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Fractal Properties of the Thyrotropic Feedback Control Implications of a Nonlinear Model Compared with Empirical Data

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Abstract

More than 70 years after the discovery of the pituitary-thyroid feedback control mechanism, a classical endocrine regulation system, most of its parameters have been identified. However, the regulation of its central component in the pituitary gland, probably responsible for pulsatile release of thyrotropin (TSH), remains obscure. In order to infer its structure from the system's behaviour, four different pituitary models were created and compared regarding their fractal properties. Based on non-competitive inhibition of TSH release by thyroid hormones – a physiologically plausible correlation – two of the models added stochastic stimulation by central signals and two added an additional intrapituitary feedback loop. The model combining non-competitive inhibition with both additional effects showed the same fractal dimensions as real time series, while simpler models exhibited significantly lower complexity in the time series they yielded. The results suggest that both effects play a role in the generation of TSH pulses in the human pituitary.

1. Introduction

Pulsatile release of hormones is a common phenomenon in endocrine systems. It is achieved by combining an analog signal encoding with amplitude or frequency modulation. Pulsatility contributes to reliable information transfer. Furthermore, the oscillating hormone levels help to prevent desensitisation of their target cells that would be caused by down-regulation of specific receptors. The pituitary-thyroid feedback control (thyrotropic feedback control) involves two classes of hormones, the peptide hormones TRH (thyroliberin) and TSH (thyrotropin) and two thyroid hormones (T_4 or thyroxine and T_3 or triiodothyronine). Although little is known about the temporal patterns of TRH levels in the portal system of the pituitary stalk, the release of TSH into blood plasma is known to occur in a pulse-like manner. Being similar to other signalling pathways based on peptide hormones the thyrotropic information transfer occurs via amplitude modulation of the TSH level. Faster oscillations with rate of 5 to 20 per 24 h are superimposed on a circadian rhythm with maximum TSH levels early in the morning.
The mechanism causing the fast TSH oscillations is unknown. The previously favored hypothesis assuming a pulsatile input of TRH at the pituitary yielding corresponding TSH pulses has been disproved by Samuels et al. [1993], who showed that subjects receiving constantly high doses of TRH still exhibited TSH levels with significant pulses. Until now TSH patterns were mainly classified by comparatively simple measures like amplitude and rate. More sophisticated approaches using methods from non-linear systems science to measure the complexity of the signal patterns have been applied to other endocrine control systems, e.g. to the release of PTH in the calcium-phosphate homeostasis.
Thyroid diseases play a crucial role in both individual and public health. The physiology of the thyrotropic feedback control and the factors influencing its behaviour are only partly understood. Previous models of the pituitary-thyroid feedback control were implemented in a "behaviourally isomorphic" way using different classes of equations (linear, logarithmic, exponential or polynomial), their parameters optimised to yield behaviour resembling that of a living organism [Danziger and Elmergreen, 1956; Roston, 1959; Norwich and Reiter, 1965; DiStefano, 1969; Saratchandran et al., 1976; Wilkin et al, 1977; Cohen, 1990 and Li et al., 1995]. Even though these models deliver possible ways in which the system might be realized, this approach also exposes the models to charges of being arbitrary.
Exhaustive investigations of the human pituitary *in vivo* are practically impossible. Therefore the objective of this study was to develop a parametrically isomorphic simulative approach for gathering information about the structure of pituitary information-processing from the system's behaviour.

2. Methods

2.1 The model

In order to elucidate the unknown mechanism of pulsating TSH release, a number of physiologically consistent models were created. Where empirically determined input-output-relations were available, all models share the same

parametrically isomorphic basis. Modifications have been implemented at the level of the pituitary gland, whose dynamic properties are not yet well characterized.

The system was analysed in two ways: First, the equations were solved analytically to obtain instant solutions of the mean equifinal hormone levels. In a second step, a computer simulation was generated to obtain time series of the respective hormone levels. The simulation program was developed in Pascal on an Apple Macintosh workstation.

The model was based on two principal mechanisms of biological information transfer, the Michaelis-Menten-Hill kinetics and the ASIA element, supplemented by several feedback loops for the binding of hormones to plasma proteins.

Michaelis-Menten-Hill kinetics are known to determine the behaviour of enzymatic conversion processes and receptor-mediated signal transduction systems. The subsystems respond with

$$y_a = \frac{G x_e}{D + x_e} \tag{1}$$

to an input signal x_e, where G is the maximum possible response of the transduction element and D is the input signal yielding half of the maximum response G.

The temporal behaviour of the system's variables was modelled with ASIA elements (analog signal memory with intrinsic adjustment) that essentially consists of a variable stimulating its own degradation with

$$\frac{dy}{dt} = \alpha x(t) - \beta y(t) \tag{2}$$

in a first order linear feedback loop [Dietrich 2000]. Here y denotes the output signal, α the input gain factor and β a gain factor for output extinction. In the equifinal state the subsystem's behaviour will converge to

$$y_\infty = \frac{\alpha x(t)}{\beta} \tag{3}$$

with a first order time constant of

$$\tau_1 = \frac{1}{\beta} \quad . \tag{4}$$

Binding of thyroid hormones to plasma proteins was simulated in a 0th order linear feedback loop according to the mass action law with

$$[H_F] = [H_T] - K[P][H_F] \quad , \tag{5}$$

where [*HF*] denotes the concentration of the free hormone, [*HT*] the total hormone level, K a binding constant and [*P*] the concentration of the respective plasma protein, e.g. TBG. In equilibrium, a level of

$$[H_F] = \frac{[H_T]}{1 + K[P]} \tag{6}$$

will result.

For each level of signal transfer the respective equations were mapped to values taken from empirical studies (Tables 2 to 4).

Obviously, information processing at the pituitary level occurs in a more complex way. Due to the paucity of empirical input-output relations four distinct subsystems were created differing in the temporal pattern of TRH release into the hypothalamo-pituitary portal vessels as well as the presence or absence of an ultra-short feedback loop connecting level and release of pituitary TSH (Fig. 1). Common to all four models was the assumption of a non-competitive inhibition of TSH release by receptor bound triiodothyronine ($[T_3]_R$) in the form of

$$\frac{d[TSH]}{dt} = \frac{\alpha_S G_H [TRH]_O}{(D_H + [TRH]_O)(1 + L_S[T_3]_R)} - \beta_S [TSH] \tag{7}$$

$[TRH]_O$ is the TRH-level in the pituitary stalk vessels; see Tables 2 and 3 for an explanation of other symbols.

Further variants 3 and 4 of the pituitary model include an ultra-short feedback mechanism of TSH in the pituitary interstitium $[TSH]_Z$ on its own release according to

$$\frac{d[TSH]}{dt} = \frac{\alpha_S G_H [TRH]_O}{(D_H + [TRH]_O)(1 + L_S[T_3]_R) Z} - \beta_S [TSH] \tag{8}$$

with

$$Z = \left(1 + \frac{S_S[TSH]_z}{D_S + [TSH]_z}\right) \quad . \tag{9}$$

The pituitary models 1 and 3 assume a portal TRH level that is – except for circadian variation – constant, whereas versions 2 and 4 implement additional stochastic variations of the TRH level in the hypothalamo-pituitary vessels. To be congruent with observations made with other peptide hormones the TRH-fluctuations were simulated with a Gaussian random generator delivering a log-normal distribution.

Table 1: Characteristics of the four variants of the pituitary model (CV = circadian variation, LGN = log-normal Guassian noise:

Version	TRH level	Ultra-Short Feedback
1	CV	Omitted
2	CV and LGN	Omitted
3	CV	Present
4	CV and LGN	Present

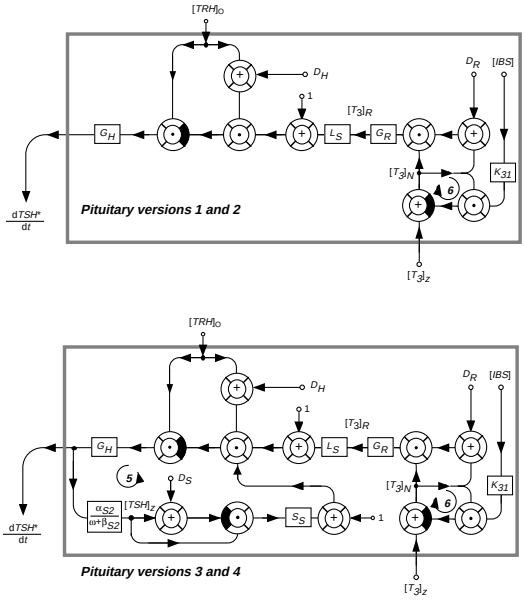

Figure 1: Different versions of the pituitary model

Table 2: Numerical implementation of the Michaelis-Menten-Hill kinetics. Empirically determined values from D'Angelo et al. [1976], Dumont and Vassart [1995], Greenspan [1997], Lazar and Chin [1990], Okuno et al., [1979], van Doorn and van der Heide [1985], Visser et al. [1983] and from own data.

Symbol	Explanation	Value
GH	Secretion capacity of the pituitary	817 mU/s
DH	Damping constant (EC50) of TRH at the pituitary	47 nmol/l
GT	Secretion capacity of thyroid gland	3.4 pmol/s
DT	Damping constant (EC50) of TSH at the thyroid gland	2.75 mU/l
GD1	Maximum activity of type I deiodinase	28 nmol/s
KM1	Dissociation constant of 5'-deiodinase I	500 nmol/l
GD2	Maximum activity of type II deiodinase	4.3 fmol/s
KM2	Dissociation constant of 5'-deiodinase II	1 nmol/l
GR	Maximum gain of TRβ receptors	1 mol/s
DR	EC50 for central T3	100 pmol/l
SS	Brake constant of TSH ultra-short-feedback	100 l/mU
DS	EC50 for TSH at the pituitary	50 mU/l

Table 3: parameterization of ASIA elements. Empirical values from [Benvenga and Robbins, 1998; Duntas *et al.*, 1990; Greenspan 1997; Grußendorf 1988; Odell *et al.*, 1967; Oppenheimer et al. 1967]

αR	Dilution factor for peripheral TRH	0.4 l-1
βR	Clearance exponent for TRH	2.3 e-3 s-1
αS	Dilution factor for TSH	0.4 l-1
βS	Clearance exponent for TSH	2.3 e-4 s-1
αT	Dilution factor for T4	0.1 l-1
βT	Clearance exponent for T4	1.1 e-6 s-1
$\alpha 31$	Dilution factor for peripheral T3	2.6 e-2 l-1
$\beta 31$	Clearance exponent for T3*P*	8 e-6 s-1
$\alpha 32$	Dilution factor for central T3	1.3 e5 l-1
$\beta 32$	Clearance exponent for central T3	8.3 e-4 s-1
$\alpha S2$	Dilution factor for pituitary TSH	2.6 e5 l-1
$\beta S2$	Clearance exponent for central TSH	140 s-1

Table 4: Dissociation constants of hormone binding. Values from Li et al. [1995].

$K30$	Dissociation constant T3-TBG	2 e9 l/mol
$K31$	Dissociation constant T3-IBS	2 e9 l/mol
$K41$	Dissociation constant T4-TBG	2 e10 l/mol
$K42$	Dissociation constant T4-TBPA	2 e8 l/mol

2.2 Fractal dimensioning

In order to compare simulated to real time series, recordings made from volunteers by Brabant et al. [1990], Greenspan et al. [1986] and Samuels et al. [1990] were digitized and processed by two programs for calculating the fractal dimensions of the signal patterns.

The first measure of complexity used was the fractal capacity dimension (D_0). This approach covers the graphical representation of the time series with squares of successively varied border-length s using the mesh-counting theorem. For each length it counts the number $N(s)$ of squares covering the curve. With

$$D_0 = \lim_{s \to 0} \frac{\log N(s)}{\log \frac{1}{s}} \tag{10}$$

the capacity dimension can be calculated and compared for real and simulated time series.

By means of a second approach to determine the data's complexity the so-called correlation dimension D_2 [Loistl and Betz 1996] was calculated.

After embedding the time series $x1$, $x2$, $x3$ … x_N into the m-dimensional vector

$$\aleph_i = \left(x_i, x_{i+p}, x_{i+2p}, \ldots, x_{i+(m-1)p}\right) \tag{11}$$

the local density

$$n_i(\mathrm{e}) = \frac{1}{N} \sum_{j=1}^{N} u_0(\varepsilon - || \aleph_j - \aleph_i ||) \tag{12}$$

as relative number of neighbour points of an attractor point $\aleph_i$ whose distance is smaller than ε could be calculated with the heaviside function

$$u_0(x) = \begin{matrix} 0, x < 0 \\ 1, x > 0 \end{matrix} . \quad (13)$$

Subsequently by averaging over several reference points the correlation integral

$$C(\varepsilon) = \frac{1}{M^2} \sum_{\substack{i,j=1 \\ i \neq j}}^{M} u_0(\varepsilon - || \aleph_j - \aleph_i ||) \quad (14)$$

as the number of correlated vectors normalized over the number of possible vector pairs M^2 could be calculated.
For each embedding dimension, formally similar to the definition of the capacity dimension, a specific local correlation dimension D_2 can be obtained from

$$D_2 = \lim_{\varepsilon \to 0} \frac{\log C(\varepsilon)}{\log \varepsilon} . \quad (15)$$

The first maximum of the local correlation dimensions D_2, arranged by increasing embedding dimension m, was regarded as a global correlation dimension of the time series.
Eight real time series adopted from Brabant et al. [1990], Greenspan et al. [1986] and Samuels et al. [1990] were respectively compared with 8 time series generated from each pituitary model.
The capacity-dimension was calculated with the Fractal Dimension Calculator 1.5 by Paul Bourke (Astrophysics and Supercomputing Centre, Swimburne University of Technology, Hawthorn, Melbourne, Australia, available via http://astronomy.swin.edu.au/pbourke/fractals/fracdim/).
Correlation and embedding dimensions were calculated with the application C(D2) (J. W. Dietrich, University of Munich, Germany, available from http://link.medinn.med.uni-muenchen.de/cybermed/nonlin/cd2/).

3. Results

All four models showed the same results for equifinal hormone levels as those obtained by analytically solving the model equations for TSH, FT_4 and FT_3. The equation system is solved via a cubic equation as *casus irreducibilis* with three mathematically real solutions. Only one of these solutions is realizable in a biological context, the other two results being negative (Table 5).

Table 5: Solutions for the equilibrium levels of the simulated hormone levels (see text for explanation):

Parameter	Solution 1	Solution 2	Solution 3
TSH	1.8 mU/l	-1.2 mU/l	-1.2 mU/l
FT4	1.4 ng/dl	-2.4 ng/dl	-2.4 ng/dl
FT3	3.5 pg/ml	-6.0 pg/ml	-6.0 pg/ml

Obviously, the simulated parameters are located within known reference regions for healthy individuals.

The differences between the four variants are disclosed in the comparison of the time series delivered by the computer simulations (Fig 2).

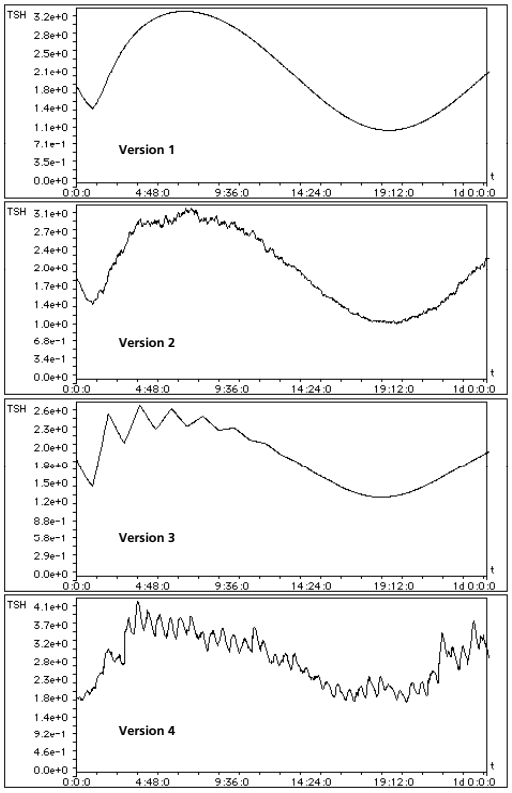

Figure 2: The behaviour of the four versions of the pituitary model (time series over 24 hours simulated time).

Fractal properties are implied by the four variants as shown in Table 6 and Fig. 3.

Table 6: Fractal properties of the models and empirical time series (D_0: Capacity Dimension, D_2: Correlation Dimension, m: Embedding Dimension, **: p<0,001, t-test for independent samples, comparison of empirical and simulated time series):

Mean Dimensions	D_0	D_2	m
Empirical	1.20	1.75	19.63
Model 1	0.96**	0.76**	1.00**
Model 2	1.04**	0.77**	1.00**
Model 3	0.99**	0.74**	1.13**
Model 4	1.18	1.91	20.14

As revealed by all dimension measures, the pituitary models 1, 2 and 3 exhibit significantly lower complexity than real time series, whereas the fractal behaviour of model 4 is comparable to that of empirical data (except for a smaller variance of simulated time-series for the capacity dimension).

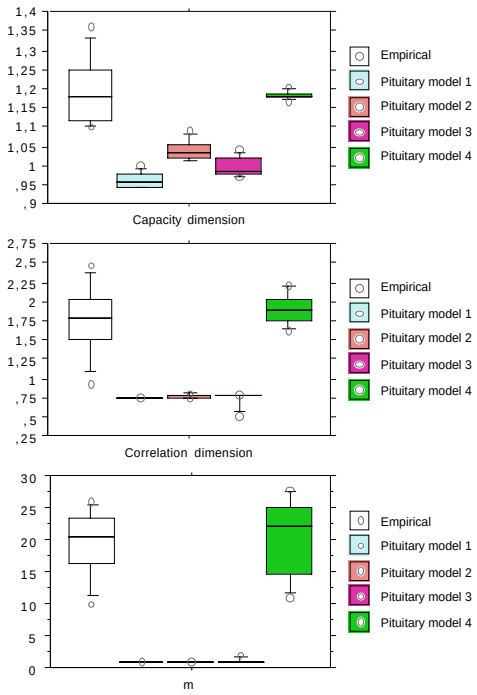

Figure 3: Fractal Dimensions of the four pituitary models compared with empirical data.

4. Discussion

The existence of a feedback loop interconnecting pituitary and thyroid gland has been known for decades [Aron 1929, Crew 1930]. Nevertheless, the algorithms of information processing inside the pituitary remained unclear.

The inhibiting effect of TSH on its own release has been observed in animals [Kakita and Odell 1986]. There is controversy whether or not this kind of "Ultra Short Feedback" exists in humans, although Prummel et al. [1997] found TSH receptors in human pituitary tissue.

Like other peptide hormones, TSH is secreted episodically. As TRH pulses have been ruled out as the cause of these rhythms, the location and nature of the pulse generator remain obscure.

Apart from the mechanisms occuring in the central organs, the physiology of thyroid regulation seems to be well characterized. Therefore, it was possible to develop a model relying predominantly on empirical input-output relations (again except from pituitary regulation). This parametrically isomorphic model could then be used to test different variants for the as-yet unknown information processing within the pituitary gland.

In the form of a Michaelis-Menten-Hill kinetic with one additional non-competitive inhibitory site, the first pituitary model was physiologically plausible but relatively simple. Alternative models added stochastic stimulation by TRH and an ultra-short feedback loop inhibiting the TSH release by interstitial thyrotropin in the pituitary.

While all variants yielded the same equilibrium hormone levels, their behaviour over time was different. All versions failed to reach the complexity of real time series – with the exception of the fourth model.

It may appear to be trivial to observe that the rising complexity within an information processing structure parallels the increasing complexity of the time series. Nevertheless, the fact that simulated time series from model 4 show nearly identical dimensions as real time series, supports the hypothesis that they may be caused by isomorphic processes. Certainly, the system's behaviour *in vivo* will be influenced by additional factors, an assumption that is supported, e.g., by the larger standard deviation of natural capacity and correlation dimensions as compared with simulated data.

The results of the simulations suggest that regulation of thyroid activity might be more complex than simple non-competitive inhibition of the TRH mediated activation of TSH release. Together with the identification of TSH receptors in the pituitary tissue [Prummel et al. 1997] our results support the hypothesis that an ultra-short feedback loop in the pituitary gland may also play a role in human physiology.

When inspecting the simulated time series (Fig. 2) it is striking to note that the amplitudes of the TSH pulses increase when the circadian rhythms yield a maximum of the basal TSH activity. This observation can also be made with empirical data. However, this effect has hitherto rarely been described, e.g. in Adriaanse et al. [1993].

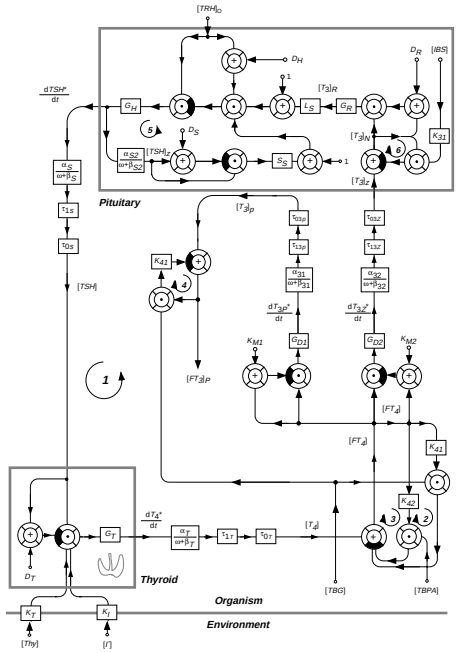

Figure 4: Information processing structure of the overall system according to version 4 of the pituitary model.

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