

## Equilibrium behaviour of feedback-coupled physiological saturation kinetics

**J. W. Dietrich**

Medizinische Klinik I,  
Endokrinologie und Diabetologie,  
BG-Kliniken Bergmannsheil,  
Klinikum der Ruhr-Universität Bochum,  
Buerkle-de-la-Camp-Platz 1,  
D-44789 Bochum, F. R. Germany  
johannes.w.dietrich@bergmannsheil.de

**B. O. Boehm**

Sektion Endokrinologie  
Abteilung Innere Medizin I,  
Medizinische Klinik,  
Universitätsklinikum Ulm,  
Robert-Koch-Str. 8,  
D-89081 Ulm, F. R. Germany  
bernhard.boehm@medizin.uni-ulm.de

### Abstract

In a simplifying manner biological feedback-control systems use to be described as linear circuits with subtractive comparison elements, although in living organisms most signal transduction pathways are known to have saturable characteristics, as described by Michaelis-Menten-Hill kinetics.

Therefore, while linearisation methods supply a straightforward way for modelling biological information processing structures they also expose the models to charges of being arbitrary. Furthermore, they fail to provide realistic hypotheses on the pathogenesis of diseases.

An alternative approach that comprises formulating parametrically isomorphic models directly incorporates empirically obtained properties of the involved transfer elements.

With a novel universal model for nonlinear biological processing structures (MiMe control-model) we show that results of both analytical solving of involved equations and computer simulation are in better agreement with physiology than those of traditional models.

In conclusion it seems that parametrically isomorphic modelling of feedback control with Michaelis-Menten-kinetics may provide a general and universal method for characterizing biological information processing structures.

### 1. Introduction

In an often unpredictable world biological feedback-control systems (FCS) are a *sine-qua-non* for maintaining the homeostasis of critical variables that determine the organism's internal environment [Bernard, 1859 and 1878; Cannon, 1926]. Irrespective of their physiological embodiment in form of e.g. neural impulses, hormones, cytokines or enzyme cascades they usually act as non-linear systems, whose elements exhibit saturation characteristics like Michaelis-Menten-Hill kinetics.

However, for decades biological control circuits have used to be described in an oversimplifying manner as linear systems being comprised of proportional elements

and controllers in form of subtractive modulator elements (Fig. 1).

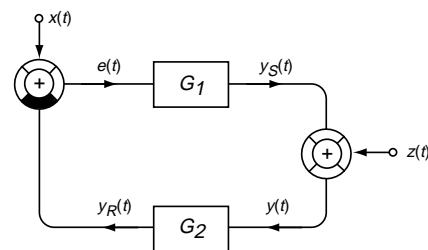


Fig. 1: A simple proportional feedback loop with set point  $x(t)$  and load  $z(t)$ . See appendix for a legend of symbols.

Considering the recursive description of this linear feedback loop with

$$y(t) = G_1 x(t) - G_1 G_2 y(t) + z(t) \quad (1.1)$$

we receive the equifinal solution as

$$y^{(\infty)} = \frac{G_1 x^{(\infty)} + z^{(\infty)}}{1 + G_1 G_2} \quad (1.2)$$

In the past, models of this type enjoyed great popularity in the description of biological information processing structures [Cruse, 1981; Röhler, 1973; Varjú, 1977; Danziger and Elmergreen, 1956; DiStefano, 1969; DiStefano and Stear, 1968; Norwich and Reiter, 1965; Roston 1959], when they pioneered mathematical modelling of closed feedback loops. Their methodological principle is based on approximating the real system by a linearised substitution system, whose parameters are repetitively adjusted until the simulated output corresponds to the known behaviour of the real system. Although this approach provided new and valuable insights into general navigational principles of life, it lacks of injectivity, i.e. uniqueness. Therefore, mapping of the real system to the model remains ambiguous, since multiple different points in the parameter space are apt to generate similar behaviour in rest. On the other hand, simulating perturbations and pathological situations like diseases uses to be very difficult in approximated models. Therefore, their

implications didn't cross the border to a real explanation of the dynamics in the intact and diseased organism. In this article we present a way to a new general theory of non-linear feedback loops in the living organism that covers a large class of physiological embodiments. The core method maps the real system to a parametrically isomorphic model that allows for direct incorporation of parameters that have been experimentally gathered.

## 2. Modelling

Transition to this injective model requires three steps. Initially, the subtractive comparison element of the FCS is replaced by a divisive controlling element. This choice is motivated by the fact that intercausal networks in living organisms are positive systems, which means that their parameters, like neuronal spike rates or hormone concentrations, can't get negative.

In a traditional view the input value  $x(t)$  would be interpreted as set point, but in the divisive model it adopts the characteristics of a target proportion of the actual value  $y_R(t)$  and the error signal  $e(t)$ . With  $z$  as disturbance variable and  $G_1$  and  $G_2$  as linear gain factors of feed forward and feedback path, respectively, in this quotient FCS the controlled variable  $y$  receives its value from the recursive equation

$$y(t) = z(t) + \frac{G_1 x(t)}{G_2 y(t)} \quad (2.1)$$

In a second step some transduction elements are replaced by those that exhibit Michaelis-Menten kinetics (MMK). MMK describes the output signal  $y_a$  as a one-to-one function of the input signal  $x_e$  with

$$y_a = \frac{G x_e}{D + x_e} \quad (2.2)$$

given the two constant and characteristic parameters  $G$  and  $D$ . Additionally, the controller is complemented by a type of degenerative feedback inhibition that prevents the output signal from getting infinite if the inhibiting input signal  $x_{e2}$  is 0, as it is known e.g. from enzymes that are regulated by v-type allostery (Fig. 2).

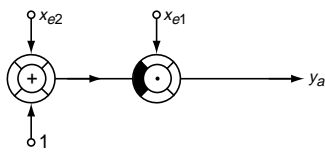


Fig. 2: Pathway for inhibition in the type of v-type allostery (VTA).

The last step consists in accounting for level-dependent degradation of signals. Different parameters like enzymes, metabolites, hormones, blood cells and even the population of whole organisms in ecosystems may be described as being located within a leaky integrating compartment whose extinction rate is proportional to the instantaneous level of the respective signal. A unified model for subsystems of this form is the ASIA element (Fig. 3) with

$$\frac{dy_a}{dt} = \alpha x_e(t) - \beta y_a(t) \quad (2.3)$$

For evaluating steady state the parameters of an ASIA element may be combined to a linear gain factor

$$G(\infty) = \frac{\alpha}{\beta} \quad (2.4)$$

as demonstrated recently in [Dietrich, 2000].

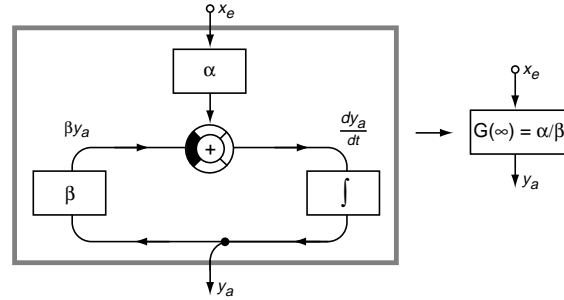


Fig. 3: Processing structure of an ASIA element with leaky-integrating characteristics (left) and a simplified substitution system for steady-state analysis (right).

With the mentioned linear and non-linear components inserted into the described divisive FCS (Fig. 4) solving the corresponding equation system delivers the recursive equation

$$y(t) = \frac{G_1 G_2 x(t)}{D_2 + D_2 G_3 y(t) + G_1 x(t)} \quad (2.5)$$

or, in terms of  $c$ ,

$$c(t) = \frac{G_1 x(t)}{1 + \frac{G_3 G_2 c(t)}{D_2 + c(t)}} \quad (2.6)$$

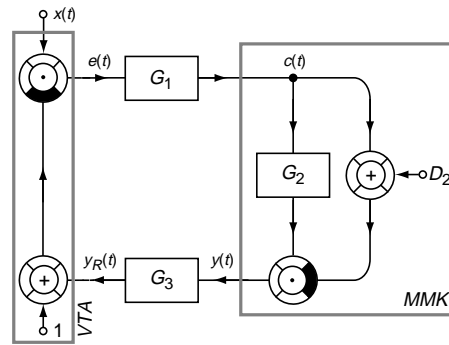


Fig. 4: MiMe-model: Processing structure with a Michaelis-Menten type transfer element (MMK) and degenerative feedback inhibition in form of v-type allostery (VTA).

By defining

$$K_1 = \frac{G_4 G_3 G_2}{D_4 + G_3 G_2} \quad (2.7)$$

and

$$K_2 = \frac{D_4 D_2}{D_4 + G_3 G_2} \quad (2.8)$$

multiple MMK elements in series can be merged to a unique virtual MMK element  $K_1 c(t) / [K_2 + c(t)]$ , so that the corresponding processing structures (Fig. 5 A) may be described with

$$c(t) = \frac{G_1 x(t)}{1 + \frac{G_5 K_1 c(t)}{K_2 + c(t)}} \quad (2.9)$$

formally similar to FCS with single MMK elements. More elaborate models cover multiple control systems organized in parallel (Fig. 5 B), whose recursive behaviour is given in the case of two pathways with

$$c(t) = \frac{G_1 x(t)}{\left(1 + \frac{G_3 G_2 c(t)}{D_2 + c(t)}\right) \left(1 + \frac{G_5 G_4 c(t)}{D_4 + c(t)}\right)} \quad (2.10)$$

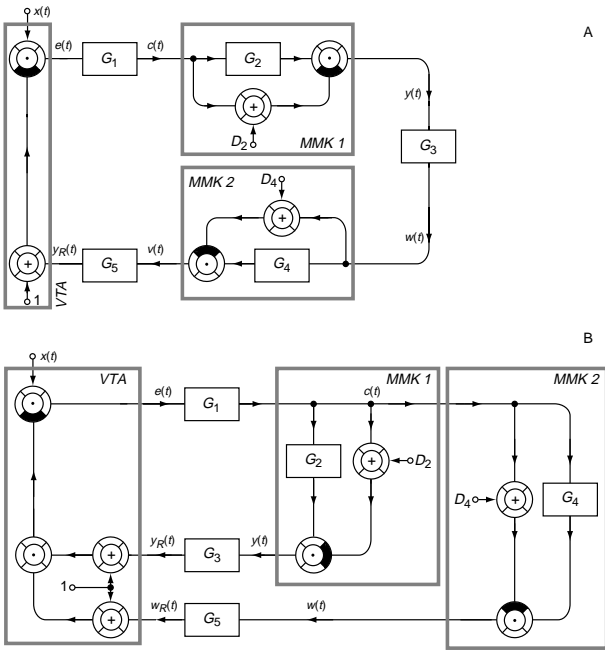


Fig. 5: MiMe-System with two Michaelis-Menten type transfer elements (MMK 1 and MMK 2) in series (A) and parallel (B) and v-type degenerative feedback (VTA).

### 3. Results

The recursive description (equation 2.1) of the divisive FCS can be solved in form of a quadratic equation to obtain the equilibrium behaviour of the information processing structure. Its equifinal value corresponds to the positive one of the two solutions

$$y(\infty)_{1,2} = \frac{z(\infty)}{2} \pm \frac{\sqrt{G_2^2 z(\infty)^2 + 4G_1 G_2 x(\infty)}}{2G_2} \quad (3.1)$$

Incorporating MMK and v-type inhibition delivers a nonlinear FCS (Fig. 4) that allows to be described with the recursive equations (2.5) and (2.6).

For  $t \rightarrow \infty$  we may define the three variables

$$a = D_2 G_3, \quad (3.2)$$

$$b = D_2 + G_1 x(t) \quad (3.3)$$

and

$$c = -G_1 G_2 x(t), \quad (3.4)$$

so that the interrelationship can also be expressed as quadratic equation

$$a y(\infty)^2 + b y(\infty) + c = 0 \quad (3.5)$$

with the two well-known solutions

$$y(\infty)_{1,2} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \quad (3.6)$$

As all parameters of the information processing structures are necessarily positive we can assume that

$$b < b^2 - 4ac > 0, \quad (3.7)$$

so that one of the solutions is positive while the second one is negative. Certainly, only the positive one of these solutions finds a physiological realization that corresponds to the equilibrium behaviour of the system.

In the case of two serially organized MMK (Fig. 5) the recursive behaviour (equation 2.9) can again be solved in the form of the quadratic equation (3.5) with the same solutions given by equation (3.6). The distinction lies in the parameters  $a$ ,  $b$  and  $c$  that are now defined with

$$a = D_1 + D_1 G_2 + x(t), \quad (3.8)$$

$$b = D_1 D_2 + D_2 x(t) - G_1 x(t) \quad (3.9)$$

and

$$c = -G_1 D_2 x(t) \quad (3.10)$$

Again, relation (3.7) proves to be true, so that the equation system has one and only one positive solution.

The system's behaviour turns out to be more complex if control systems are organized in parallel (Fig. 5). Solving equation (2.10) delivers the cubic equation

$$e c(\infty)^3 + f c(\infty)^2 + g c(\infty) + h = 0 \quad (3.11)$$

with

$$e = 1 + G_5 G_4 + G_3 G_2 + G_5 G_4 G_3 G_2, \quad (3.12)$$

$$f = D_2 + D_2 G_5 G_4 + D_4 + G_3 G_2 D_4 - G_1 x(t), \quad (3.13)$$

$$g = D_2 D_4 - (G_1 D_2 + G_1 D_4) x(t) + D_2 D_4 \quad (3.14)$$

and

$$h = G_1 D_2 D_4 x(t) \quad (3.15)$$

Parallel organization is a common feature in living systems where we often find multiple redundant pathways. As each additional MMK-based feedback loop  $n$  introduces a term of the form

$$1 + \frac{G_{2n+1} G_{2n} c(t)}{D_{2n} + c(t)} \quad (3.16)$$

in the denominator of the one-loop equation (2.6) we obtain the universal recursive equation

$$c(t) = \frac{G_1 x(t)}{\prod_{n=1}^k \left( 1 + \frac{G_{2n+1} G_{2n} c(t)}{D_{2n} + c(t)} \right)} \quad (3.17)$$

for dynamical feedback-regulated systems with Michaelis-Menten kinetics. This equation solves in the form of polynomials with grade  $n = k+1$ , where  $k$  is the number of parallel feedback loops:

$$a_n c^n(\infty) + a_{n-1} c^{n-1}(\infty) + \dots + a_1 c(\infty) + a_0 = 0 \quad (3.18)$$

Parameters of this general parametrically isomorphic model can unambiguously be mapped to empirically obtained parameters of biological information processing structures (Table 1).

Table 1: Parameters and variables of a general model with two Michaelis-Menten-kinetics in series (MiMeMod, see Fig. 5A) and of two corresponding endocrine processing structures. Values from [Byrne et al. 1994], [Jones et al. [1997 and 2000], [Kraan et al. 1998], [Lundquist and Panagiotidis 1992], [DiBartolomeis et al. 1986], [Rizza et al. 1981], [Breuninger et al. 1993] and [Magnusson et al. 1992]. APC: Volume of distribution, t1/2: Halflife.  $G_1$  and  $G_3$  represent ASIA-elements.

General Model	Glucose Control	Pituitary-adrenal axis
G1 (ASIA)	Calculated from APC and t1/2 of glucose in insulin-deficiency: 0.14 / 3.8e-5 sec/L	Calculated from APC and t1/2 of ACTH: 0.4 / 0.0002 sec/L
G2	Secretion capacity of pancreatic beta cells: 8 pmol/sec	Secretion capacity of adrenal cortex: 1.2 nmol/sec
D2	EC <sub>50</sub> of glucose at beta-cells: 5e-3 mol/L	EC <sub>50</sub> of ACTH at adrenal cortical cells: 1e-11 mol/L
G3 (ASIA)	Calculated from APC and t1/2 of insulin: 0.07 / 2.3e-3 sec/L	Calculated from APC and t1/2 of cortisol: 0.05 / 1.2e-4 sec/L
G4	Receptor gain normalized to 1	Receptor gain normalized to 1
D4	EC50 of Insulin at peripheral tissue: 1.5e-9 mol/L	EC50 of cortisol at tissue receptors: 2e-7 mol/L
G5	Effector gain estimated as 100	Effector gain normalized to 1
x(t)	Glucose production rate: 10.5 μmol/sec	Hypothalamic input (CRH signal)
e(t)	Release rate of glucose	Secretion rate of ACTH
c(t)	Blood glucose level	ACTH level
y(t)	Secretion rate of insulin	Secretion rate of cortisol
w(t)	Insulin level	Cortisol level
v(t), yR(t)	2 <sup>nd</sup> and 3 <sup>rd</sup> messengers	Intracellular signals

Table 2: Equifinal levels of variables resulting from numerical simulations with parameters of Table 1.

Signal	S1	S2
Glucose	-2.4 mmol/L	4.7 mmol/L
Insulin	-220 pmol/L	120 pmol/L
ACTH	-2.8 pmol/L	6.9 pmol/L
Cortisol	-160 nmol/L	170 nmol/L

Analytically solving the model equations yields two results, respectively, one of them being negative and the other solution being positive. The positive solution is identical to the corresponding equifinal result of numeric simulations. These latter results lie within well-known physiological reference ranges (Table 2 and Fig. 6).

Table 3: Behaviour of the model from table 1 (MiMeMod) compared with a traditional linear model (LinMod) [Bolie 1961] and the quasi-standard minimal model (MinMod) [Bergman et al. 1979 and 1980] in extreme situations of insulin-glucose metabolism. GIR: Glucose infusion rate, IAR: Insulin appearance rate, [Glc]: Glucose plasma level, IS: Insulin Secretion. \*Examples are insulinoma and insulin overdose.

Experiment	LinMod	MinMod	MiMeMod
High finite GIR	High finite IS	Infinite IS	Limited IS
Very high IAR*	[Glc] < 0	[Glc] ≥ 0	[Glc] ≥ 0

## 4. Discussion

In this paper we introduced a parametrically isomorphic approach for characterising biological information processing structures with saturable subsystems, as they are to be found in endocrine and enzymatic signalling chains. Solving the model equations both analytically and by means of computer simulation delivers results that mutually agree and that are located within known reference ranges.

Up to now, parametrically isomorphic modelling has been applied for a few biological control systems, e.g. pituitary-thyroid interaction [Dietrich et al., 2004; DiStefano et al., 1975], albeit most often for open-loop subsystems only.

Here we show a more universal way to describe closed loop systems with parametrically isomorphic modelling. Although biological FCS may exhibit a plethora of different structures we could show that typical configurations allow to be mapped to a common general model. The mathematical aspects of this model are represented by a universal recursive equation and its polynomial solution.

Certainly, this methodology turns out to be mathematically more complex than traditional approximation by linear models [Bolie, 1961; Danziger and Elmergreen, 1956; Norwich and Reiter, 1965; Roston, 1959]. Furthermore, classical stability measures as they are applied in control technology [Cruse, 1981; Röhler, 1973; Varjú, 1977; Bateson, 1996] are no longer directly applicable.

On the other hand, non-linear technique delivers better-founded results as most model parameters can be mapped to empirically obtained values like dissociation constants and maximum velocities of enzymes. Furthermore, MiMe-models are immune to certain problems like physiologically impossible infinite or negative results that traditional approaches suffer from (Table 3). Finally, for dynamic studies this approach paves a better-founded way to approximate real systems by linear substitution models, if the parameters of the linear equations (slope and axis intercept) are obtained from the tangents of the corresponding non-linear functions at the equilibrium point found in non-linear analysis.

Therefore, parametrically isomorphic models may be successfully applied to study dynamics of various disorders affecting biological information processing, where linear models failed. This can be demonstrated with examples of common endocrine diseases like diabetes mellitus, or thyroid disorders or homeostatic responses of the adrenal and/or pituitary gland [Dietrich et al, 2004].

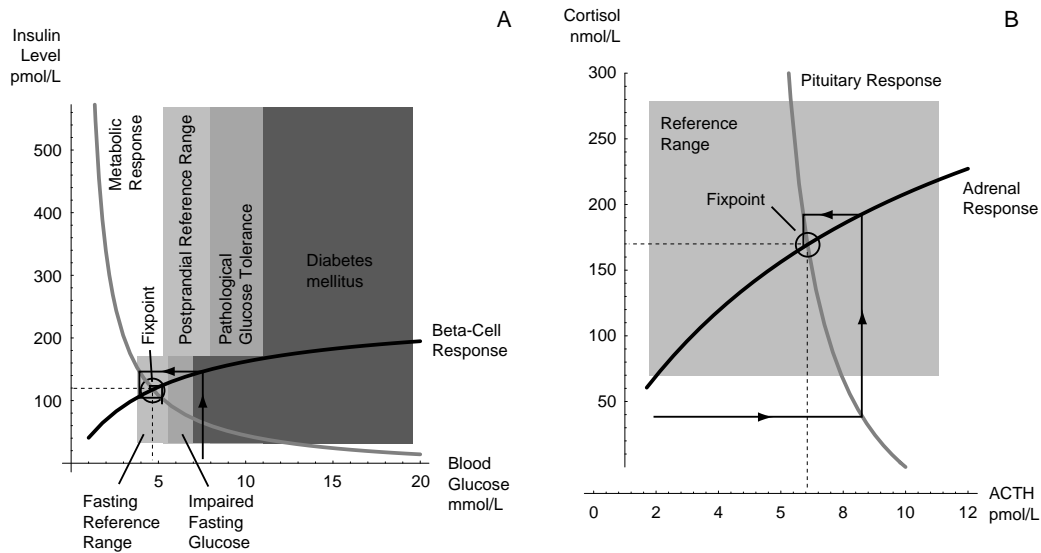


Fig. 6: Iteration plots of the two endocrine feedback control systems from table 1 and 2. The left example (A) illustrates the effects of an oral glucose tolerance test showing short overshooting compensation. The right pane (B) shows how a greater distance of the fixpoint from the curve's saturation area causes that control of adrenocortical function is more robust than glucose control. The solid line illustrates the response of beta-cells to blood glucose (A) or adrenal gland to ACTH (B). The grey line (mirrored at the bisector) represents reaction of peripheral tissues to insulin or pituitary gland to cortisol levels, respectively. The intersection point of both lines marks the fixpoint of the feedback control system with the equifinal levels of its variables.

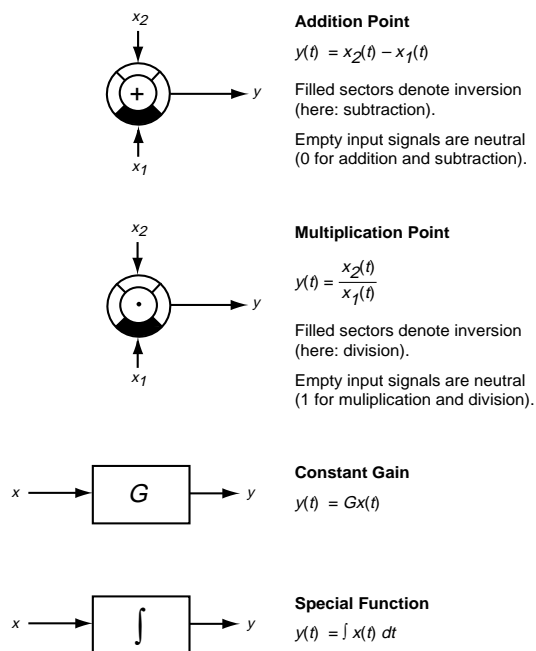
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## Appendix

Legend for IPS symbols:



Symbols used (see also [Dietrich and Boehm, 2004] for reference)