Multiscale population dynamics

Interactions between scales in developmental and reproductive biology

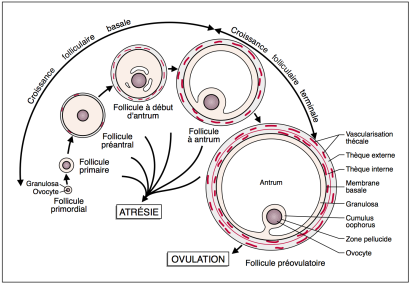
Céline Bonnet, Keltoum Chahour

CEMRACS 2018
22 Août 2018

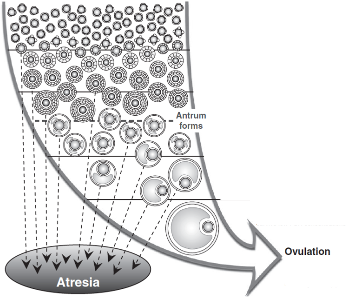
Presentation outline

- Biological background on ovarian follicles
- Modeling approaches
- Theoretical and numerical results

Main steps of follicle development : activation, growth and ovulation



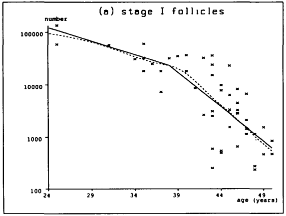
Stage-repartition of the whole follicle population



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

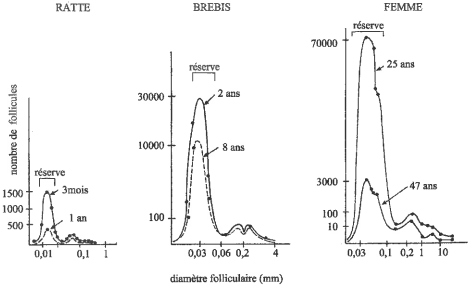
$$
\begin{array}{ccccccccc}
X_0 & \overset{\lambda_0}{\rightarrow} & X_1 & \overset{\lambda_1}{\rightarrow} & X_2 & \overset{\lambda_2}{\rightarrow} & \cdots & & X_d \\
\downarrow & & \downarrow & & \downarrow & & & & \downarrow \\
\mu_0 & & \mu_1 & & \mu_2 & & & & \mu_d
\end{array}
$$

Biological background (2)



Faddy et al., Hum.Reprod. 1995

Decrease of the quiescent follicle pool

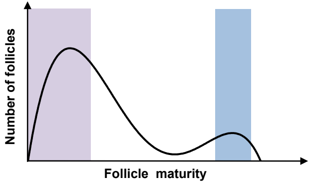


Thibault & Levasseur 2001

Size distribution of ovarian follicle population

<u>Question :</u> Can we find a nonlinear model explaining these data and integrating recent biological knowledge ?

Biological background (3) : Feedback regulations



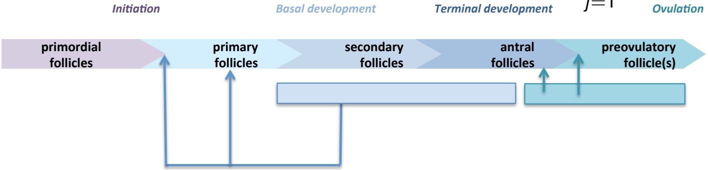
Regulation functions

$$\lambda_0(X) = \frac{c_0}{1 + K_0 \sum_{i=1}^{d} a_i X_i}, \quad a_i \in [0,1]$$

$$\mu_0(X) = \mu_0$$

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

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



Biological background (4)

Order of magnitude of the follicle population in women :

- Quiescent follicles
  At puberty : $X_0(t=0) = 10^4 - 10^6$
  At menopause : $X_0(t = \text{menopause}) < 10^2 - 10^3$
- Growing follicles
  Only 400 follicles will ever reach the pre-ovulatory stage
- **Activation influx** $\forall t, \quad \lambda_0 X_0(t) \sim$"A few per days"
- **Mathematical hypotheses :** Set $\varepsilon \sim 10^{-4}$, so that :
  $X_0(t=0) \in \frac{[1,100]}{\varepsilon}$

  $\lambda_0 = \varepsilon \bar{\lambda}_0, \ \bar{\lambda}_0 \sim 1(/d)$

  $\mu_0 = \varepsilon \bar{\mu}_0, \ \bar{\mu}_0 \sim 1(/d)$

Slow-Fast ODE System : discrete stages

$\forall t \in \mathbb{R}_+, \forall i \in \{1, \ldots, d\}$,

$$\frac{dX_0(t)}{dt} = -(\lambda_0(X(t)) + \mu_0)X_0(t)$$

$$\varepsilon \frac{dX_i(t)}{dt} = \lambda_{i-1}(X(t))X_{i-1}(t) - \lambda_i(X(t))X_i(t) - \mu_i(X(t))X_i(t)$$

$$\lambda_0(X) = \frac{c_0}{1 + K_0 \sum_{i=1}^d a_i X_i}, \quad a_i \in [0, 1]$$

$$\mu_0(X) = \mu_0$$

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

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

PDE system : continuous structuring variable

Variable of interest : $\rho(t,x)$ represents the follicle population density with size $x (x \in (0,1))$ at time $t \in (0,T)$.

$$\lambda_0(\rho(t,.)) = \frac{c_0}{1 + K_0 \int_0^1 a(y)\rho(t,y)dy}$$

$$\mu_0(\rho(t,.)) = \mu_0$$

$$\lambda(\rho(t,.),x) = \frac{f(x)}{1 + K_1(x)\int_0^1 \omega_1(y)\rho(t,y)dy}, \quad x \in (0,1)$$

$$\mu(\rho(t,.),x) = g(x)\left(1 + K_2(x)\int_0^1 \omega_2(y)\rho(t,y)dy\right), \quad x \in (0,1)$$

PDE system : nonlinear transport equation

Let $T > 0$, for all $t \in (0, T)$, for all $x \in (0, 1)$,

$$\frac{d\rho_0(t)}{dt} = -(\lambda_0(\rho(t,.)) + \mu_0)\rho_0(t)$$

$$\varepsilon\partial_t\rho(t,x) = -\partial_x(\lambda(\rho(t,.),x)\rho(t,x)) - \mu(\rho(t,.),x)\rho(t,x),$$

$$\lim_{x\to 0}\lambda(\rho(t,.),x)\rho(t,x) = \lambda_0(\rho(t,.))\rho_0(t)$$

For the initial condition :

$$\rho_0(t=0) = \rho_0^{ini}$$

$$\forall x \in (0,1),\ \rho(t=0,x) = \rho^{ini}(x)$$

PDE system : nonlinear transport equation

Let $T > 0$, for all $t \in (0, T)$, for all $x \in (0, 1)$,

$$\frac{d\rho_0(t)}{dt} = -(\lambda_0(\rho(t,.)) + \mu_0)\rho_0(t)$$

$$\varepsilon \partial_t \rho(t,x) = -\partial_x(\lambda(\rho(t,.),x)\rho(t,x)) - \mu(\rho(t,.),x)\rho(t,x),$$

$$\lim_{x\to 0} \lambda(\rho(t,.),x)\rho(t,x) = \lambda_0(\rho(t,.))\rho_0(t)$$

Question : Can we understand the limit behavior of (ρ_0, ρ) when $\varepsilon \to 0$

Reduced model : $\varepsilon = 0$ (Candidate limit)

For all $t \in (0, T)$, for all $x \in (0, 1)$,

$$\frac{d\rho_0^\infty}{dt} = -(\lambda_0(\rho^\infty(t,.)) + \mu_0)\rho_0^\infty(t)$$

$$0 = -\frac{d}{dx}\left(\rho^\infty(t,x)\,\lambda(\rho^\infty(t,.),x)\right) - \mu(\rho^\infty(t,.),x)\,\rho^\infty(t,x)$$

$$\lim_{x\to 0}\lambda(\rho^\infty(t,.),x)\rho^\infty(t,x) = \lambda_0(\rho^\infty(t,.))\rho_0^\infty(t)$$

For the initial condition :

$$\rho_0^\infty(t=0) = \rho_0^{ini}$$

Analytical solution in the linear case

$$\forall t \in [0, T], \quad \rho_0^\infty(t) = \rho_0(t) = \frac{c_0}{f(0)} \rho_0^{ini}\, e^{-(c_0+\mu_0)\, t}$$

$\forall x \in (0,1), \forall t \in (0, T)$, for appropriate f and g,

- If $t > \int_0^x \frac{\varepsilon}{f(y)} dy$,

$$\rho(t,x) = \frac{c_0}{f(0)} \rho_0^{ini}\, e^{-(c_0+\mu_0)\,(t - \int_0^x \frac{\varepsilon}{f(y)} dy)}\, e^{-\int_0^x \frac{g(y)+f'(y)}{f(y)} dy}$$

- Else,

$$\rho(t,x) = e^{-\int_{X(0;t,x)}^x \frac{g(y)+f'(y)}{f(y)} dy} \rho^{ini}(X(0;t,x))$$

Convergence theorem in the linear case

For $t > \int_0^x \frac{\varepsilon}{f(y)} dy$,

$$\rho^\varepsilon(t,x) = \frac{c_0}{f(0)} \rho_0^{ini} \, e^{-(c_0+\mu_0)\,(t - \int_0^x \frac{\varepsilon}{f(y)} dy)} \, e^{-\int_0^x \frac{g(y)+f'(y)}{f(y)} dy}$$

$\forall x \in (0,1), \forall t \in (0,T)$,

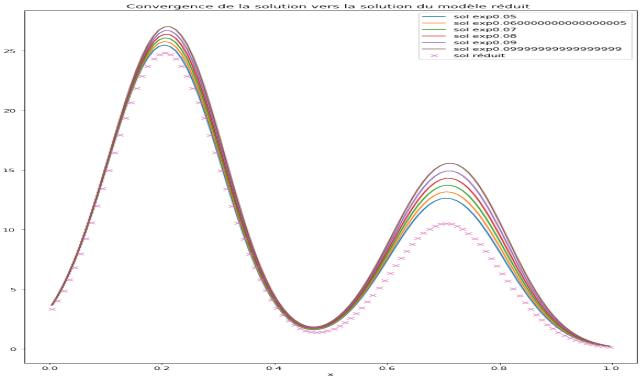
$$\rho^\infty(t,x) = \frac{c_0}{f(0)} \rho_0^{ini} \, e^{-(c_0+\mu_0)\,t} \, e^{-\int_0^x \frac{g(y)+f'(y)}{f(y)} dy}$$

Convergence Theorem

$$\forall \xi > 0, \lim_{\varepsilon \to 0} \sup_{t \in [\xi,T]} \sup_{x \in (0,1)} |\rho^\varepsilon(t,x) - \rho^\infty(t,x)| = 0$$

Numerical illustration of the convergence in the linear case

Convergence of ρ^ε towards ρ^∞ in the linear case :



PDE numerical resolution

Direct Explicit discretization in time/space

$$\rho_i^{n+1} = \rho_i^n - \frac{\Delta t}{\varepsilon \Delta x}(\lambda_{i+1}^n \rho_{i+1}^n - \lambda_i^n \rho_i^n) - \frac{\Delta t}{\varepsilon}\mu_{i+\frac{1}{2}}^n \rho_i^n$$

- Stability condition involving λ and μ.

Change of variables

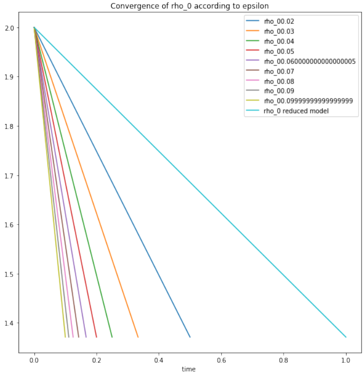
$$\tilde{\rho}(t,x) = e^{\int_0^x \frac{\mu(t_n,y)}{\lambda(t_n,y)}dy}\rho(t,x)$$

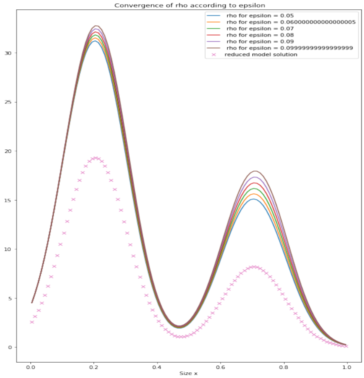
$$\rho_i^{n+1} = \rho_i^n - \frac{\Delta t}{\varepsilon \Delta x}(\lambda_{i+1}^n \rho_{i+1}^n - \lambda_i^n \rho_i^n e^{-\Delta x \frac{\mu_{i+\frac{1}{2}}^n}{\lambda_{i+\frac{1}{2}}^n}dy})$$

- Stability condition only on λ.

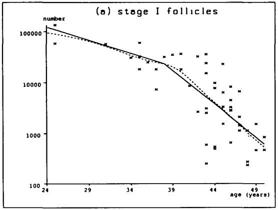
Numerical illustration of the convergence in the nonlinear case

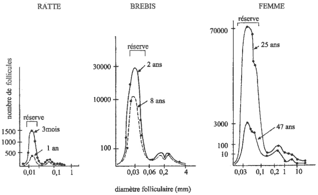
Convergence of $(\rho_0^\varepsilon, \rho^\varepsilon)$ towards $(\rho_0^\infty, \rho^\infty)$:

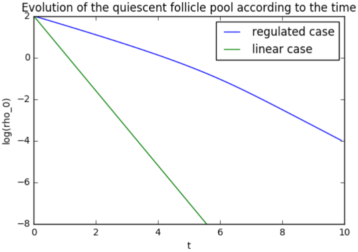


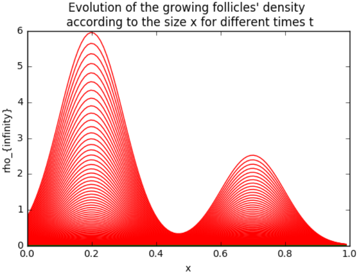


"Qualitative" fit using the reduced Model









Conclusions and perspectives

Conclusions

- Design and simulation of a slow/fast PDE model
- Convergence to a quasi steady-state reduced model
- Qualitative behavior consistent with available data

Work in progress

- Proof of convergence in $\varepsilon \to 0$ in the general case
- Quantitative fitting (parameter estimation)
- Stochastic models to represent small population sizes

Conclusions and perspectives

Conclusions

- Design and simulation of a slow/fast PDE model
- Convergence to a quasi steady-state reduced model
- Qualitative behavior consistent with available data

Work in progress

- Proof of convergence in $\varepsilon \to 0$ in the general case
- Quantitative fitting (parameter estimation)
- Stochastic models to represent small population sizes

Thanks for your attention !