Coupling physiologically-based kinetic models of endocrine axes with structured cell population dynamics models: an integrative approach of reproductive toxicity

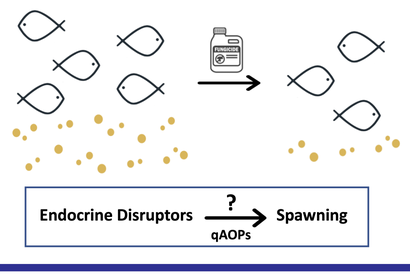
Rémy Beaudouin[1], Frédérique Clément[2], Louis Fostier[2,3,a], Tu-Ky Ly[1,b], Violette Thermes[4], Chiara Villa[2,c], Romain Yvinec[2,3]

[1]Unité INERIS METO, Verneuil-en-Halatte [2]EPC MUSCA, Centre Inria de Saclay [3]Unité UMR PRC, Centre INRAE Val-de-Loire [3]LPGP, Centre INRAE de Rennes

[a]louis.fostier@inria.fr (M2) [b]Tu-ky.LY@ineris.fr (M1) [c]chiara.villa@inria.fr (M3)

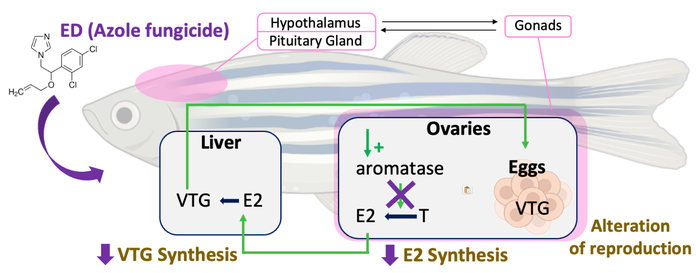
Context and motivation: regulating endocrine disruptors via quantitative Adverse Outcome Pathways

The impact of micropollutants on living organisms is a major concern for health and the environment.
Endocrine disruptors (EDs), found in many everyday products (e.g. fungicides), interfere with physiological endocrine levels and can alter major biological functions, such as the reproductive function. Fish are species of interest in toxicology, because their aquatic living environment and their physiology make them particularly sensitive to pollutants.

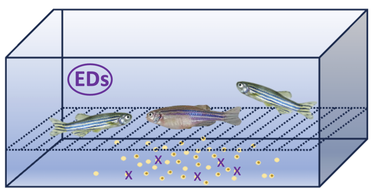


Chemical risk assessment is needed to guide regulations on ED-containing products. One must: (i) characterise the ED mode of action, (ii) prove adverse effects at levels of biological organisation relevant for hazard assessment, (iii) establish cause-and-effect relationship between the mode of action and the adverse effects.
This can be achieved via mathematical/computational models, known as **quantitative Adverse Outcome Pathways (qAOPs)**.

M1: an ODE-based model of endocrine axes



In [1,2] we develop a qAOP linking external exposure and internal ED levels in key organs of adult female zebrafish, allowing for mechanistic predictions of their detrimental effects on the Hypothalamus-Pituitary-Gonadal axis, central to endocrine regulation of the reproductive function.



Data collected:

Endocrine endpoints (E2, VTG, etc) and ED levels in key organs, egg count and size, under ED exposure and in control conditions. [Enriched with data from the literature]

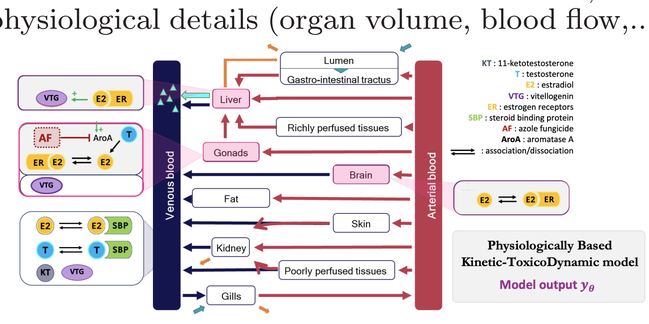
Key dynamics and the ODE model [1]

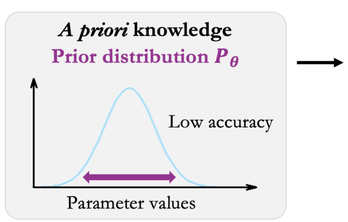
Key dynamics:
- ▷ EDs: azole fungicides (imazalil, prochloraz) inhibit expression of aromatase, enzyme responsible for **estradiol (E2)** synthesis in the gonads.
- ▷ E2 promotes synthesis of **vitellogenin (VTG)**, the precursor egg yolk lipoprotein, in the liver.

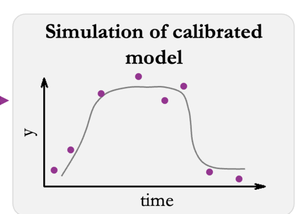
ODE model: The quantity $P_{i,c}(t)$ of compound i (e.g. hormone, ED) in body compartment c (e.g. liver, gonads) satisfies an ODE in the form

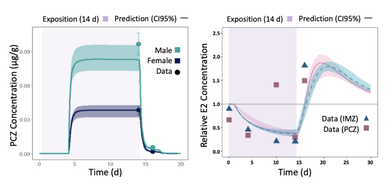
$$\dot{P}_{i,c} = \underbrace{F^{In}_{i,c}\left(P_{i,:}\right) - F^{Out}_{i,c} P_{i,c}}_{Influx/outflux} + \underbrace{D_{i,c}\left(P_{:,c}\right)}_{Dynamics}, \quad (1)$$

$D_{i,c}$ modelling synthesis, clearance, ..., $F^{In/Out}_{i,c}$ physiological details (organ volume, blood flow,...).







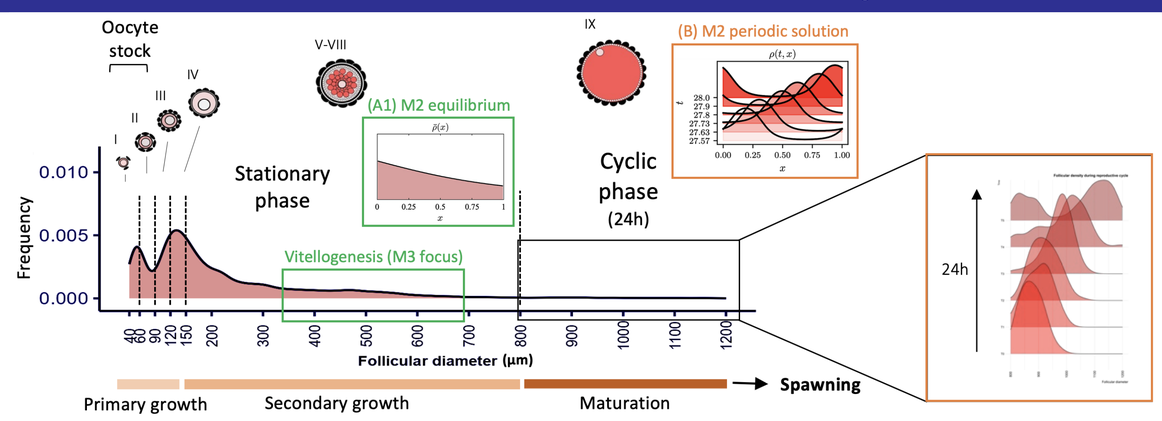


Methods:
- ▷ Priors: truncated normal distribution
- ▷ Data: log-normal distribution
- ▷ Markov Chain Monte Carlo

[1] Ly, Chadili, Palluel, Le Menach, Budzinski, Tebby, Hinfray and Beaudouin. *PBK-TD modelling of the gonadotropic axis: Case study with two azole fungicides in female zebrafish.* Aquatic Toxicology, 283, p.107337, 2025.

[2] Ly, De Oliveira, Chadili, Le Menach, Budzinski, James, Hinfray, Beaudouin. *Imazalil and prochloraz toxicokinetics in fish probed by a physiologically based kinetic (PBK) model.* Environmental Science and Pollution Research, 31(40), 52758–52773, 2024. →

M2: a size-structured PDE model of oocyte maturation



Hormone levels → Oocyte maturation → Spawning

Spawning events (frequency, egg number and size) result from the maturation of oocytes (female germ cells), which is tightly regulated by hormones (e.g. E2) at different maturation stages.

Observations from data:
Size-dependent oocyte density distributions obtained in medaka [3] reveal different dynamics at different stages of the maturation process.

The PDE model and key analytical results [4]

Let the density $\rho(t,x) \geq 0$ of oocytes at time t and of size x satisfy

$$\begin{cases} \partial_t \rho(t,x) + \partial_x \left(\Lambda(P(t),x)\,\rho(t,x)\right) = 0, \quad x \in (0,1), \quad t > 0 \\ \Lambda(P(t),0)\,\rho(t,0) = r(P(t)), \quad t > 0 \\ \rho(0,x) = \rho_0(x), \quad x \in (0,1) \end{cases} \quad (2)$$

with growth rate Λ, recruitment rate r and interaction terms (hormones)

$$P(t) = (P_i(t))_{1 \leq i \leq N} \in \mathbb{R}^N, \quad P_i(t) = \int_0^1 \omega_i(x)\rho(t,x)\,\mathrm{d}x. \quad (3)$$

- Existence and uniqueness of globally bounded weak solutions [Characteristics method + Banach fixed point Theorem].
- Stationary solutions are defined by $\bar{\rho}(x) = \frac{r(\bar{P})}{\Lambda(\bar{P},x)} \in C^1([0,1],\mathbb{R}_+)$ iff $\bar{P}$ is a fixed point of $F : \mathbb{R}^N \mapsto \mathbb{R}^N$ defined by $F_i(P) = \int_0^1 \omega_i(x)\frac{r(P)}{\Lambda(P,x)}\mathrm{d}x$.
- For $\Lambda(P,x) = f(x)g(P)$, let $b := \frac{r}{g}$ and $\mathcal{T} := \int_0^1 \frac{\omega}{f}\mathrm{d}x$. Then:

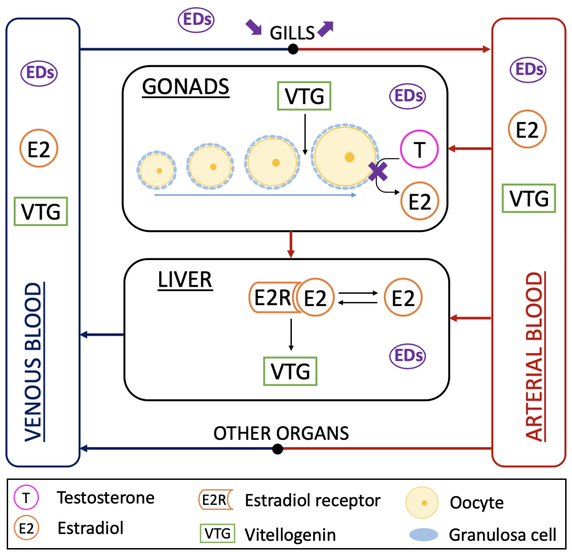
(A1) If $\nabla b(\bar{P}) \geq 0$ and $\mathcal{T} \cdot \nabla b(\bar{P}) < 1$, $\bar{\rho}$ is locally asymptotically stable;
(A2) If $\nabla b(\bar{P}) \geq 0$ and $\mathcal{T} \cdot \nabla b(\bar{P}) > 1$, $\bar{\rho}$ is unstable;
(B) If $\nabla b(\bar{P}) < 0$, we may observe a periodic solution (Hopf bifurcation);
[Implicit time scaling, local linearisation, Hopf bifurcation Theorem].

*The model reproduces the **stationary (stable equilibrium)** **and** the **cyclic phase (Hopf bifurcation)** of oocyte size distributions. The behaviour is **modulated by the environmental feedback (nonlocal interaction term)** of hormone levels.*

[3] Lesage, Thomas, Pécot, Ly, Hinfray, Beaudouin, Neumann, LovellBadge, Bugeon, Thermes. *An end-to-end pipeline based on open source deep learning tools for reliable analysis of complex 3D images of ovaries.* Development, 150(7), dev201185, 2023.

[4] Clément, Fostier, Yvinec. *Well-posedness and bifurcation analysis of a size-structured population model : Application to female gametes dynamics.* Accepted at SIAM Journal on Applied Dynamical Systems, in print, 2024. →

M3: Coupling models M1 and M2



This work (M2-M3) is part of the OVOPAUSE project (ANR-22-CE45-0017)

Endocrine Disruptors —M1→ Hormone levels —M2→ Oocyte maturation → Spawning

Coupling models in the vitellogenic phase

During the **vitellogenic phase** of oocyte maturation, growth is mostly driven by VTG accumulation. We couple the models via the interaction term (3):

- the oocyte growth rate in (2) depends on levels of VTG in the gonads ($P_{V,g}$)

$$\Lambda(P_{V,g}(t),x) := \lambda_V \left[\frac{d(x)}{d_M}\right]^2 \frac{P_{V,g}(t)}{K_V + P_{V,g}(t)} + \lambda_B, \quad d(x) = d_m + x(d_M - d_m),$$

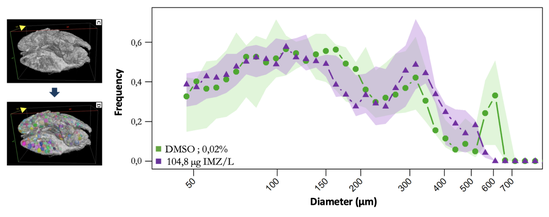
with VTG absorption proportional to the oocyte's surface ($d(x)$: diameter); then in (1) we have $D_{V,g} := -\eta_V \int_0^1 \left[\Lambda(P_{V,g}(t),x) - \lambda_B\right]\rho(t,x)\mathrm{d}x$;

- Synthesis of E2 in the gonads ($P_{E,g}$) in (1) is mediated by aromatase (a)

$$D_{E,g} := \eta_E \int_0^1 a(x)\frac{P_{T,g}}{K_T + P_{T,g}}\rho(t,x)\mathrm{d}x, \quad a(x) \propto \exp\left[-\left(\frac{x - x_M}{\sigma_a}\right)^2\right],$$

knowing that aromatase expression $a(x)$ correlates with oocyte size.

Next steps and challenges:
- ▷ Extending analysis of M2 to M3;
- ▷ Calibrating M3 with data from [1-3], including oocyte size distributions.



oVoTox

This work is part of the project 23FC3R-009 (OvoTox), with the financial support of GIS FC3R on funds managed by Inserm.