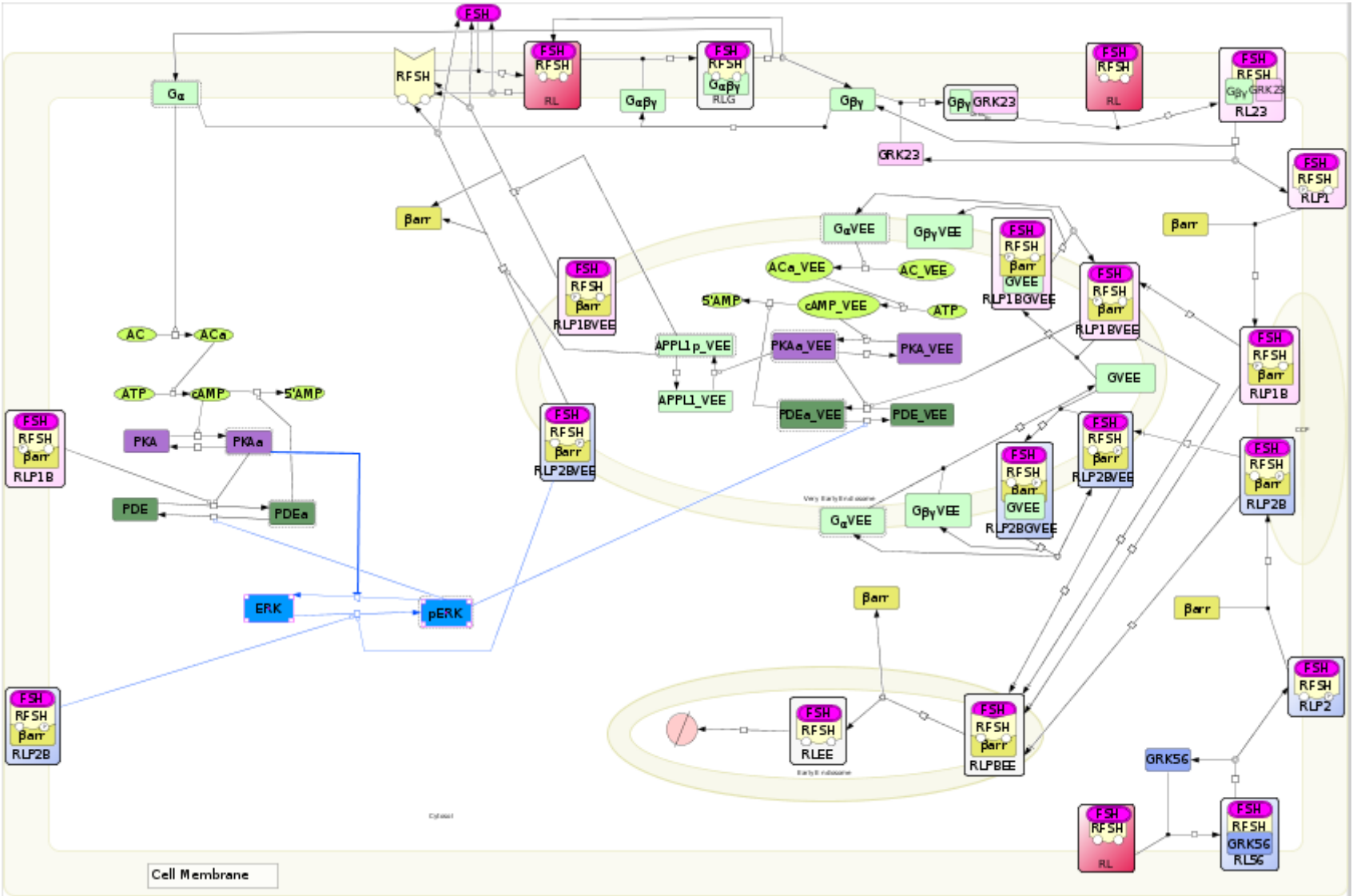
- FSHR signaling network and short-term cAMP induction.
- Long-term regulation of the FSHR network during follicular selection.

$\Rightarrow$ The Cellular "switch" is a pre-requisite for follicle selection .

$\Rightarrow$ This switch is implemented at molecular level by the FSHR network and cAMP output (which is a good marker of follicle maturity).

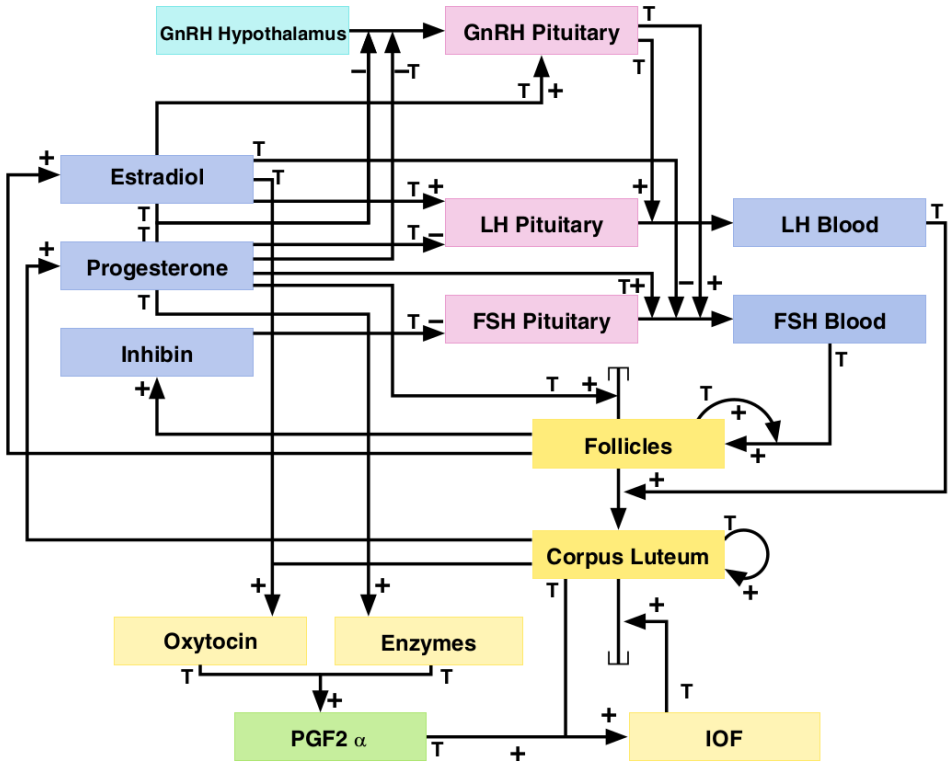


FSHR networks : very complicated dynamics !



Summary

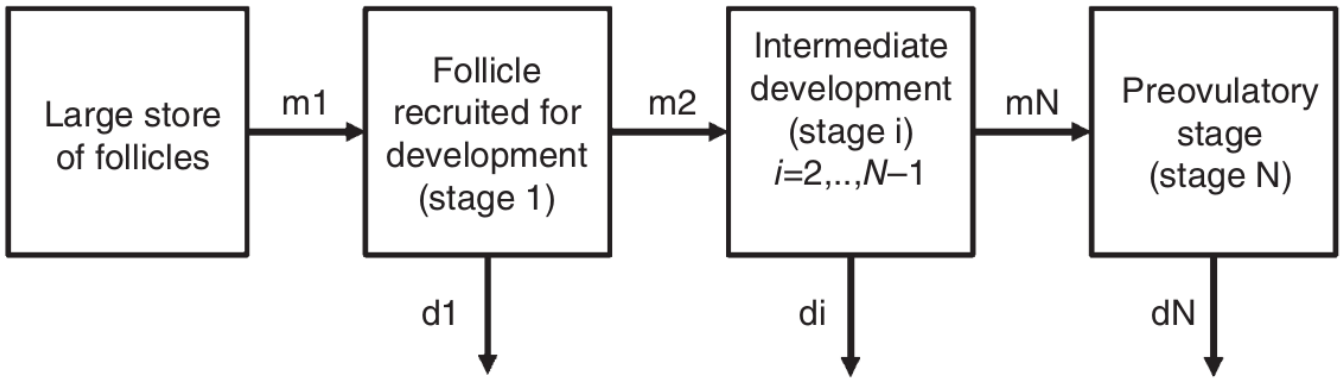
- Circulating hormones dynamical models (Selgrade's model)
  - ⋆ Purely hormonal dynamics
  - ⋆ limit cycles in compact delay differential equation models of the ovarian cycle



Stötzel et al., Therio. 2012

Summary

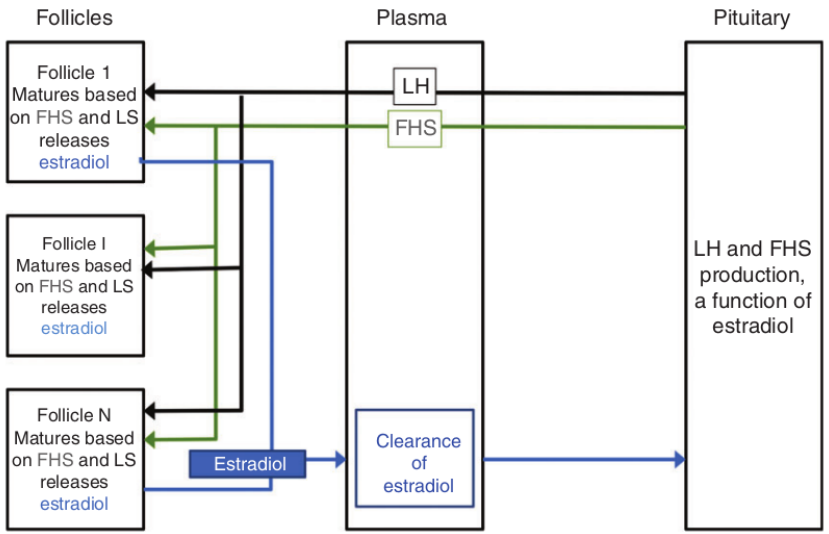
- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
  - ⋆ Reproductive lifespan timescale
  - ⋆ Follicle communication and "hormonal control" through population feedback



Clark & Kruger, WIREs Syst Biol Med 2017

Summary

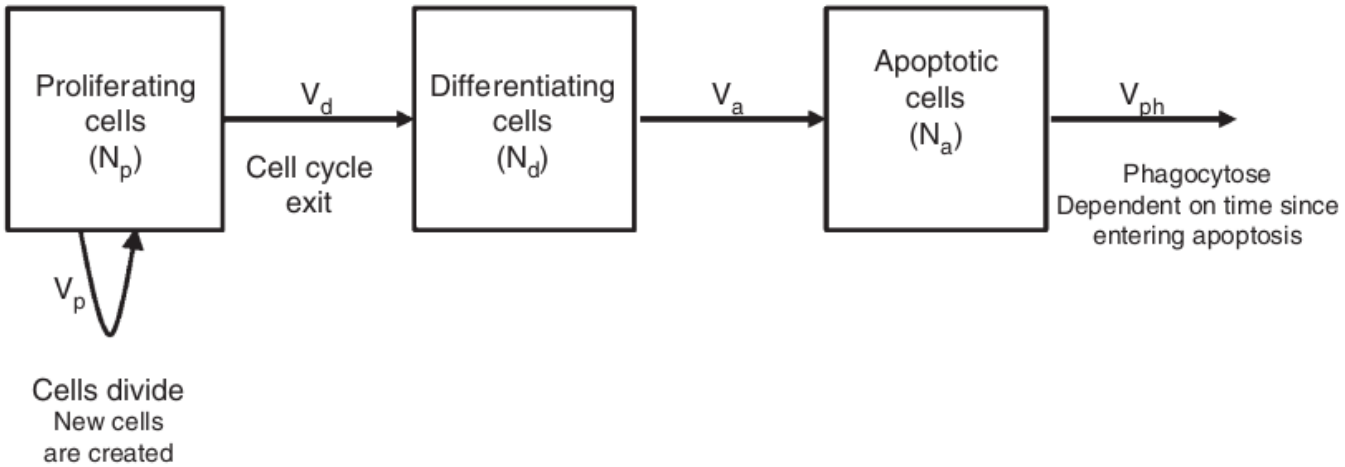
- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
  - ⋆ Ovarian cycle / follicle cohort timescale
  - ⋆ Follicle cohort subject to a shared hormonal environment
  - ⋆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



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)
- 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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Summary

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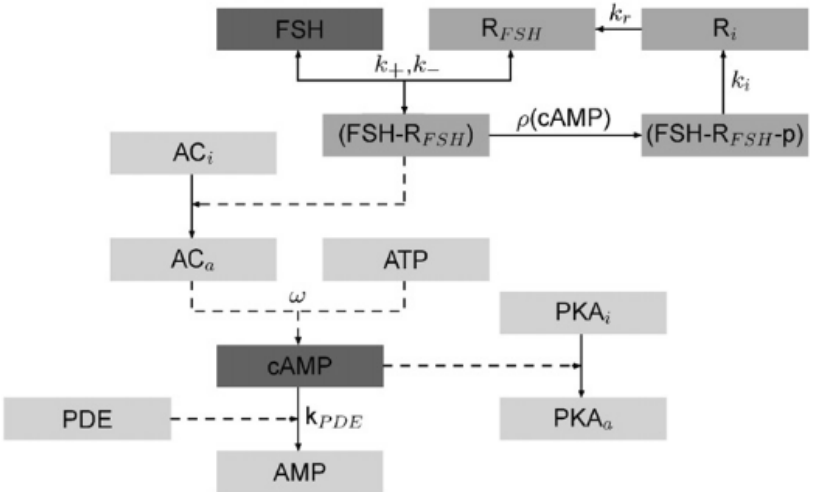
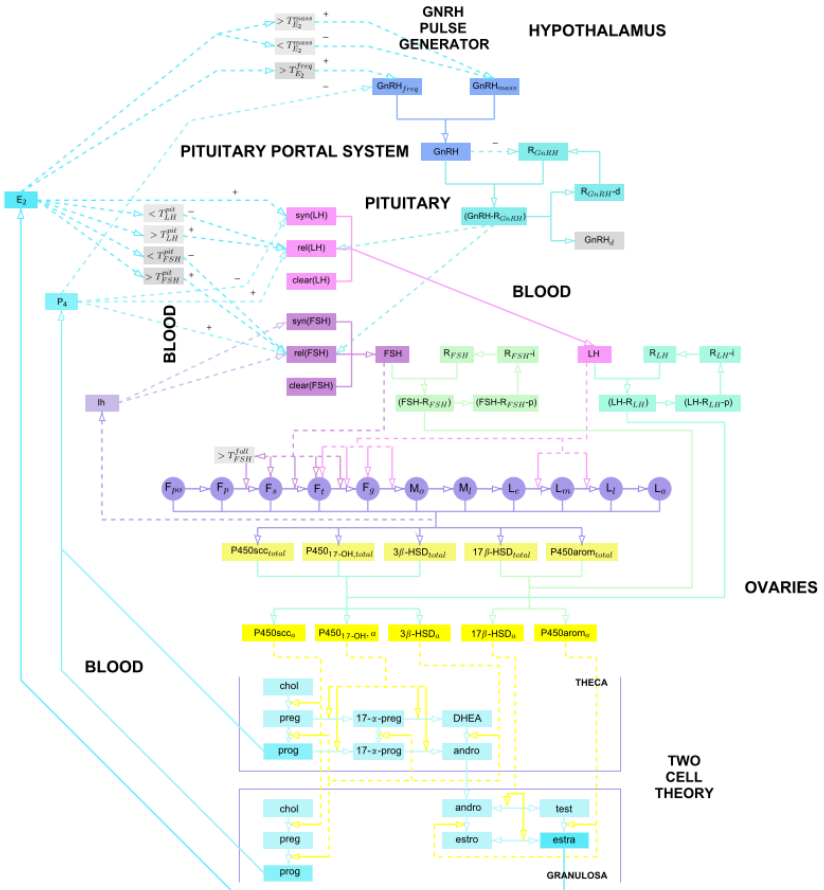
- Cell dynamics in a single follicle (Clément's model)
- Intra-cellular dynamics (Clément / Quignot & Bois)
  - ⋆ Steroidogenesis, cAMP response



Reinecke & Deuflhard,JTB 2007

Multiscale Models of ovarian follicle selection

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



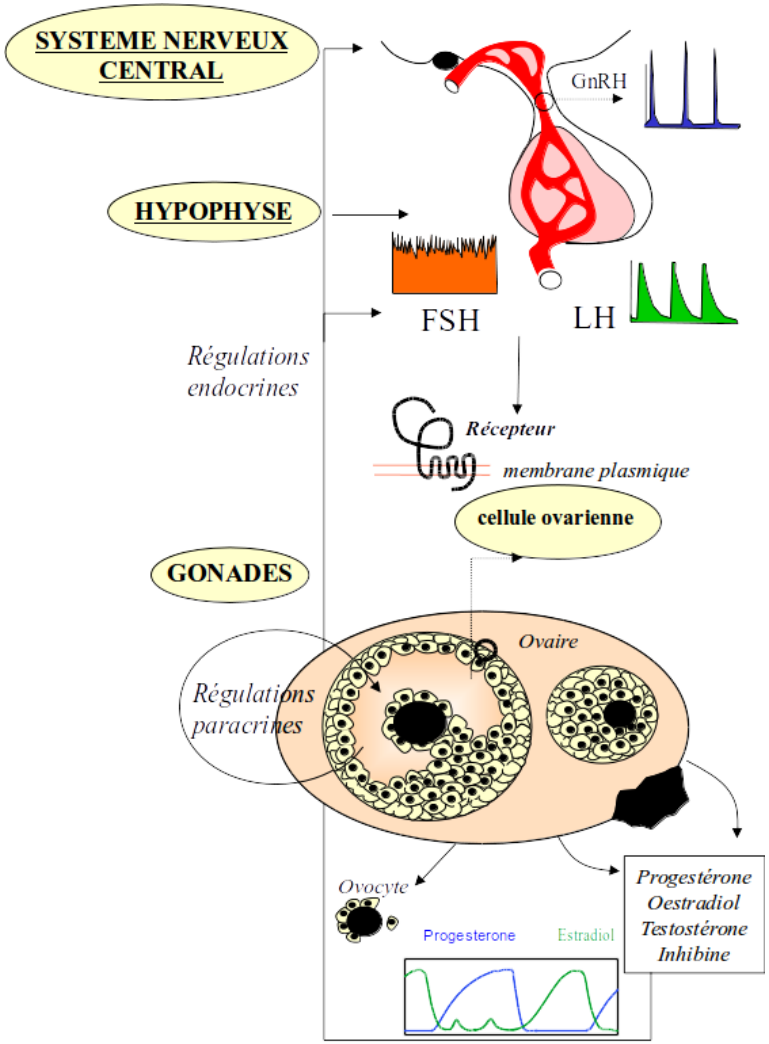
Reinecke & Deuflhard,JTB 2007

- ⋆ 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.

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.



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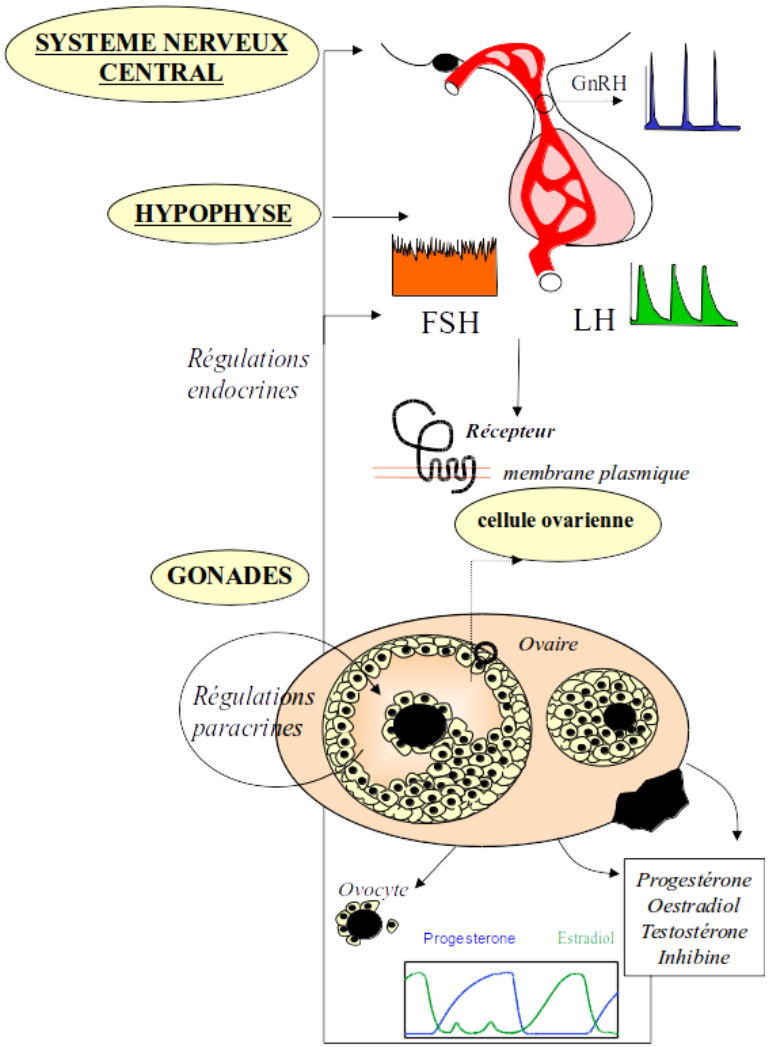
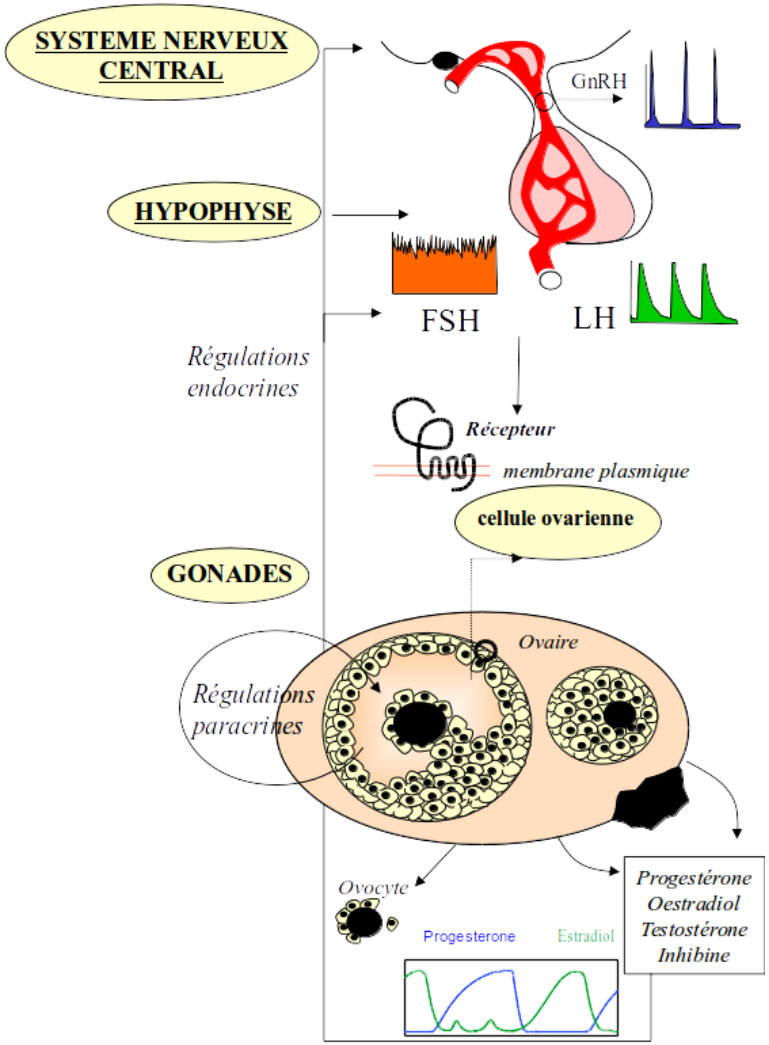


Thank you for your attention !

Le système reproducteur féminin des mammifères : un système multi-échelle complexe

- **Signaux neuro-hormonaux**
  Encodage et décodage
- Gamétogenèse
  Dynamique de population
- Croissance d'un follicule
  Morphodynamique de cellules
- Niveau intra-cellulaire
  réseaux de signalisation

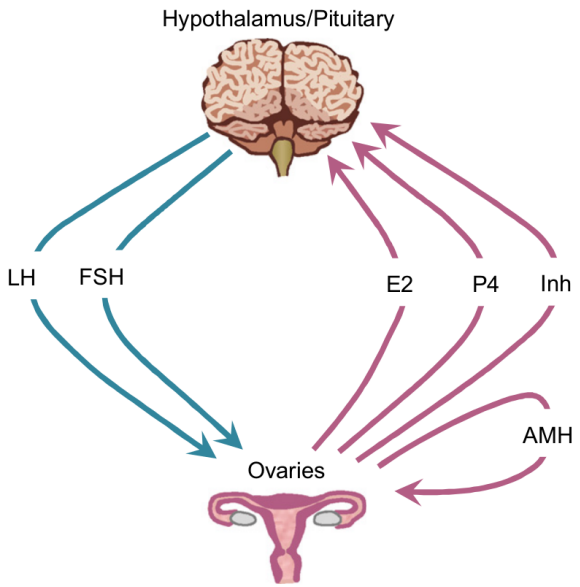


R.Y., P. Crépieux, E. Reiter, A. Poupon, F. Clément, *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.

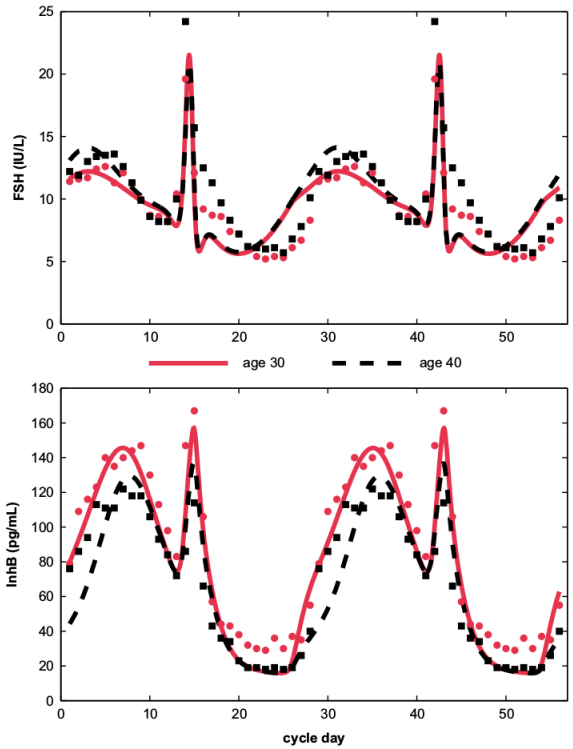
F. Clément, P. Crépieux, R. Y., and D. Monniaux. Mathematical modeling approaches of cellular endocrinology within the hypothalamo-pituitary-gonadal axis. Mol. Cell. Endocrinol., 2020.

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



Margolskee & Selgrade, JTB 2013

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

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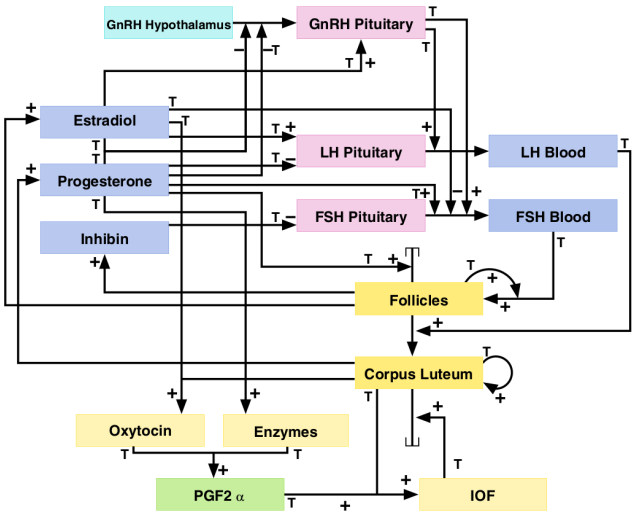
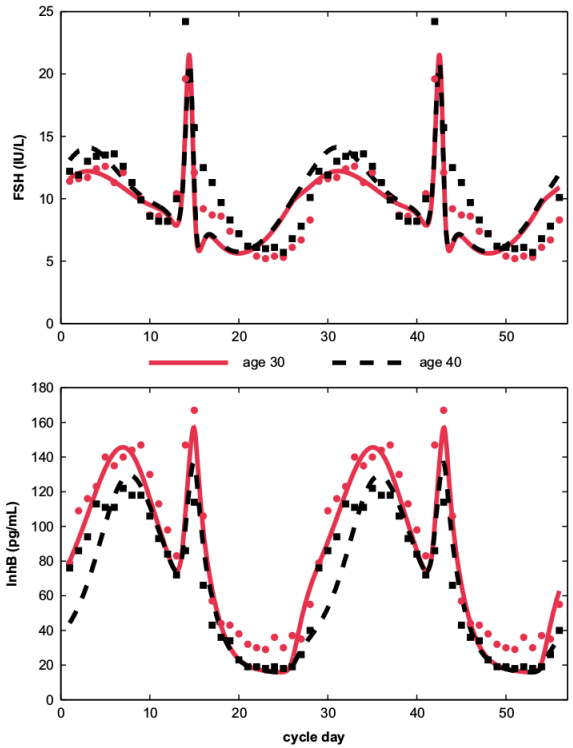


Stötzel et al., Therio. 2012



Margolskee & Selgrade, JTB 2013

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