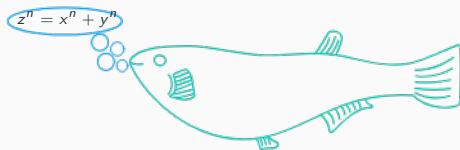


A model of oocyte population dynamics for fish oogenesis

SMAI 2025



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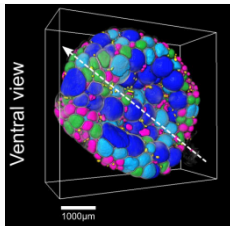
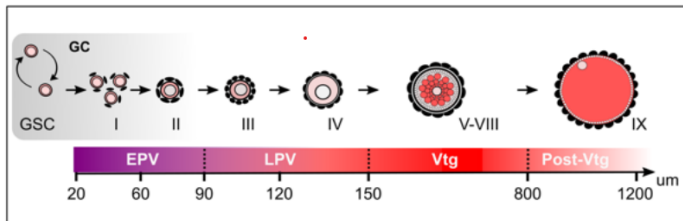


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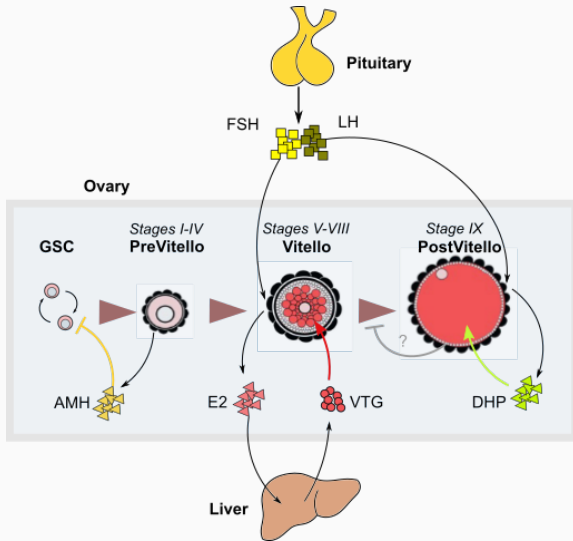
Fish oogenesis : Process which leads to the formation of eggs

Oocyte maturation in ovaries, under hormonal control (LH,FSH, AMH, E2, DHP)



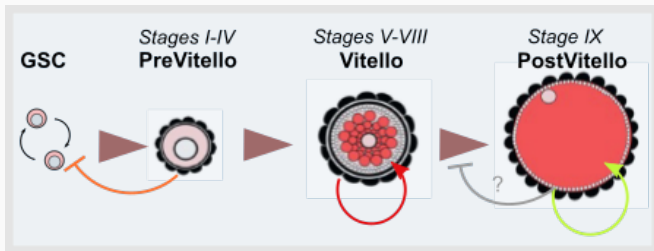
3D reconstruction of an ovary Lesage et al. 2020

Hormonal control - cell interactions



Hormonal control - cell interactions

Under fast hormonal dynamics assumptions, we can do a quasistatic approximation on the hormonal dynamics: cell interactions are considered 'direct' (instantaneous):



Modeling

Quasilinear size structured pop. model

$$\begin{cases} \partial_t \rho(t, x) + \partial_x (\Lambda(P(t), x) \rho(t, x)) = 0, & x \in (0, 1), \quad t \geq 0 \\ \Lambda(P(t), 0) \rho(t, 0) = r(P(t)) \\ \rho(t = 0, x) = \rho_0(x), & x \in (0, 1) \end{cases}$$

with $P(t) = (P_i(t))_{1 \leq i \leq N} \in \mathbb{R}^N$, $P_i(t) = \int_0^1 \omega_i(y) \rho(t, y) dy$

- Growth speed $\Lambda > 0$, $\Lambda \in C^2([0, 1] \times [0, +\infty)^N)$, in particular Λ has a strictly positive minimum on any compact set.
- Recruitment rate $r \geq 0$, $r \in C^2([0, +\infty), [0, +\infty)^N)$, and $r(P) \leq r_0 + \sum_{i=1}^N r_i P_i$
- Size-dependant hormonal expressions: $\forall i, \omega_i \geq 0$, lipschitz continuous on $[0, 1]$

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Well-posedness, long-time behavior (stationary distributions, periodic solution, stability)

Theorem (Existence-Unicity of a global solution)

For each $\rho_0 \in L^\infty(0, 1)$, the problem admits a unique global solution $\rho \in C^0([0, T]; L^1(0, 1)) \cap L^\infty((0, T) \times (0, 1))$, $\forall T > 0$. Furthermore, ρ verifies :

$$\begin{cases} \rho(t, x) = \rho_0(\beta) e^{-\int_0^t \partial_x \Lambda(P(\theta), \xi(\theta)) d\theta}, & \xi_0(t) \leq x \leq 1, 0 \leq t \leq T \\ \rho(t, x) = \frac{r(P(\alpha))}{\Lambda(P(\alpha), 0)} e^{-\int_\alpha^t \partial_x \Lambda(P(\theta), \xi(\theta)) d\theta} & \text{else} \end{cases} \quad (1)$$

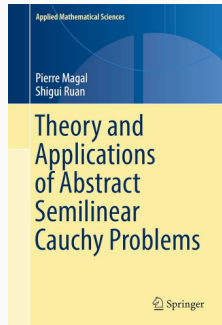
where $\frac{d\xi}{ds}(s; t, x) = \Lambda(P(s), \xi(s; t, x))$, $\xi(t; t, x) = x$,
 $\xi(\theta) := \xi(\theta; t, x)$, $\xi_0(t) := \xi(t; 0, 0)$,
 α and β verify $\xi(\alpha(t, x); t, x) = 0$, $\beta(t, x) = \xi(0; t, x)$

Proof : local well-posedness : characteristics method + Banach fixed point argument applied to the integral equation with respect to P , and by iterating we construct a global solution

Long-time behavior - state of the art

"Strategy" : Stationary densities are linked to an integral equation on P .
Local stability/instability can be determined by linearization.

- Semilinear model $\Lambda = \Lambda(x)$: PLS and Hopf bif. th.
- Quasilinear model with $\Lambda = f(x)g(P)$: PLS and Hopf. bif. th. thanks to a time-rescaling $s = \int_0^t g(P(u))du$
- General Quasilinear model : good hope but not yet established Barril et al. 2022



The study of the stationary model and of the linearized PDE is model specific (depends on the recruitment rate, growth speed, weight functions)

Stationary solutions

Proposition

$\bar{\rho} \in C^1([0, 1], \mathbb{R}_+^*)$ defined by

$$\bar{\rho}(x) = \frac{r(\bar{P})}{\Lambda(\bar{P}, x)} \text{ on } [0, 1]$$

is a stationary solution if, and only if \bar{P} is a fixed point of $F : \mathbb{R}^N \mapsto \mathbb{R}^N$ defined by

$$F(P)_i = \int_0^1 \omega_i(x) \frac{r(P)}{\Lambda(P, x)} dx$$

As a corollary, if $\frac{r}{\Lambda}$ is bounded, then there exists at least one stationary solution (Brouwer's fixed point theorem).

Characteristic equation

Proposition

The spectrum of the operator associated to the linearized PDE is only constituted of eigenvalues, which are the zeros of a characteristic function. When $\Lambda(x, P) = f(x)g(P)$, this function is given by:

$$\Delta(\lambda) := 1 - \nabla b(\bar{P}) \cdot \int_0^1 \frac{\omega(x)}{f(x)} e^{-\lambda \Gamma(x)} dx$$

with $\Gamma(x) := \int_0^x \frac{1}{f(y)} dy$ and $b = \frac{r}{g}$

To determine stability of stationary densities, we have to determine the location of the roots of the characteristic equation in the complex plane.

Local stability

We assume $\Lambda(x, P) = f(x)g(P)$ (separable growth speed)

Proposition

If $\bar{\rho}$ is a steady state, and $\nabla b(\bar{P}) \geq 0$, then :

- $\bar{\rho}$ is locally asymptotically stable if $1 > \int_0^1 \frac{\omega}{f} \cdot \nabla b(\bar{P})$
- $\bar{\rho}$ is unstable if $1 < \int_0^1 \frac{\omega}{f} \cdot \nabla b(\bar{P})$

and transversality conditions of the Hopf bif. th. are never satisfied.

Local stability

We assume $\Lambda(x, P) = f(x)g(P)$ (separable growth speed)

Proposition

If \bar{p} is a steady state, and $\nabla b(\bar{P}) \geq 0$, then :

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Proposition

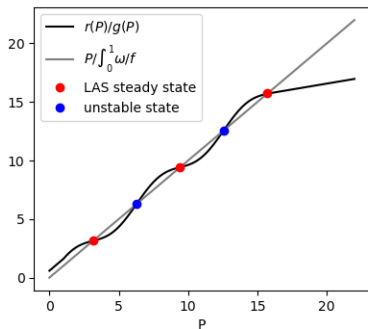
If $\omega(x) \equiv \omega \in \mathbb{R}^N$ is constant, then :

- \bar{p} is locally asymptotically stable if $1 > \int_0^1 \frac{\omega}{f} \cdot \nabla b(\bar{P})$
- \bar{p} is unstable if $1 < \int_0^1 \frac{\omega}{f} \cdot \nabla b(\bar{P})$

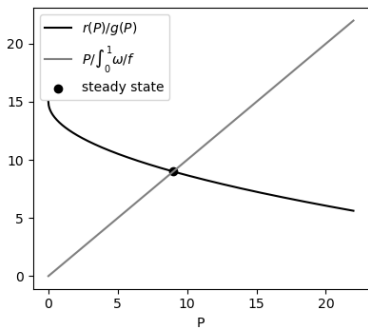
and transversality conditions of the Hopf bif. th. are never satisfied.

Local stability

We assume $P \in \mathbb{R}$ and $b = \frac{r}{g}$ monotonous with respect to P .



b increasing



b decreasing

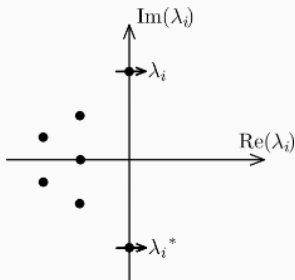
If b is increasing or P is the total mass (ω constant), then local stability is easy to determine. If b is decreasing and ω is not constant, then we have to study the characteristic equation carefully.

Hopf bifurcation

We consider a model parameter c_r , such that $r = r(P, c_r)$.

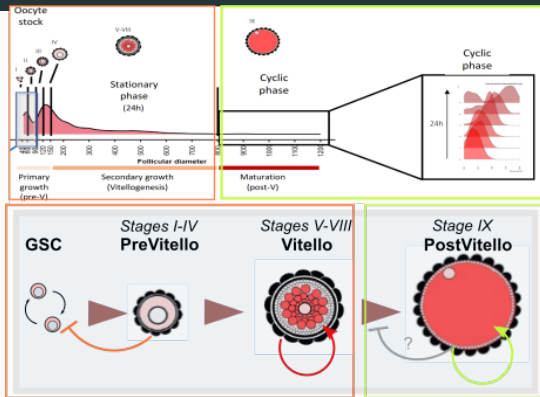
Proposition (Hopf bifurcation (section 6.2. in Magal and Ruan 2018))

If a pair of conjugated simple eigenvalues of the linearized PDE around the stationary density "cross the imaginary axis" in c_r^ , then for $c_r > c_r^*$ close to c_r^* , there exists a periodic density (i.e. $\rho(t + T, \cdot) = \rho(t, \cdot)$).*



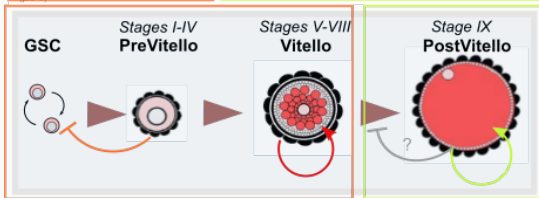
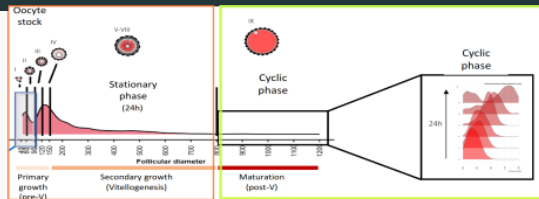
Back to oogenesis

Model behavior



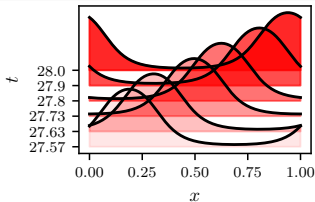
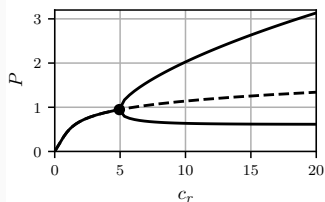
- Unique stationary density (quasilinear model), stability?
- Unique stationary density (quasilinear model with separable growth speed), periodic densities can appear

Model behavior



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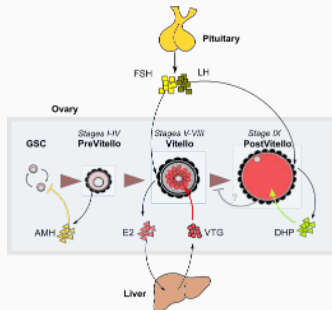
PostV model, bifurcation analysis w.r.t. the basal recruitment rate



Conclusion and perspectives

Study qualitatively a model encompassing **all stages** of oocyte growth and with the whole **hormonal dynamics**.

- Formal long-time behavior analysis following recent works of Barril, Calsina, Diekmann on quasilinear models
- Numerical bifurcation analysis after model reduction (to an ODE system) by pseudospectral approximation (Scarabel, Vermiglio, Breda,...)



Inverse problem

Linear (adult) model identifiability

$$\begin{cases} \partial_t \rho(t, x) + \partial_x (f(x) \rho(t, x)) = 0, x \in (0, 1), t \geq 0 \\ f(0) \rho(t, 0) = r(t) \\ \rho(t=0, x) = \rho_0(x), x \in (0, 1) \end{cases}$$

If we observe for all times:

- S : spawn $S(t) = f(1)\rho(t, 1)$,
- ρ : density
- m : cumulated density $m(t, x) = \int_0^x \rho(t, y) dy$

Then the **linear model is theoretically identifiable**:

- $r(t) = \partial_t m(t, 1) + S(t)$
- $f(x) = \frac{r(t) - \partial_t m(t, x)}{\rho(t, x)} = \frac{\partial_t m(t, 1) + S(t) - \partial_t m(t, x)}{\rho(t, x)}$, $t > 0$ fixed

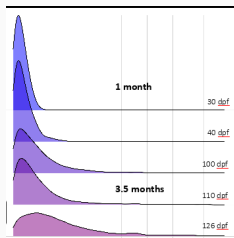
Nonlinear (juvenile) model identifiability

Juvenile fish: only AMH feedback

$$\left\{ \begin{array}{l} \partial_t \rho(t, x) + \partial_x (f(x) \rho(t, x)) = 0, x \in (0, 1), t \geq 0 \\ f(0) \rho(t, 0) = r(P(t)) \\ \rho(t=0, x) = \rho_0(x), x \in (0, 1) \\ P(t) = \int_0^1 \omega_{AMH}(x) \rho(t, x) dx \end{array} \right.$$

If we observe (for all times):

- S : spawn (or outflux)
- m : cumulated density
- ρ : density



Then the **model is theoretically identifiable**:

- $r(P(t)) = \partial_t m(t, 1) + S(t)$
- $f(x) = \frac{r(P(t)) - \partial_t m(t, x)}{\rho(t, x)} = \frac{\partial_t m(t, 1) + S(t) - \partial_t m(t, x)}{\rho(t, x)}, t \text{ fixed}$

$$\begin{cases} \frac{\partial \rho(t,x)}{\partial t} + \frac{\partial}{\partial x} (\Lambda(P(t), x)\rho(t, x)) = 0 \\ \Lambda(P(t), 0)\rho(t, 0) = r(P(t)) \\ P(t) = \int_0^1 \omega(x)\rho(t, x)dx \end{cases}$$

The idea is to rewrite the PDE to avoid the approximation of the integral terms $P(t) = \int_0^1 \omega(x)\rho(t, x)dx$ by quadrature methods:

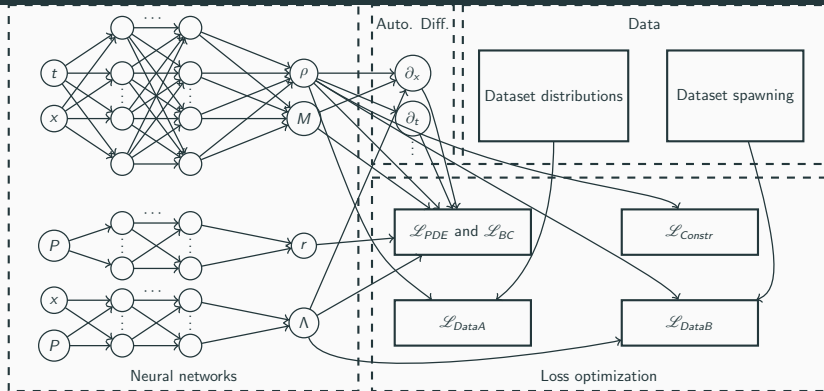
PINN methodology - nonlinear model

$$\begin{cases} \frac{\partial \rho(t,x)}{\partial t} + \frac{\partial}{\partial x} (\Lambda(P(t), x)\rho(t, x)) = 0 \\ \Lambda(P(t), 0)\rho(t, 0) = r(P(t)) \\ P(t) = \int_0^1 \omega(x)\rho(t, x)dx \end{cases}$$

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$$\begin{cases} \frac{\partial \rho(t,x)}{\partial t} + \frac{\partial}{\partial x} (\Lambda(M(t, 1), x)\rho(t, x)) = 0 \\ \Lambda(M(t, 1), 0)\rho(t, 0) = r(M(t, 1)) \\ \partial_x M(t, x) = \omega(x)\rho(t, x) \\ M(t, 0) = 0 \end{cases}$$

PINN methodology - nonlinear model



$$\mathcal{L}_{PDE} = \frac{1}{N_{PDE}} \sum_{i=1}^{N_{PDE}} |\partial_t \rho(t_i, x_i) + \partial_x (\Lambda(M(t_i, 1), x_i) \rho(t_i, x_i))|^2 + |\partial_x M(t_i, x_i) - \omega(x_i) \rho(t_i, x_i)|^2$$

$$\mathcal{L}_{Data} = \frac{1}{N_A} \sum_{i=1}^{N_A} |\rho(t_i, x_i) - \rho_i|^2$$

$$\mathcal{L}_{BC} = \frac{1}{N_B} \sum_{i=1}^{N_B} |\rho(t_i, 0) \Lambda(M(t_i, 1)) - r(M(t_i, 1))|^2 + |M(t_i, 0)|^2$$

Linear BINN on synthetic data

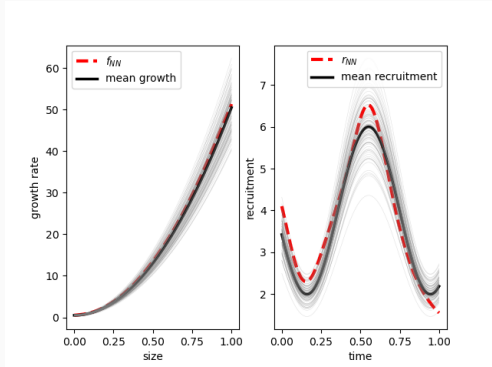
We generate data at the same time points as the experimental data, with individual-dependant growth rate and recruitment rate : Individual i :

$$f_i(x) = \alpha_i^f(1 + 50x^2) + \epsilon_i^f \text{ with } \alpha_i^f \sim \mathcal{N}(1, \sigma), \epsilon_i^f \sim \mathcal{N}(0, \sigma) \text{ and}$$
$$r_i(t) = \alpha_i^r(2 + \sin(8(t + 2))) + \epsilon_i^r \text{ with } \alpha_i^r \sim \mathcal{N}(1, \sigma), \epsilon_i^r \sim \mathcal{N}(0, \sigma)$$

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Mean synthetic growth rate and recruitment rate vs BINN prediction,

$$\sigma = 0.1$$

Fit the model on true data to investigate the recruitment dynamics (linear model) and feedback mechanisms (nonlinear model):

- *AMH* feedback with juveniles data
- *E2 – VTG* feedback loop with data of fish exposed to endocrine disruptors
- *DHP* feedback with spawning cycle data