2019-01617 - Doctorant F/H Stochastic multiscale modeling in developmental and reproductive biology

Type de contrat : CDD de la fonction publique
Niveau de diplôme exigé : Bac + 5 ou équivalent
Fonction : Doctorant

A propos du centre ou de la direction fonctionnelle

Located at the heart of the main national research and higher education cluster, member of the Université Paris Saclay, a major actor in the French Investments for the Future Programme (Idex, LabEx, IRT, Equipex) and partner of the main establishments present on the plateau, the centre is particularly active in three major areas: data and knowledge; safety, security and reliability; modelling, simulation and optimisation (with priority given to energy).

The 450 researchers and engineers from Inria and its partners who work in the research centre's 28 teams, the 60 research support staff members, the high-level equipment at their disposal (image walls, high-performance computing clusters, sensor networks), and the privileged relationships with prestigious industrial partners, all make Inria Saclay Ile-de-France a key research centre in the local landscape and one that is oriented towards Europe and the world.

Contexte et atouts du poste

The modeling of morphogenesis processes with successive maturation stages generally involves structured population models. Individuals are sorted according to a phenotypic structuring variable (e.g. maturity), and the whole population evolves through birth and death processes. This project focuses on the multiscale model of the whole process of ovarian follicle development, a complex and tightly regulated, long-lasting developmental and reproductive process characterized by well documented anatomical and functional stages. We have recently developed a multiscale model based on Continuous-time Markov Chains (CTMC) in order to study the influence of nonlinear and nonlocal regulations on the populations of ovarian follicles all along the reproductive life. The model monitors both the progressive exhaustion of an initially huge reserve of quiescent follicles, and the repartition of the growing follicles into different maturity stages. Such a repartition is shaped by both the asynchronous activation of quiescent follicles and hormonally-mediated interactions between follicles. Up to now, we have mainly dealt with the population feedback exerted onto the activation rate, while the growth rate in early growing follicles is also subject to other follicles' feedback, and the ultimate selection of terminally developing follicles results from a competition-like process culminating in ovulation. The main objective of the PhD work is both to pursue the theoretical, numerical and statistical analysis recently performed on the CTMC model, and to extend the modeling framework to refine the description of ovarian folliculogenesis. The PhD results will help get insight into the physiological control of the ovarian reserve, and the very low ratio of ovulating follicles (one-in-a-thousand amongst the quiescent follicles), which is of major interest for the management of the reproductive resources, whether in a clinical, breeding or biodiversity context.

1 Bonnet, C. et al. Multiscale population dynamics : interactions between scales in developmental and reproductive biology. hal-02075253

Phd School : EDMH

Mission confiée

The CTMC model accounts for finite population behavior, and is characterized by two distinct timescales, which leads to a nontrivial singular perturbation problem. We have been able to prove, in the linear case and a specific weakly-nonlinear case, that the whole follicle population can be efficiently described by a reduced stochastic model (i.e. in the limit of the singular parameter, epsilon=0), which captures the slow exhaustion of the reserve and the fast quasi steady-state of the maturity repartition. The first objective of the PhD is to obtain rigorous results on the link between the original and reduced model, using the formalism of stochastic multiscale analysis (limit theorem, averaging, singular perturbation). We will also investigate the behavior of the stochastic model in a large population limit, which leads to deterministic structured population models, also studied in 1. Additionally, we will assess the (stochastic) decay rate of the reserve, as well as stopping times corresponding to reaching critical developmental steps. The second objective of the PhD is to enrich and extend the initial model. We will refine the description of the final maturity stages to account for the (neuro-)endocrine control exerted onto the ovulation process, and witnessed by the dynamics of ovarian cycles, which span over a much shorter time horizon than the whole folliculogenesis. Such an extension will require considering one more timescale, hence dealing with a multiple timescale problem, and will result in a cyclic behavior. The introduction of the fastest timescale will thus lead to quasi-limit cycle dynamics, that will in turn impact the slower growth of intermediate follicles. To assess the initial size of the follicle reserve, we will also get interested in the reserve formation during the embryonic life, involving the recruitment of somatic (follicular) cells by the germ cells. We will design a complementary CTMC model representing the lineage of germ cells from the beginning of their commitment up to the differentiated germ cell, the oocyte enclosed in a follicle. In this model, cell events will be characterized by the type of mitotic divisions (symmetric or asymmetric, renewing or proliferating) and the number of division rounds undergone by progenitor cells before their final commitment to meiosis, the germ cell-specific division, possibly accompanied by cell death. We will assess, analytically when tractable, or numerically otherwise, the size of the final oocyte pool, and the (dynamic) repartition between progenitor cell types.
Principales activités
Finally, the different models analyzed and developed during the PhD will be qualitatively and quantitatively compared to experimental data in several vertebrate species, in a comparative physiology framework.

Compétences
A general background in applied mathematics is required, including solid notions in the analysis and simulation of stochastic processes. Competences in mathematical biology in general, and population dynamics in particular, would be appreciated.

Avantages
- Subsidized meals
- Partial reimbursement of public transport costs
- Leave: 7 weeks of annual leave + 10 extra days off due to RTT (statutory reduction in working hours) + possibility of exceptional leave (sick children, moving home, etc.)
- Possibility of teleworking (after 6 months of employment) and flexible organization of working hours
- Professional equipment available (videoconferencing, loan of computer equipment, etc.)
- Social, cultural and sports events and activities
- Access to vocational training
- Social security coverage

Rémunération
Monthly gross salary (1st and 2nd year) : 1.982 euros, (3rd year) : 2.085 euros

Informations générales
- **Thème/Domaine** : Modélisation et commande pour le vivant
  Calcul Scientifique (BAP E)
- **Ville** : PALAISEAU
- **Centre Inria** : CRI Saclay - Île-de-France
- **Date de prise de fonction souhaitée** : 2019-10-01
- **Durée de contrat** : 3 ans
- **Date limite pour postuler** : 2019-05-11

Contacts
- **Equipe Inria** : M3DISIM
- **Directeur de thèse** :
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A propos d’Inria
Inria, l’institut national de recherche dédié aux sciences du numérique, promeut l’excellence scientifique et le transfert pour avoir le plus grand impact. Il emploie 2400 personnes. Ses 200 équipes-projets agiles, en général communes avec des partenaires académiques, impliquent plus de 3000 scientifiques pour relever les défis des sciences informatiques et mathématiques, souvent à l’interface d’autres disciplines. Inria travaille avec de nombreuses entreprises et a accompagné la création de plus de 160 start-up. L'institut s'efforce ainsi de répondre aux enjeux de la transformation numérique de la science, de la société et de l’économie.

Consignes pour postuler
- **Sécurité défense** :
  Ce poste est susceptible d’être affecté dans une zone à régime restrictif (ZRR), telle que définie dans le décret n°2011-1425 relatif à la protection du potentiel scientifique et technique de la nation (PPST). L’autorisation d’accès à une zone est délivrée par le chef d’établissement, après avis ministériel favorable, tel que défini dans l’arrêté du 03 juillet 2012, relatif à la PPST. Un avis ministériel défavorable pour un poste affecté dans une ZRR aurait pour conséquence l’annulation du recrutement.

- **Politique de recrutement** :
  Dans le cadre de sa politique diversité, tous les postes Inria sont accessibles aux personnes en situation de handicap.

  **Attention** : Les candidatures doivent être déposées en ligne sur le site Inria. Le traitement des candidatures adressées par d'autres canaux n'est pas garanti.