Fractal Properties of the Thyrotropic Feedback Control

Implications of a Nonlinear Model Compared with Empirical Data

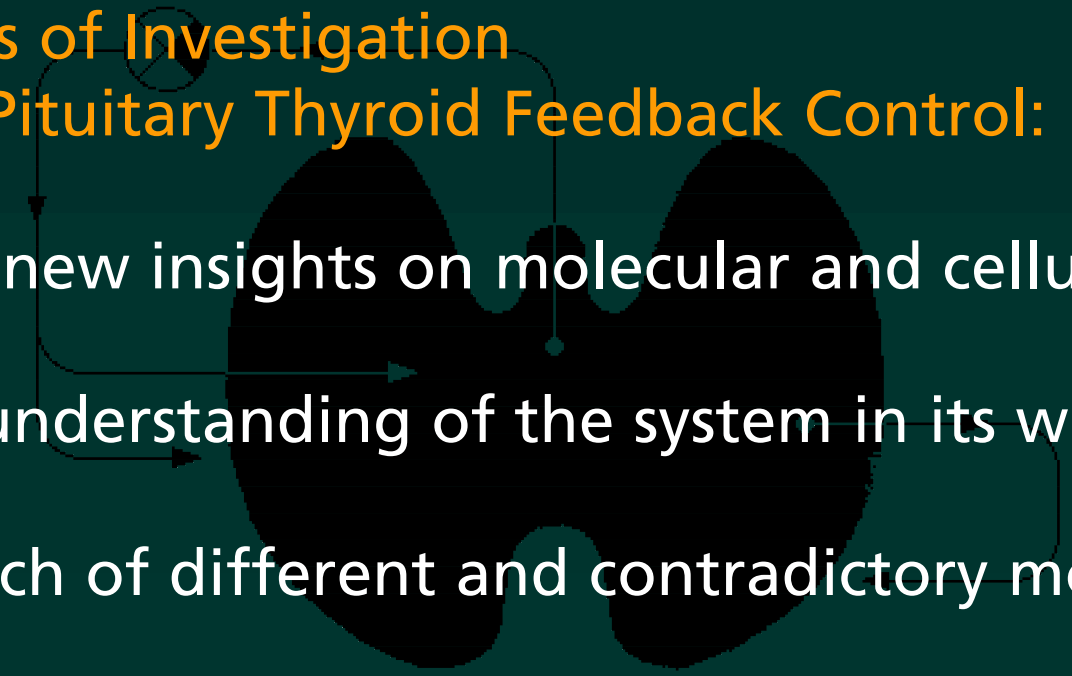
J. W. Dietrich, A. Tesche, C. R. Pickardt and U. Mitzdorf

Medizinische Klinik, Klinikum Innenstadt, University of Munich, F. R. Germany

Chirurgische Klinik, Klinikum Innenstadt, University of Munich, F. R. Germany

Institut für Medizinische Psychologie, University of Munich, F. R. Germany

The Thyrotropic Feedback Control
Is it really well known?

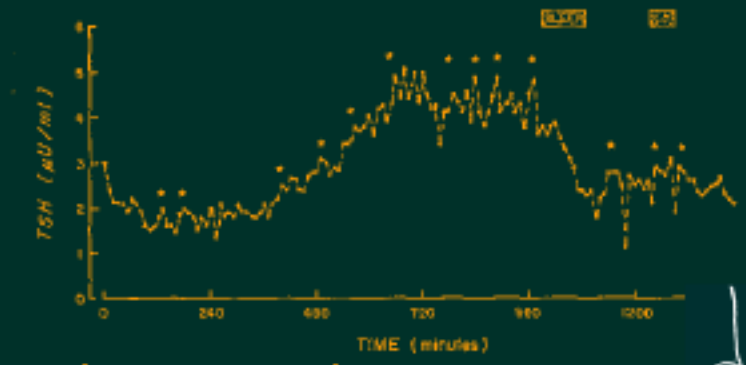


70 Years of Investigation
on the Pituitary Thyroid Feedback Control:

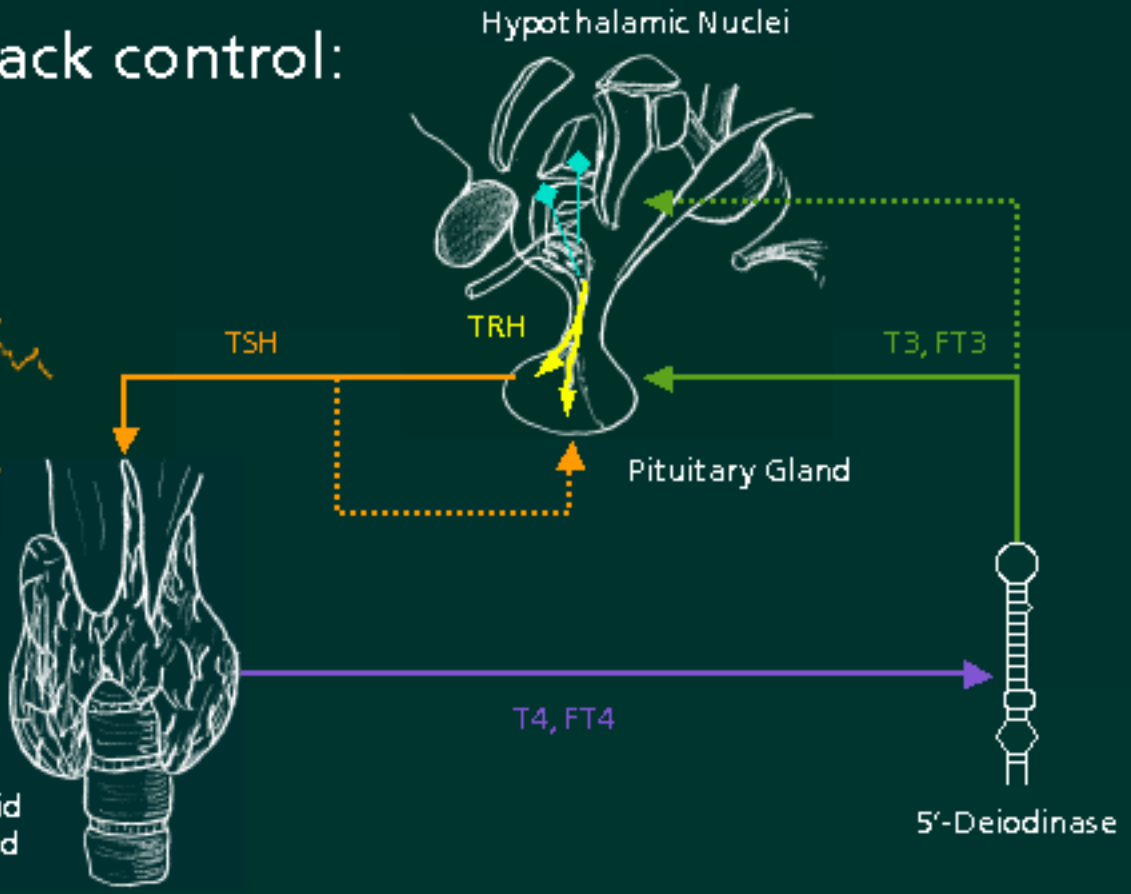
- Many new insights on molecular and cellular level.
- Poor understanding of the system in its whole.
- A bunch of different and contradictory models.
- Still open questions.

The Thyrotropic Feedback Control Overview

Overview of feedback control:



[Greenspan 1986]

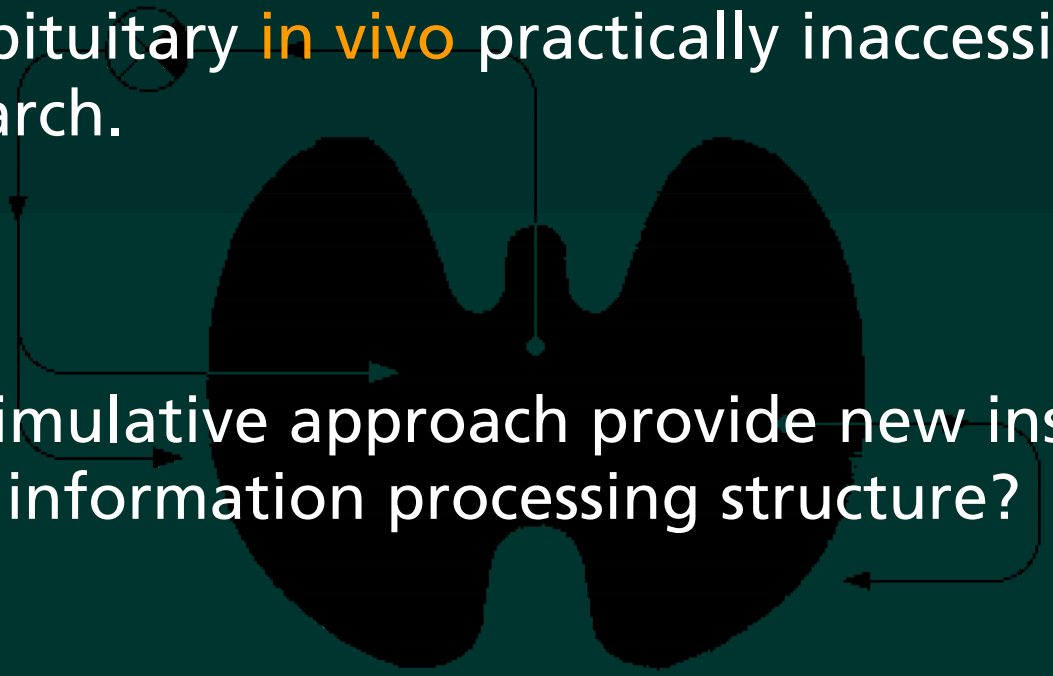


Mechanisms yielding TSH pulses are still unknown.

J. W. D. 2002

The Thyrotropic Feedback Control Model based inference

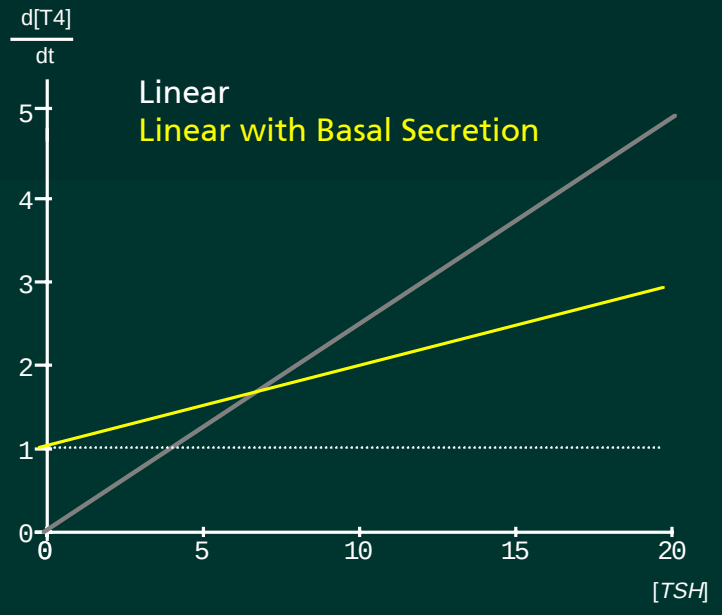
Human pituitary in vivo practically inaccessible for research.



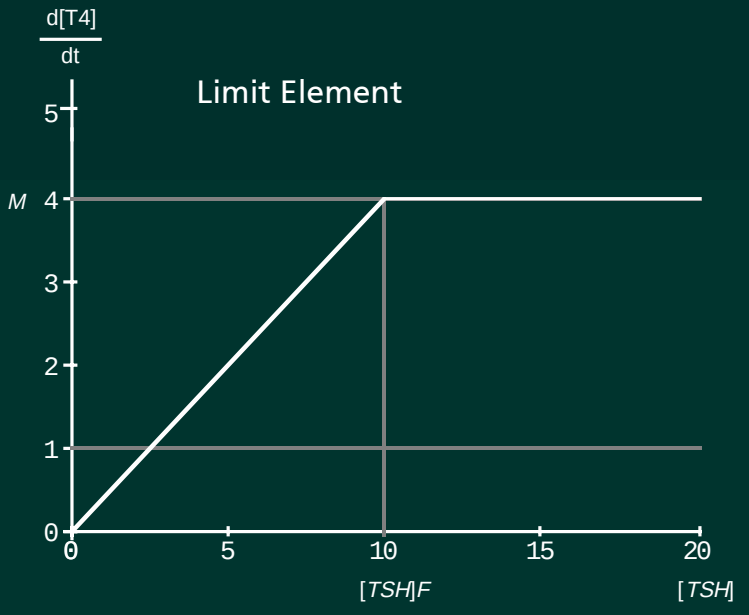
Does a simulative approach provide new insights into the information processing structure?

The Thyrotropic Feedback Control Different Models

"Behaviourally isomorphic" models:



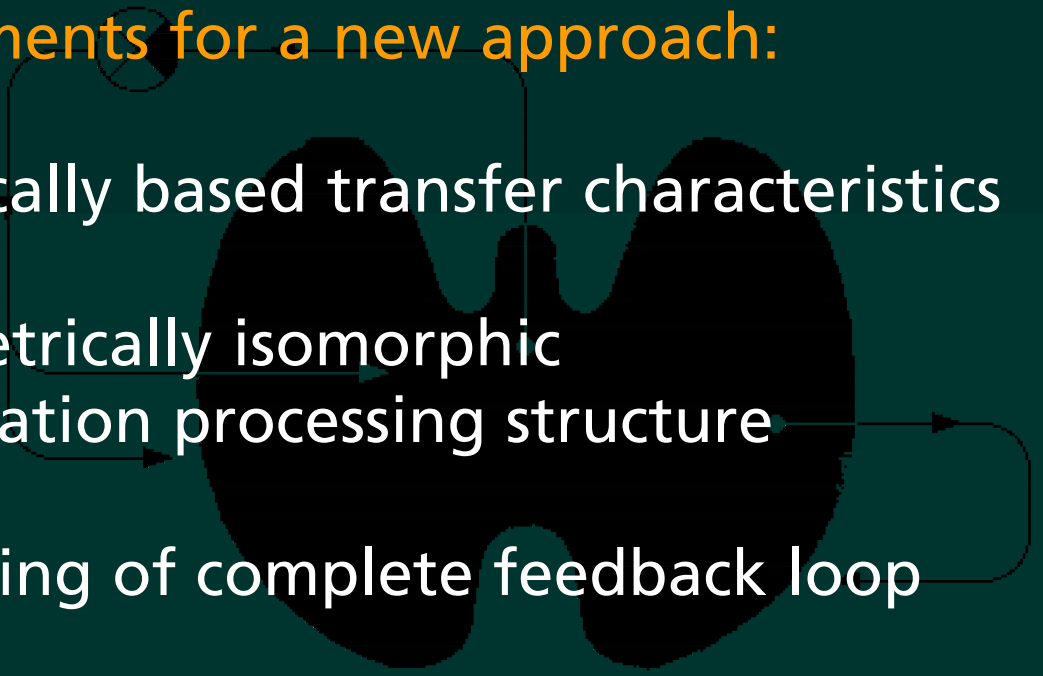
Danziger and Elmergreen 1956
Norwich and Reiter 1965
Roston 1959
DiStefano 1969



Wilkin et al. 1977

J. W. D. 2002

The Thyrotropic Feedback Control
A New Model (I)



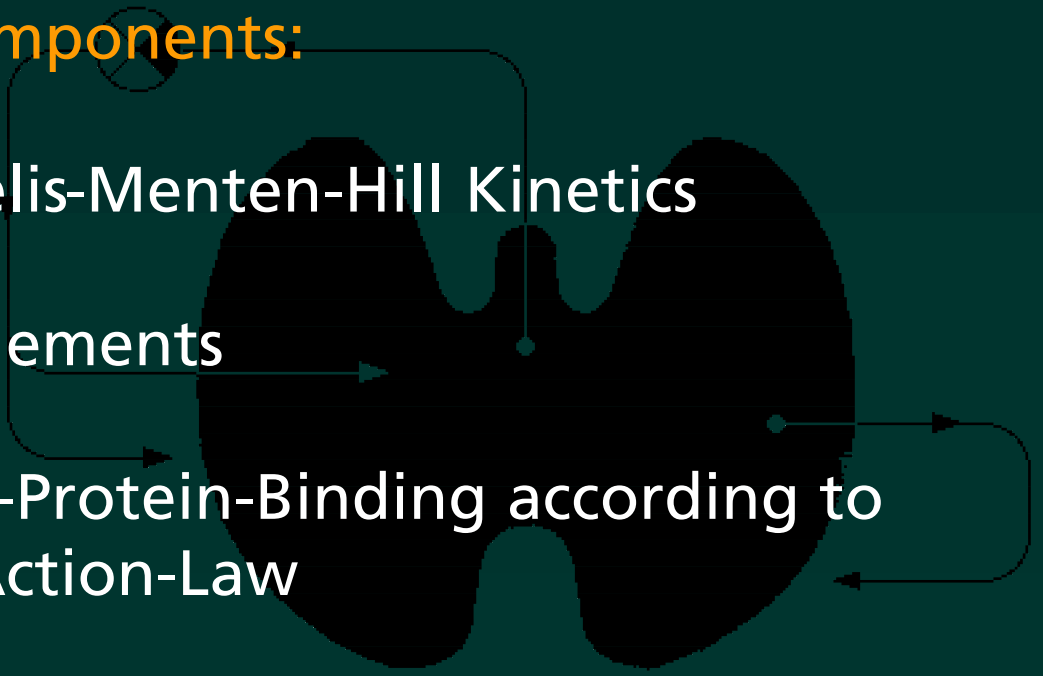
Requirements for a new approach:

- Empirically based transfer characteristics
- Parametrically isomorphic information processing structure
- Modelling of complete feedback loop

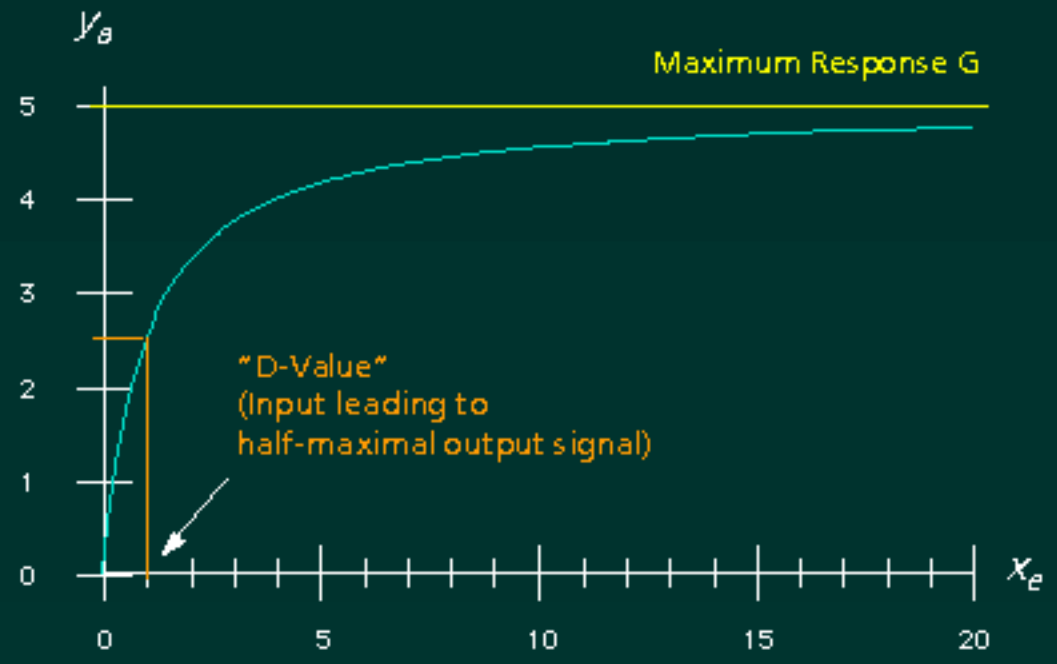
The Thyrotropic Feedback Control
A New Model (II)

Main Components:

- Michaelis-Menten-Hill Kinetics
- ASIA-Elements
- Plasma-Protein-Binding according to Mass-Action-Law
- Non competitive quotient inhibition (NCQI)

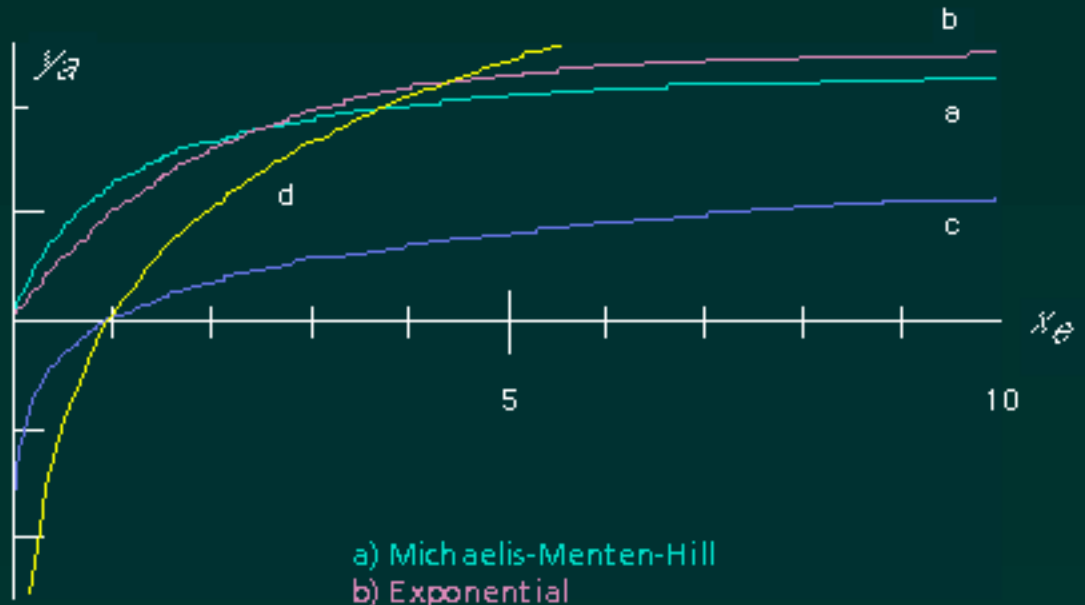


The Thyrotropic Feedback Control Michaelis Menten Hill Kinetics



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

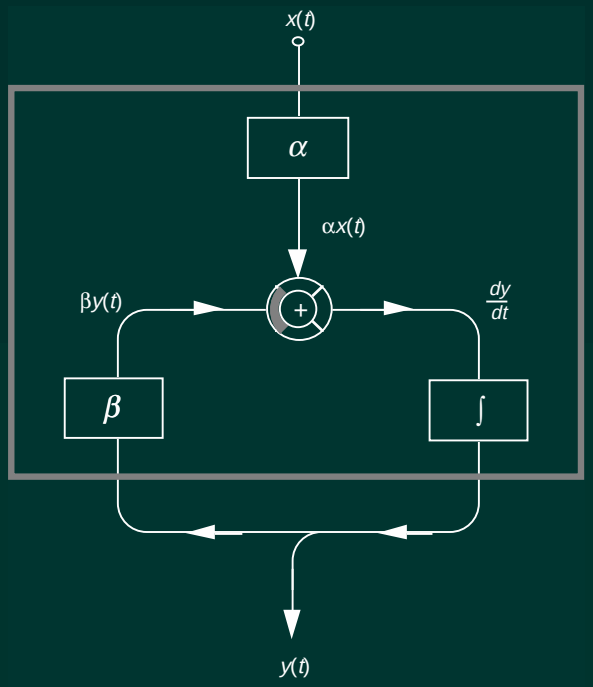
The Thyrotropic Feedback Control Different Nonlinear Models

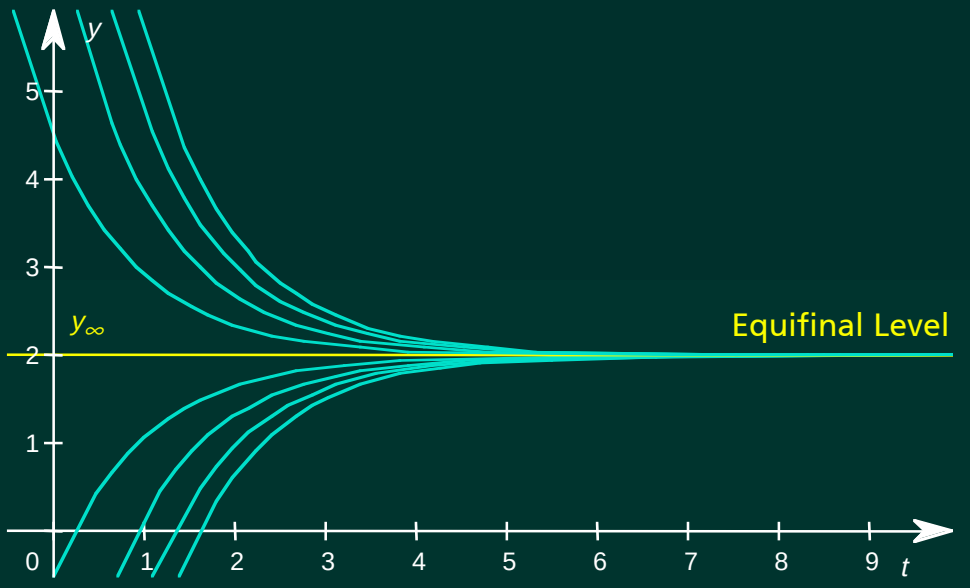


a) Michaelis-Menten-Hill
b) Exponential
c) Logarithmic
d) Logarithmic, adapted for x_e=4

J. W. D. 2002

The Thyrotropic Feedback Control ASIA Element





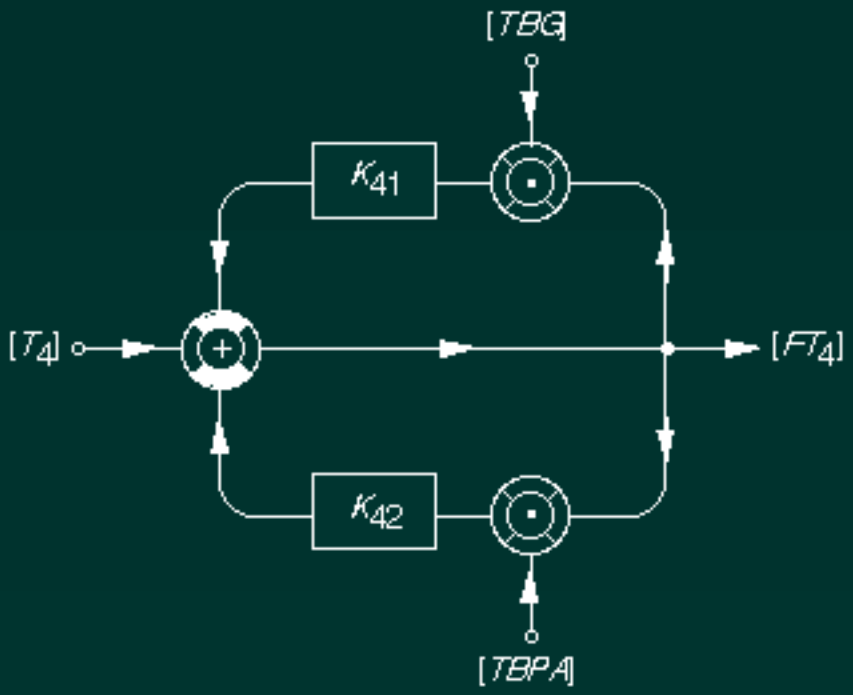
$$\frac{dy}{dt} = \alpha x(t) - \beta y(t)$$

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

$$\tau_1 = \frac{1}{\beta}$$

J. W. D. 2002

The Thyrotropic Feedback Control Plasma Protein Binding



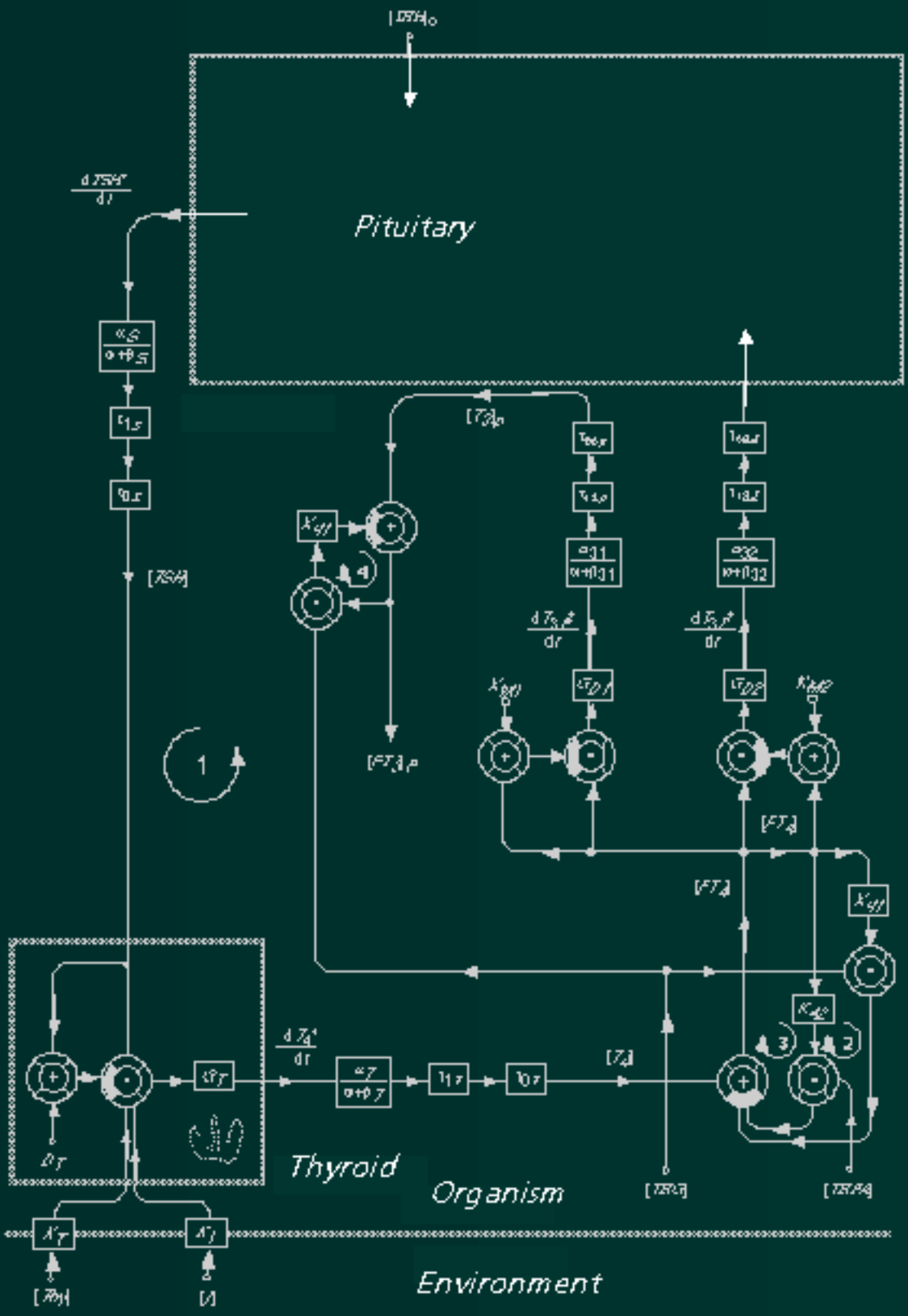
$$[BT_4] = K_{41}FT_4[TBG] + K_{42}FT_4[TBPA]$$

$$[FT_4] = [T_4] - [BT_4]$$

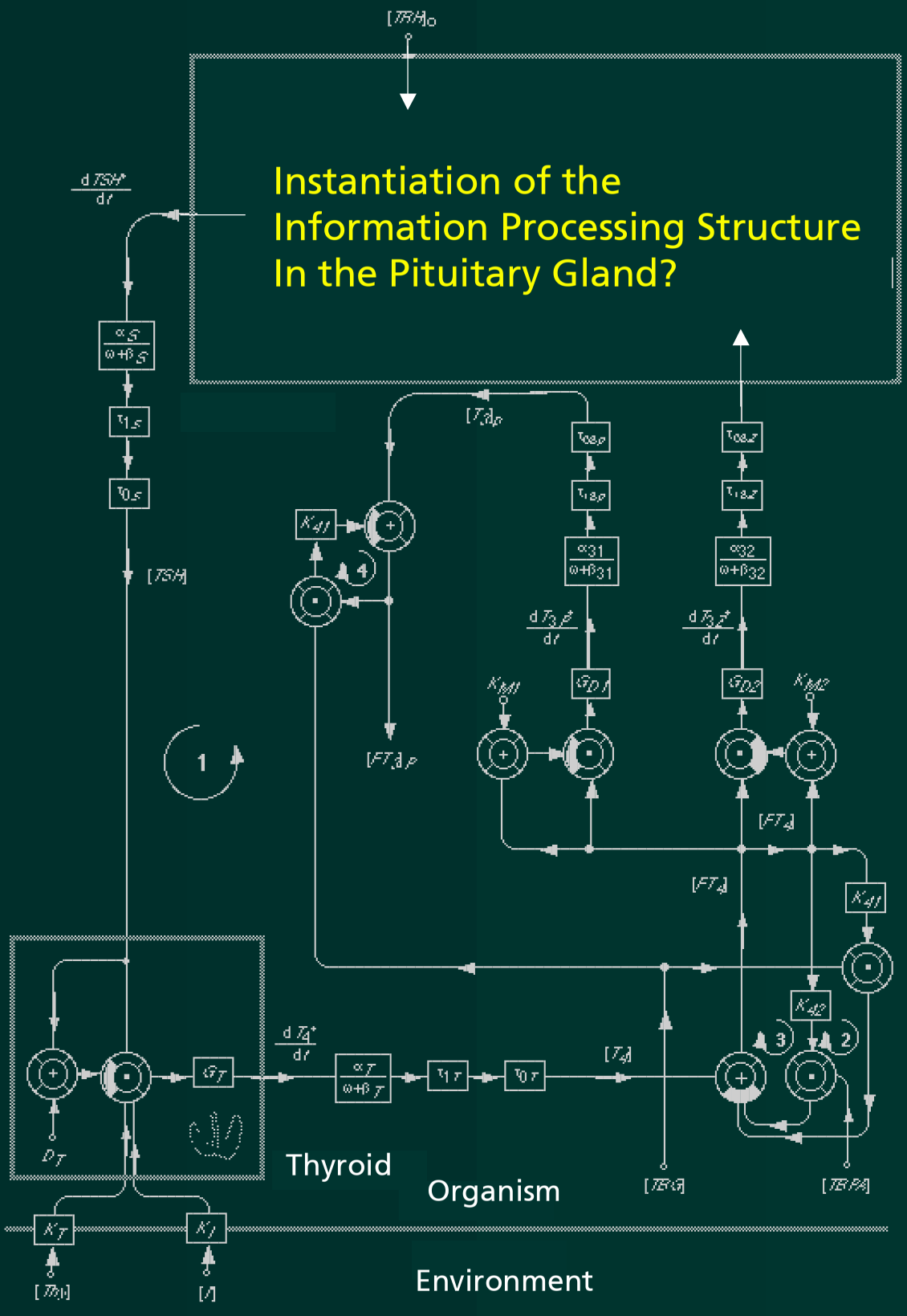
$$[FT_4] = \frac{[T_4]}{1 + K_{41}[TBG] + K_{42}[TBPA]}$$

$$[FT_3]_P = \frac{[T_3]_P}{1 + K_{30}[TBG]}$$

The Thyrotropic Feedback Control Universal Model



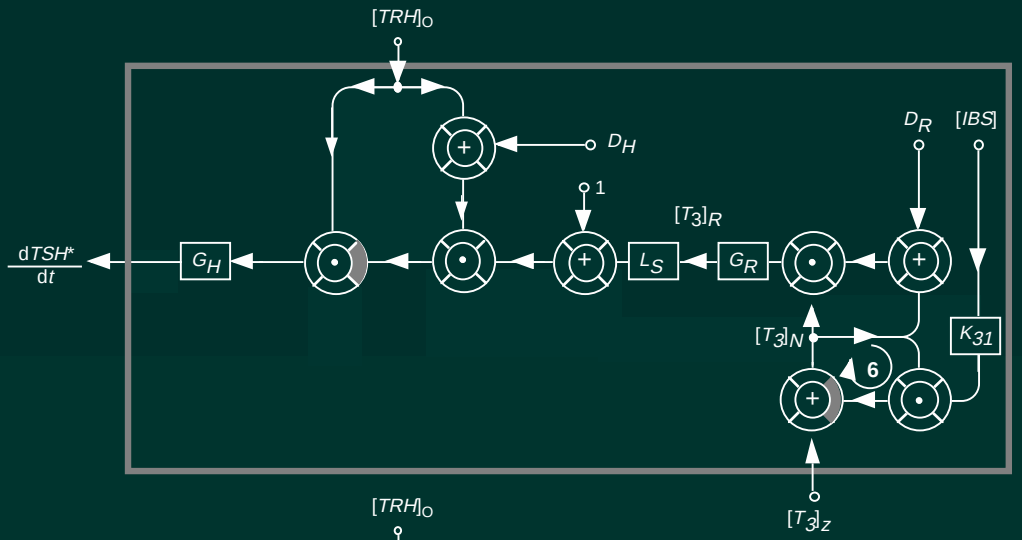
The Thyrotropic Feedback Control Universal Model



The Thyrotropic Feedback Control
Possible Pituitary Models

Models 1 and 2:

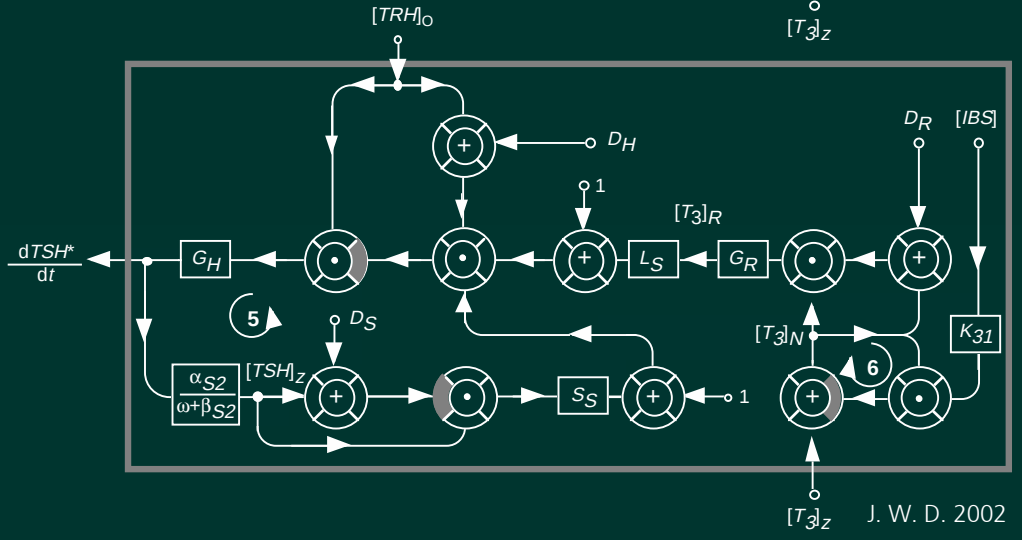
$$\frac{d[TSH]}{dt} = \frac{\alpha_S \, G_H \, [TRH]_O}{(D_H + [TRH]_O)\,(1 + L_S[T_3]_R)} - \beta_S \, [TSH]$$



Models 3 and 4:

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

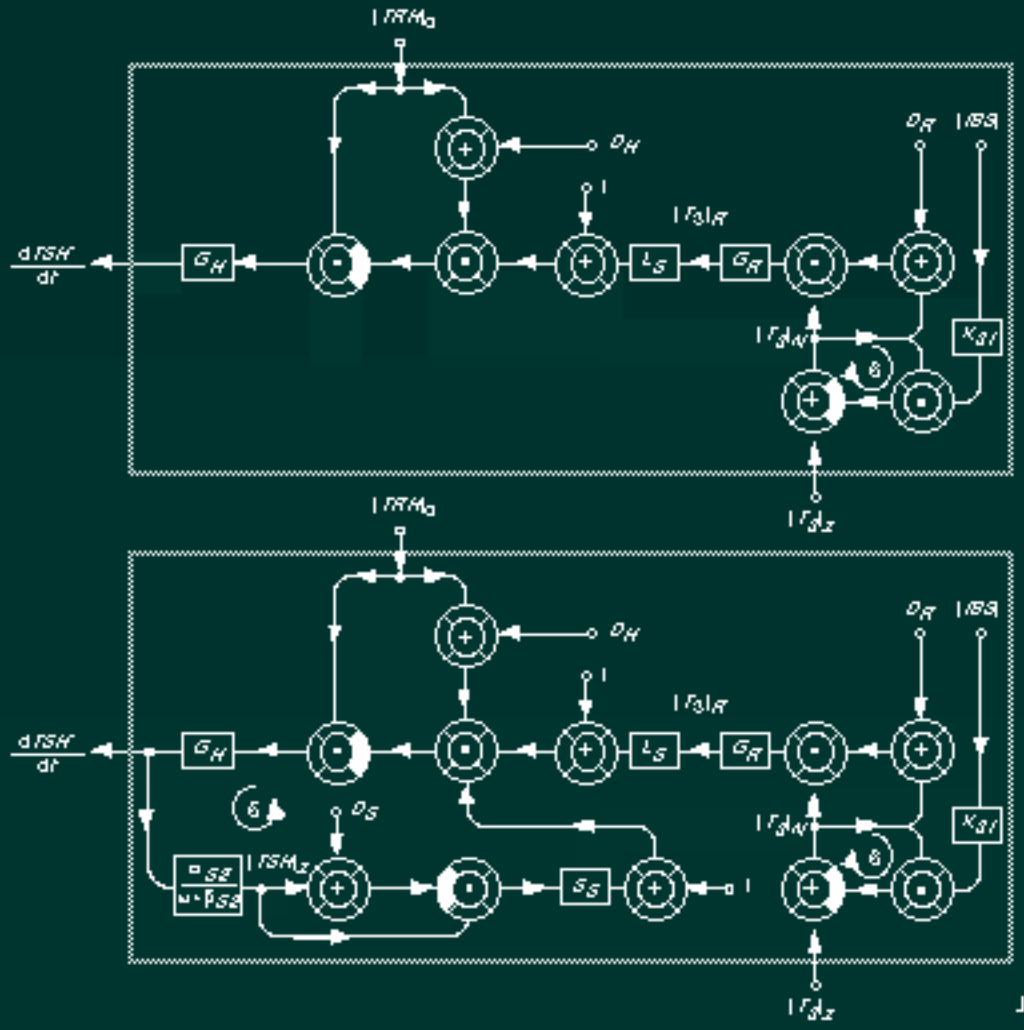
$$Z = (1 + \frac{S_S[TSH]_z}{D_S + [TSH]_z})$$



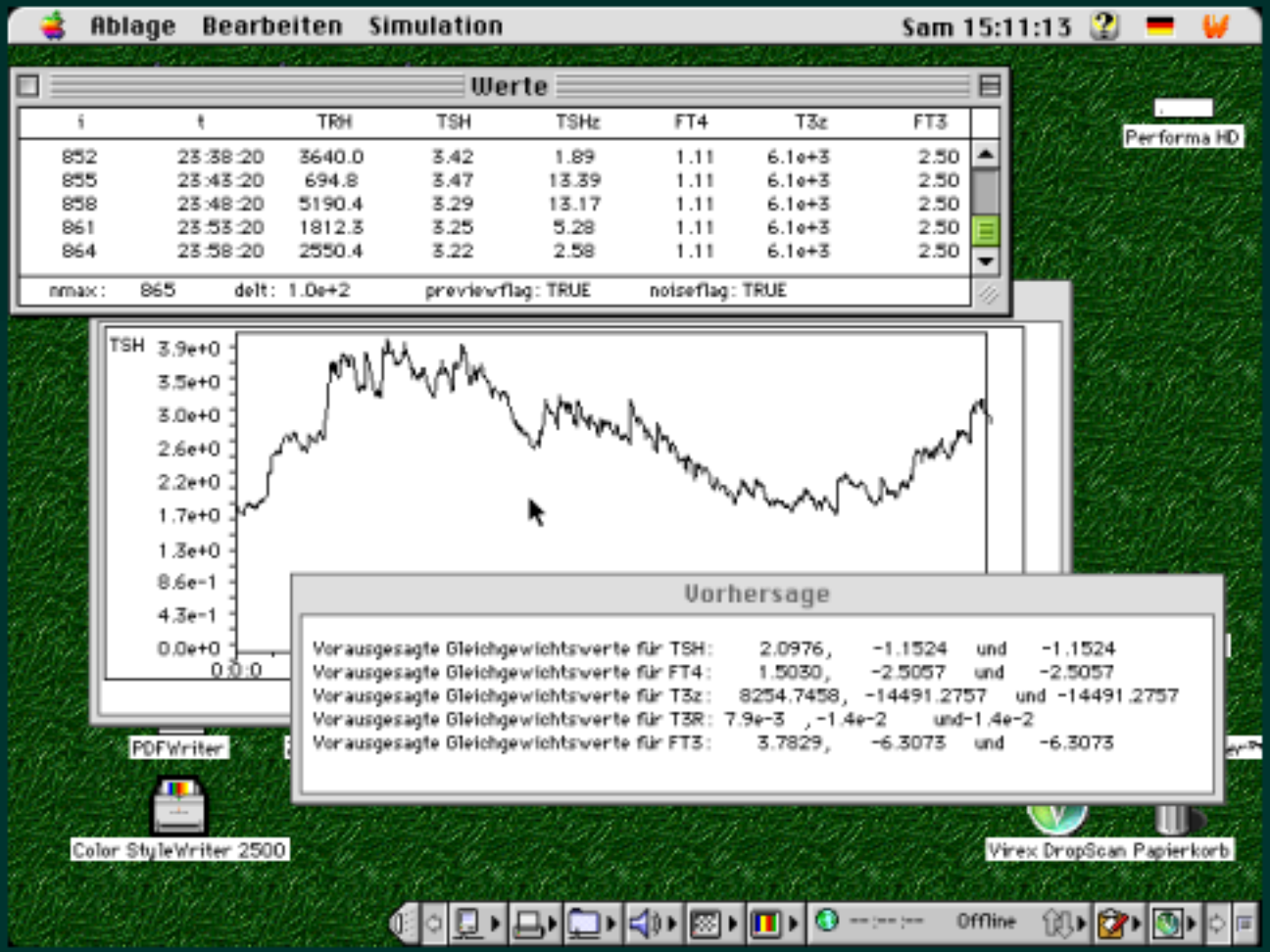
J. W. D. 2002

The Thyrotropic Feedback Control
Possible Pituitary Models

	CV	LGN	Ultrashort Feedback
Version 1	+	-	-
Version 2	+	+	-
Version 3	+	-	+
Version 4	+	+	+



The Thyrotropic Feedback Control Computer Simulations



J. W. D. 2002

The Thyrotropic Feedback Control Comparing Different Models

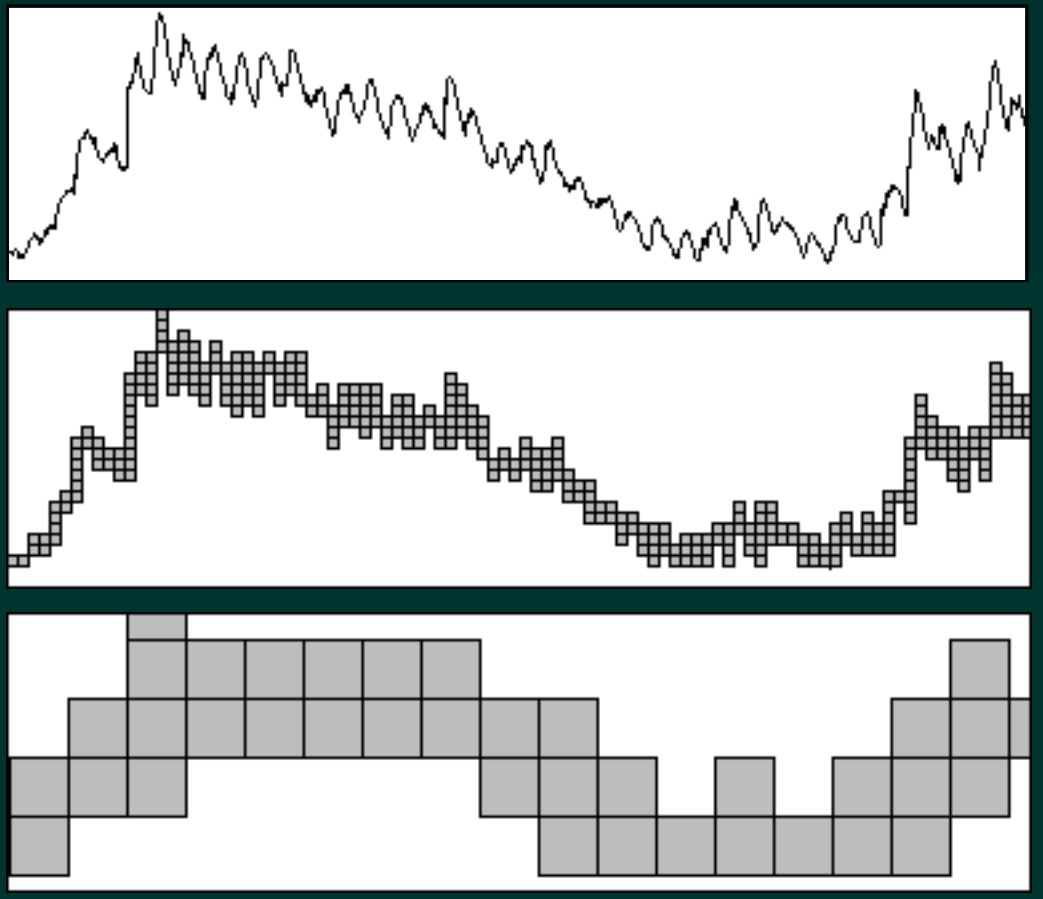
Methods for characterization:

- Equifinal equilibrium hormone levels
- Qualitative inspection of signal course
- Fractal analysis of time series

The Thyrotropic Feedback Control Fractal Dimensioning (I)

Capacity dimension:

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



The Thyrotropic Feedback Control Fractal Dimensioning (II)

Correlation dimension:

$$\vec{x}_i = \left(x_i,\ x_{i+p},\ x_{i+2p},\ \ldots,\ x_{i+(m-1)p}\right)$$

$$C(\varepsilon) = \frac{1}{M^2} \sum_{\substack{i,j=1 \\ i \neq j}}^{M} u_0\left(\varepsilon - \left|\left| \vec{x}_j - \vec{x}_i \right|\right|\right)$$

$$n_i(\varepsilon) = \frac{1}{N} \sum_{j=1}^{N} u_0\left(\varepsilon - \left|\left| \vec{x}_j - \vec{x}_i \right|\right|\right)$$

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

$$u_0(x) = \begin{matrix} 0,\ x \leq 0 \\ 1,\ x > 0 \end{matrix}$$

The Thyrotropic Feedback Control Results (I)

Results

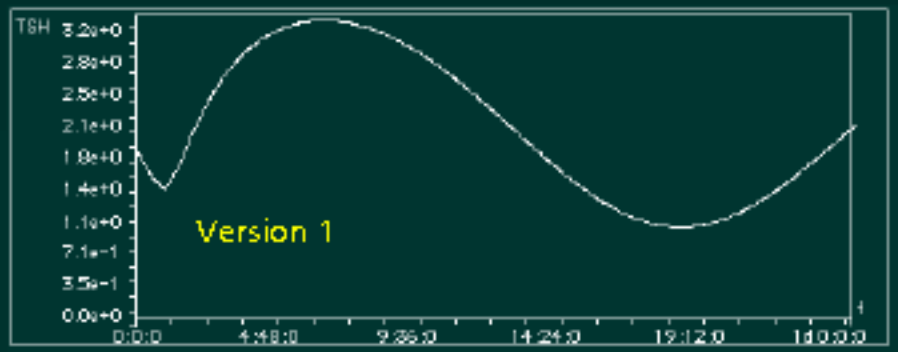
The Thyrotropic Feedback Control Results (I)

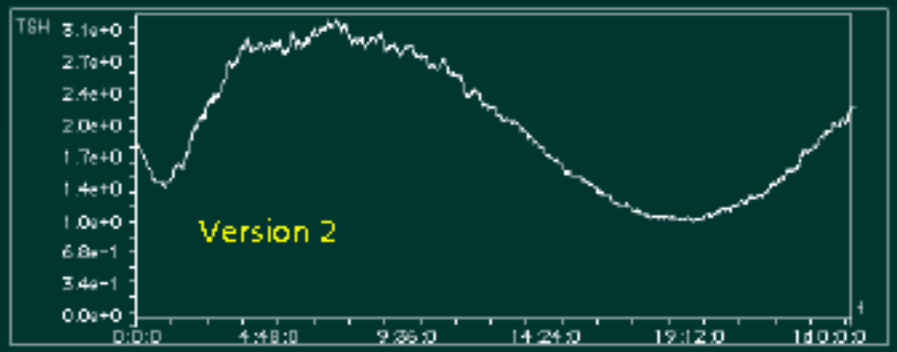
Analytic solutions for Equilibrium levels:

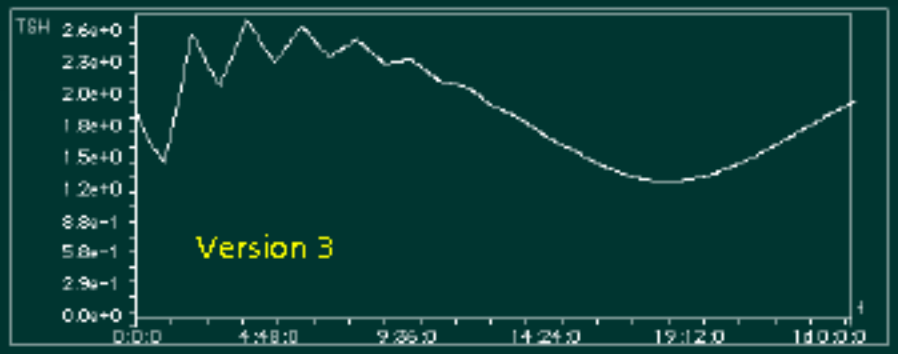
Parameter	Solution 1	Solution 2	Solution 3
TSH	1.8 mU/l	-1.2 mu/l	-1.2 mu/l
FT4	1.4 ng/dl	-2.4 ng/dl	-2.4 ng/dl
FT3	3.5 pg/ml	-6.0 pg/ml	-6.0 pg/ml

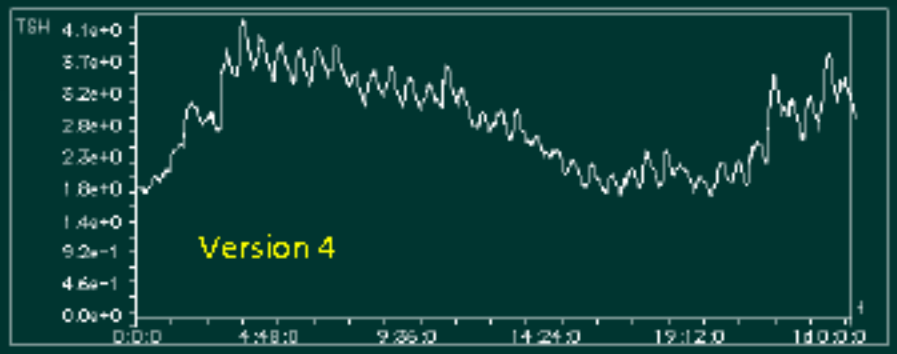
The Thyrotropic Feedback Control Results (II)

Simulated Time Series:









The Thyrotropic Feedback Control Results (III)

Fractal Dimensions:

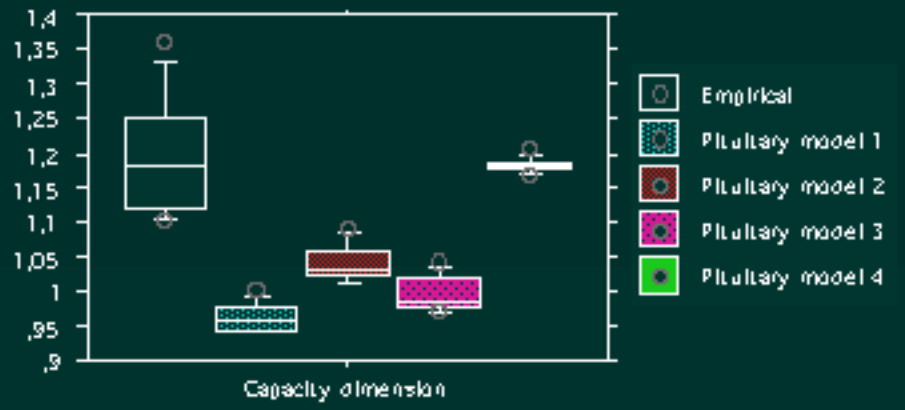
Dimension (Mean)	D_0	D_2	m
Empirical	1.20	1.75	19.63
Model 1	0.96**	0.76 **	1.00 **
Model 2	1.04 **	0.77 **	1.00 **
Model 3	0.99 **	0.74 **	1.13 **
Model 4	1.18	1.91	20.14

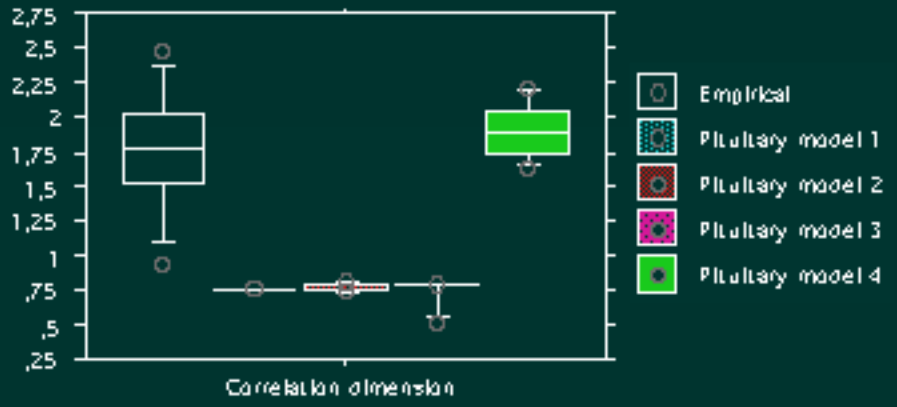
**: p<0.001

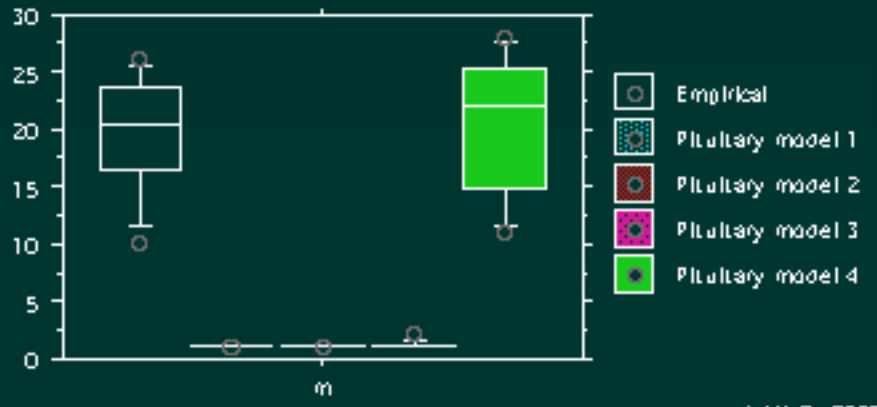
J. W. D. 2002

The Thyrotropic Feedback Control Results (IV)

Fractal Dimensions:

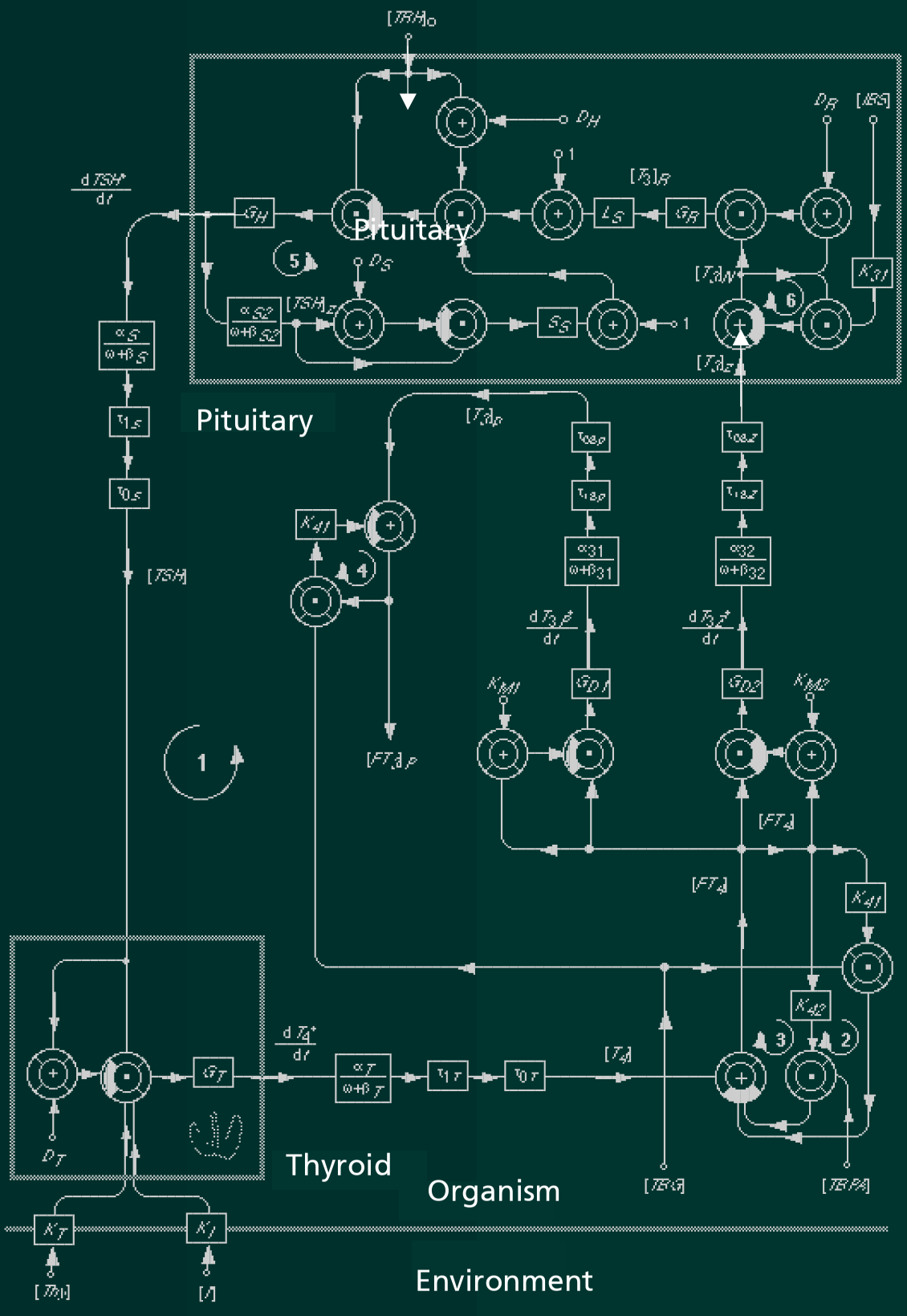






J. W. D. 2002

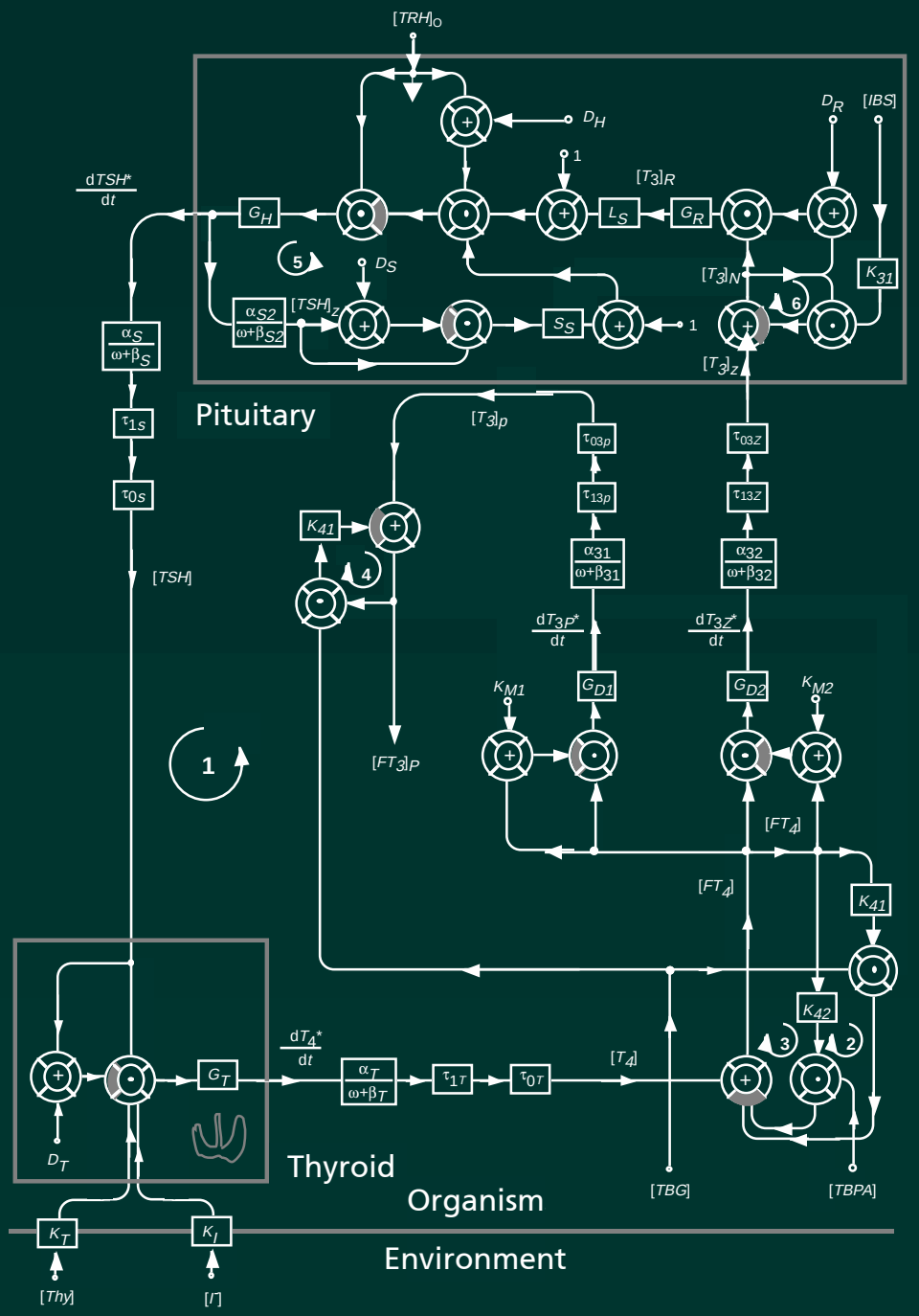
The Thyrotropic Feedback Control Possible Complete Model



The Thyrotropic Feedback Control
Possible Complete Model

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

$$Z = (1 + \frac{S_S[TSH]_z}{D_S + [TSH]_z})$$



The Thyrotropic Feedback Control Conclusion

- Non competitive quotient inhibition (NCQI) acts as sufficient explanation for emergence of equifinal levels in both healthy and diseased state.
- Simple NCQI fails to deliver plausible time series.
- Combination of NCQI with noise and ultra-short feedback of TSH might be an explanation for the dynamics of nature.

The Thyrotropic Feedback Control
Additional Information

Point your browser to:

http://spina.medical-cybernetics.de

or

http://link.medinn.med.uni-muenchen.de/spina/