Building a model of the Hypothalamic-Pituitary-Gonadal (HPG) axis

Supervisory team:
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Project description:
Gonadotropin-releasing hormone (GnRH) is secreted from hypothalamic neurones to control secretion of the gonadotropin hormones LH and FSH form the anterior pituitary, and thereby mediates central control of reproduction. It secretion is pulses and its effects are dependent on pulse characteristics (particularly pulse frequency). One of the most important recent discoveries in the field of reproduction is that of the KNDy system. This is a peptidergic neuronal oscillator th at drives pulsatile GnRH secretion. It also mediates feedback effects of gonadal steroid hormones that are essential for key reproductive processes such as the timing of puberty and seasonal breeding (i.e. in farm animals) and the fine-tuning of gonadotropin secretion across the ovarian cycle. All of these components (hypothalamic pulse generator/pituitary pulse decoder/gonads) are absolutely essential for human reproduction so it is perhaps not surprising that all three are sites for therapeutic intervention, just as perturbation of any of them can cause infertility in disease states. We are convinced that mathematical and statistical approaches are required to fully understand such a complex system. To this end we have already generated a sophisticated mathematical model of the neuronal oscillator that we have trained on wet-lab. data and are now using to explore possible mechanisms for modulation by gonadal steroids. Similarly, we have developed a mathematical model for the decoding of pulse dynamics by pituitary gonadotropes and have used this to explore cell-cell variability in responses to GnRH and its impact on information transfer. We now plan to take a similar approach to modelling effects of gonadotropin hormones on gonadal function, where we will have to introduce population dynamics as an additional feature (i.e. growth of granulosa cells before ovulation and formation of luteal cells thereafter). We then plan to simplify these sub-system models so that the components can be assembled into a meaningful model of the entire hypothalamo-pituitary-gonadal system.

In this project the student will learn:

- Mathematical modelling of the hypothalamic pulse generator, the pituitary pulse decoder and the effects of LH and FSH on gonadal cells.
- Numerical optimisation by performing parameter fitting and sensitivity analysis using combination of available experimental data sets to parametrise and validate model components.
- Simplification of the sub-system models (as informed by sensitivity analysis) and again, training on system wet-lab data.
- Computational methods that allow the generation of testable model predictions regarding the reproductive system and its components across the lifespan.