Cemracs 2018 Research project - Multiscale population dynamics : interactions between scales in developmental and reproductive biology

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In the field of mathematical biology, the modeling of morphogenesis processes with successive maturation stages (such as neurogenesis, hematopoiesis ...) generally involves structured population models. In such models, individuals are sorted according to a structuring variable according to their phenotype (e.g. maturity), and the whole population evolves through birth and death processes.
This project focuses on the multiscale modeling of the whole process of ovarian follicular development, a complex and tightly regulated developmental and reproductive process characterized by well documented anatomical and functional stages (Figure 1).
Our starting point will be former, rather descriptive approaches providing a description of the number of ovarian follicles in different maturation stages (see e.g. [2, 3, 1, 4]). These studies are quite well suited to fitting experimental follicle counts, yet they have disregarded the intrinsic nonlinear nature of the mechanisms underlying follicular development. We intend to enrich these approaches, in order to take into account the new knowledge available on follicle development and its control by growth factors and hormones.
The objective of this project is to develop relevant formalisms for structured populations, in order to study the influence of nonlinear and nonlocal regulations on the populations of ovarian follicules all along the reproductive life.
We will design a nonlinear structured population model as a nonconservative transport partial differential equation with nonlocal interactions entering the boundary condition, the transport velocity, and the death term :

$$
(1)\qquad \begin{aligned}
\frac{\partial \rho(t,x)}{\partial t} + \frac{\partial \left(\lambda(t,x)\rho(t,x)\right)}{\partial x} &= -\mu(t,x)\rho(t,x)\,, t>0, 0<x<1\,,\\
\lim_{x\to 0}\left(\lambda(t,x)\rho(t,x)\right) &= \lambda_0(t)\rho_0(t)\,,\\
\lim_{x\to 1}\left(\lambda(t,x)\rho(t,x)\right) &= 0\,,\\
\frac{d\rho_0(t)}{dt} &= -\lambda_0(t)\rho_0(t)\,.
\end{aligned}
$$

In Eq. (1), ρ represents a time-dependent density of follicle population, structured by a maturity variable. $x \in \mathbb{R}^+$, and ρ_0 represents the number of primordial follicles. The initiation process is modeled by the boundary condition at $x = 0$, which simultaneously decreases the pool of quiescent primordial follicles at speed λ_0. The maturity process goes on at speed $\lambda(.,x)$ for a maturity level $x \in (0,1)$. All along their development, follicles are subject to degeneration at rate μ. Ovulatory follicles leave the system thanks to the Dirichlet boundary condition at $x = 1$.
The initiation, maturation and degeneration functions are maturity and population-dependent feedback terms, taking into the interactions between follicles. We assume that the feedback functions are given by weighted moments, for instance

$$
(2)\qquad \lambda_0(t) = \frac{c_0}{K_0 + \int_0^\infty w_0(x)\rho(t,x)}\,,\quad \lambda(t,x) = \frac{f(x)}{K_1 + \int_0^\infty w_1(x)\rho(t,x)}\,.
$$

The final stages of maturation (x close to 1) are embedded within the endocrine dynamics of ovarian cycles (with a few weeks periodicity), yet we will not considered the control of the ovarian cycle in our model.

The work will first consist in studying the well-posedness of the model and developing efficient numerical schemes dealing accurately with the specific boundary condition. Then, the long-time convergence will be investigated with the aim to assess the convergence speed (rate of exhaustion of the follicle pool) as well as the limit distribution profile (existence of an auto-similar distribution). The model outputs (follicle numbers and distribution, transit times between developmental stages) will be confronted to experimental data to calibrate the model parameters and test functional hypotheses. A specific focus will be put on predicting the number of follicles targetable by therapeutic treatments (assessment of the ovarian reserve size [5]).

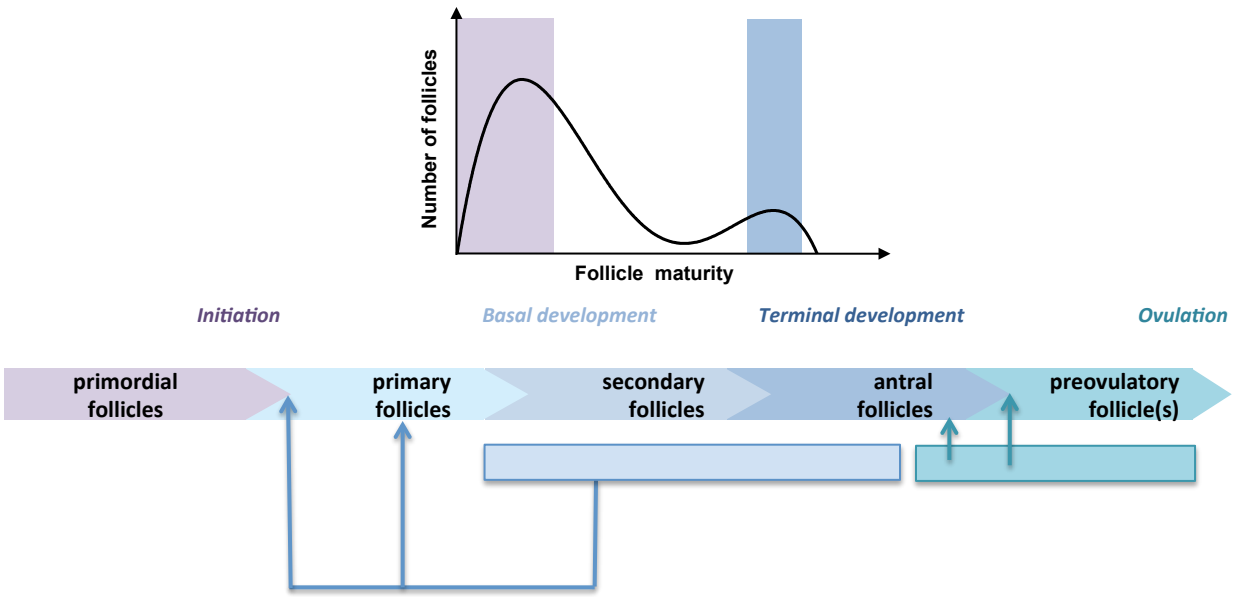

FIGURE 1. Schematic view on the main stages of follicular development. *Bottom panel. Ovarian folliculogenesis is a unique instance of development still occurring during adulthood. Follicles are spheroidal structures sheltering the oocyte (female germ cell). Their development spans several months, starting from the time when primordial follicles leave the quiescent pool and initiate a process of growth and functional maturation ending up either by ovulation (release of a fertilizable oocyte), or (in most of the cases) degeneration at any stage of development. After initiation, follicular development can be separated into two distinct periods, even if it is a continuous process. During basal development, the morphological structure of the follicle settles progressively as an antral follicle (spheroidal structure with a central cavity). The early stages are subject to local ovarian controls, emanating from the inhibition exerted by some growing follicles (blue bar) on earlier stages (blue arrows). The latest stages are subject to (neuro-)endocrine controls, amounting to competition between follicles with close maturation stages (green bar and arrows). Top panel. The initiation leads to the progression exhaustion of the pool of quiescent follicles (which takes tens of years in the human species), yet the distribution of follicles into maturation stages remains similar during a whole of the reproductive life.)*

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