Mathematical secrets of the female cycle

Susanna Röblitz and Peter Deuflhard

A detailed understanding of the human menstrual cycle is both medically and economically important. In close funded cooperation over years with the pharmaceutical company Pfizer the mathematical model GynCycle [1] has been developed as a basis to study the administration of drugs. Three main steps had to be taken: (I) from a physiological model to a compartment model, (II) from the compartment model to a differential equation model, (III) identification of unknown parameters from comparison with measurements.

Step (I) means the establishment of the governing regulatory circuit. Figure 1 shows the compartments hypothalamus, pituitary gland, and ovaries, connected by the bloodstream. In the hypothalamus, the hormone GnRH (gonadotropin-releasing hormone) is formed, which reaches the pituitary gland through a portal system in the form of pulses and stimulates the release of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone) into the bloodstream. The gonadotropins regulate the processes in the ovaries, i.e., the multi-stage maturation process of the follicles, the ovulation and the development of the corpus luteum, which control the synthesis of the steroids progesterone and estradiol and of the hormone inhibin. Through the blood, these hormones reach the hypothalamus and pituitary gland, where, in turn, they influence the formation of GnRH, LH and FSH.

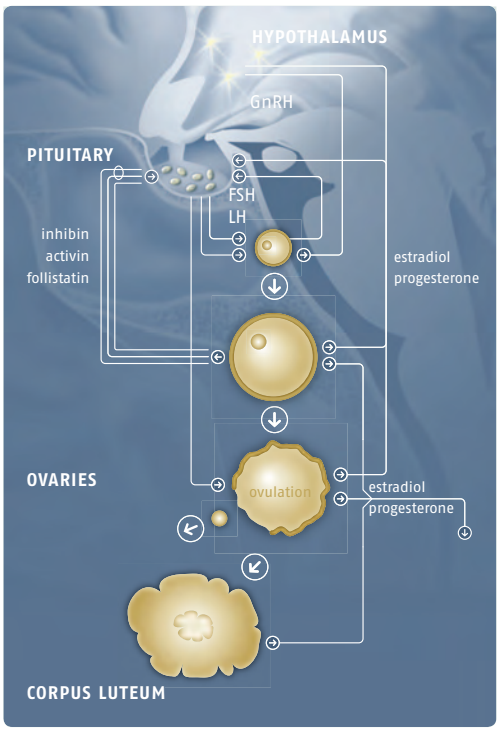

Figure 1. *Physiological compartments of the human menstrual cycle*

Step (II) comprises the mathematical description of the physiological processes by means of ordinary differential equations (ODEs) that describe the time dependent behavior of the species concentrations involved. In order to be able to formulate the ODEs, the occurring physiological and biological processes must be known quite accurately. In reality, however, the exact chemical reaction mechanisms are often not understood in sufficient detail; rather one only knows whether certain hormones exert either a stimulating or an inhibiting effect on other hormones – here modeled by Hill functions. If the reaction mechanisms are known more specifically, e.g., from a database, more detailed equations can be formulated. Once all processes are included in the model, a large system of ODEs arises.

Step (III), the identification of unknown parameters occurring in the models, is still mathematically challenging. Only few of them can be measured or associated with approximate ranges of values. The aim is to identify interpretable parameter values, so that not only the modeled concentration curves match measured data, but also predictions can be made beyond the domain covered by given measurements. Subtle mathematical techniques are needed to measure the quality of these approximations; we used sophisticated affine covariant Gauss-Newton methods. For other researchers in systems biology, we

developed the public domain software package BioPARKIN.

Our model GynCycle [1] describes the idealized cycle of an idealized woman. The model consists of 33 ODEs and generates periodic solutions with a mean period of 28 days. From the 114 unknown parameters, 24 could be determined from blood measurement values of LH, FSH, E2, and P4 for healthy women (Pfizer study). In addition, data from the additional administration of GnRH analogues were used, increasing the number of identifiable parameters to 63. There exist two types of analogues: GnRH "agonists" act like natural GnRH, whereas GnRH "antagonists" block the action of natural GnRH. Both are used to either delay or enhance the cycle, thereby regulating the time-point of ovulation. GnRH analogues are applied in reproductive medicine as well as in the treatment of diseases that go along with endocrine disorders like cancer, endometriosis, or PCOS (polycyclic ovarian syndrome).

Crucial for the drug efficiency are time-point, dosage, and duration of medication. Figure 2 shows the long-time administration of a GnRH agonist suppressing ovulation for three months. This simulation result agrees with clinical observations. Such dosage recommendations, however, apply to "average" patients. In order to determine a therapy for real patients, individual models would be necessary. For such models, data over at least two cycles would need to be collected, a setting that can only be realized within hospital care. Together with medical doctors, biologists, and computer scientists from different European countries, we will continue our work within an EU funded project on patient-specific models and treatment strategies for infertility-related endocrinological diseases.

Further reading

[1] S. Röblitz, C. Stötzel, P. Deuflhard, H. Jones, D.-O. Azulay, P. van der Graaf, and S. Martin. A mathematical model of the human menstrual cycle for the administration of GnRH analogues. *J. Theoretical Biology*, 321:8–27, 2013.

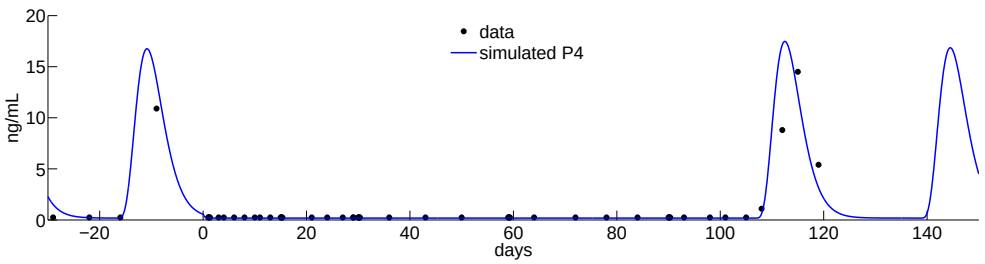

Figure 2. *Long-time administration of the GnRH agonist Nafarelin suppresses ovulation for several months, indicated here by the absence of corpus luteum producing progesterone (P4)*