Discrete-continuous Mathematical Modeling of Endocrine Systems with Pulsatile Secretion *

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This talk presents an overview of recent developments in system-level mathematical modeling of endocrine systems with pulsatile secretion by pulse-modulated feedback. An application to modeling of non-basal testosterone regulation is provided. Techniques for parameter estimation of the pulse-modulated mathematical model are discussed.

Hormone secretion is performed by endocrine glands directly into the blood stream in continuous (basal) or pulsatile (non-basal) manner. Interacting via blood, endocrine glands build up dynamical control loops characterized by self-sustained oscillations in the concentrations of the involved hormones. This process of "continuous dynamic equilibration" is also referred to as homeostasis and is believed to constitute the basis of the biological self-regulation, [1].

a) Smith models of endocrine regulation: Oscillations in biological feedback systems arise for a broad range of system parameters which property is not always captured by mathematical models whose behavior depends considerably on the exact parameter values, [2]. With respect to endocrine regulation, mostly feedback nonlinearities and time delays were employed for achieving sustained periodical solutions in mathematical models. The trivial solution of the classical delayed-feedback Smith model of testosterone regulation [3] is proven to be asymptotically stable [4], under mild assumptions on the nonlinearity. However, under piecewise linear (affine) nonlinearities in the feedback path of the Smith model, complex dynamical phenomena such as multiple periodical orbits and chaos arise in the system in some subspaces of the parameter space, [5], [6]. Significant parameter sensitivity of the periodical solutions with respect to e.g. hormone kinetics and the time-delay values is though observed. Taking into account the principle importance of sustained oscillations in endocrine systems, the existence of asymptotically stable solutions in a mathematical model of hormone regulation is not biologically feasible.

b) Pulse-modulated Smith models: The concept of amplitude and frequency pulse-modulated feedback appears naturally in pulsatile hormone regulation. The rationale is summarized e.g. in [7] : "Pulse-modulated feedback allows greater control, is more robust to degradation, and is generally more energy-efficient. Moreover, pulsatile signals enable, in principle, to communicate information to the target cell in pulse amplitude, pulse duration, pulse shape and inter-pulse interval. Quiescent inter-pulse intervals are biologically essential to allow target receptor recovery."

A parsimonious mathematical model describing pulsatile endocrine regulation and lending itself to mathematical analysis is suggested in [8] and studied in detail in [9]. It is hybrid in nature and can be seen as a generalization of the Smith model with the nonlinear static feedback exchanged for a combined frequency and amplitude modulator. The model does not, by design, have any equilibria and always possesses a 1-cycle, i.e. a periodic solution with one modulated pulse in the least period. It is also shown to exhibit complex nonlinear dynamics such as cycles of higher periodicity and chaos [10].

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Recently, the analysis of the pulse-modulated Smith model has been extended to the case of delayed feedback [11]. A somewhat surprising result is that the introduction of time delay in the continuous part of the pulse-modulated system does not significantly change the dynamics of the closed-loop system. Furthermore, in many cases, a time delay simplifies the signal shape of the periodic solutions, reducing orbits (n-cycles) of high order to orbits of lower order.

c) Parameter estimation: Specialized methods for parameter estimation in the pulse-modulated model of endocrine regulation have been developed. One of them, [12], is based on the mathematical machinery of constrained nonlinear least-squares minimization and tailored to address the issue of under-sampled data. Typically, a hormone data set for the GnRH-LH-Te axis is collected with 10 *min* sampling, which is three-four times slower compared to a theoretically motivated rate. The sparse sampling results in LH pulses being described by 10-14 measured data points each. To improve the estimation accuracy, it is suggested in [12] that the parameter estimate minimizes the least-squares loss function under constraints derived from the model. Peak time, peak amplitude, and positivity of the model can serve as such constraints. An alternative approach is based on continuous system identification in Laguerre domain and deals with the low sampling rate by projecting the data onto a continuos orthonormal functional basis, [13]. *A priori* information about the largest half-life time in the hormone system is taken into account in this technique through the tuning of the Laguerre parameter in the chosen functional basis.

d) Estimation results: The two considered identification approaches are tested on hormone data comprising LH serum concentration measurements in a young human male. The data are provided by Prof. Veldhuis of Mayo Clinic and described in [14]. The data are collected at a sampling time of 10 *min* starting from 18.00 until 14.00 on the following day, see Fig. 1. This results in heavily undersampled data as a calculated from the system dynamics sampling rate should be 2-3 times faster, [9].

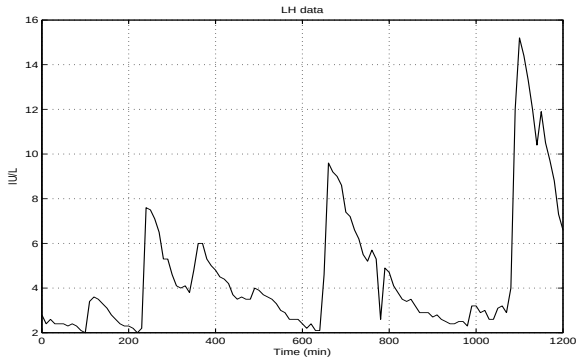

Fig. 1. Measured LH concentration for 20 hours

The data set is separated into major individual pulses. Out of these partial data sets, the ones that indicate the possibility of a secondary pulsatile release are considered. Since the focus is on the pulsatile hormone regulation, the basal level of each pulse is subtracted from the hormone concentration value.

Fig. 2 depicts estimation results achieved on a typical data set. As expected, the nonlinear least-squares method gives a better estimate in terms of maximum peaks of the first and secondary pulse. The possibility to assign larger weights to important sampling instances in vicinity of assumed firing times gives better results at estimating the concentration peak resulting from the secondary release of GnRH. However, in terms of overall loss function, Laguerre identification performs better, with reasonable estimates of the dynamics and second releases as well.

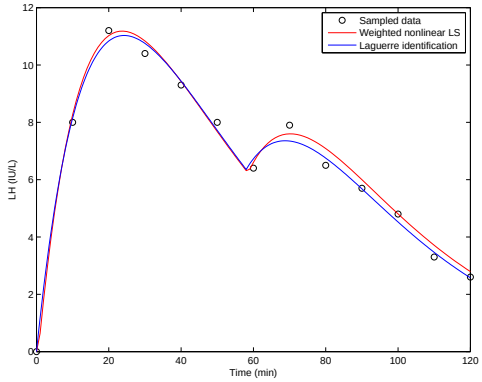

Fig. 2. Estimation results on real data representing an LH pulse with primary and secondary release of GnRH, loss function of weighted nonlinear least squares = 1.0872, loss function of Laguerre identification = 0.9978.

e) Conclusions: A pulse-modulated feedback model of non-basal endocrine regulation is discussed with respect to the modeling of testosterone regulation in the human male. It is also expected to be useful for modeling endocrine regulation via other hypothalamic releasing hormones. Two model parameter estimation techniques are outlined and exhibit encouraging results on experimental data.

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