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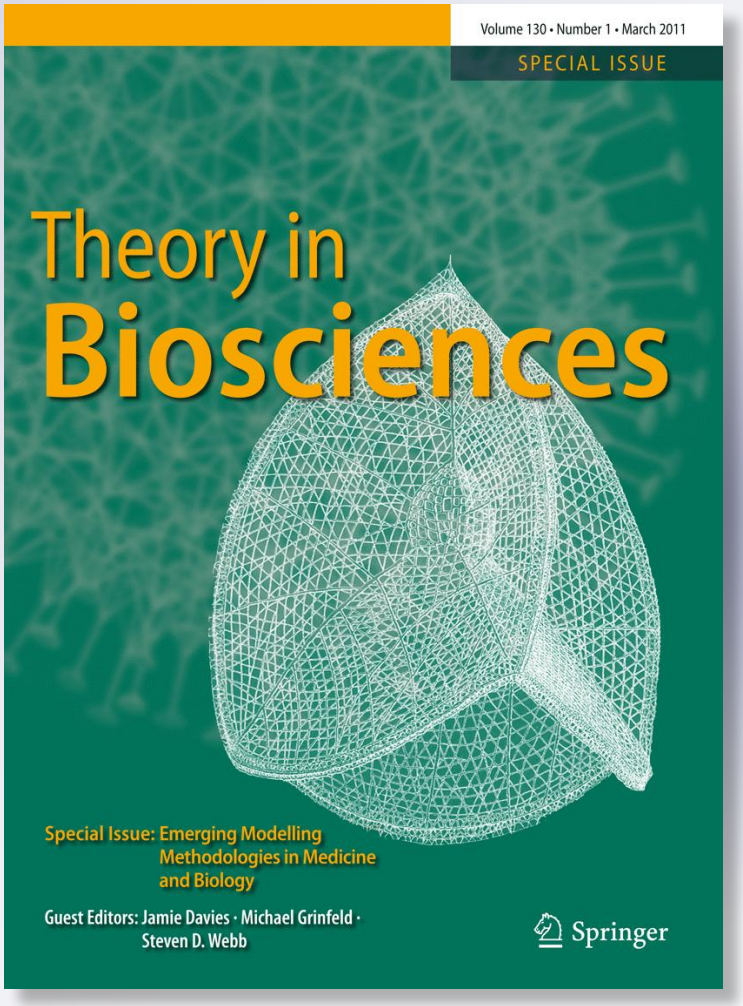

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ORIGINAL PAPER

Systemic investigation of a brain-centered model of the human energy metabolism

Britta Göbel · Dirk Langemann

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Abstract The regulation of the human energy metabolism is crucial to ensure the functionality of the entire organism. Deregulations may lead to severe pathologies such as diabetes mellitus and obesity. The decisive role of the brain as active controller and heavy consumer in the complex whole-body energy metabolism is the object of recent research. Latest studies suggest the priority of the brain energy supply in the competition between brain and body periphery for the available energy resources. In this paper, a systemic investigation of the human energy metabolism is presented which consists of a compartment model including periphery, blood, and brain as well as signaling paths via insulin, appetite, and ingestion. The presented dynamical system particularly contains the competition for energy between brain and body periphery. Characteristically, the hormone insulin is regarded as central feedback signal of the brain. The model realistically reproduces the qualitative behavior of the energy metabolism. Short-time observations demonstrate the physiological periodic food intake generating the typical oscillating blood glucose variations. Integration over the daily cycle yields a long-term model which shows a stable behavior in accordance with the homeostatic regulation of the energy metabolism on a long-time scale. Two types of abstract constitutive equations describing the interaction between compartments and signals are taken into consideration. These are nonlinear and linear representatives from the class of feasible relations. The robustness of the model against the choice of the representative relation is linked to evolutionary stability of existing organisms.

Keywords Systems biology · Mathematical model · Human energy metabolism · Selfish-Brain · Qualitative model · Model sensitivity

B. Göbel (✉)
Institute of Mathematics, Graduate School for Computing in Medicine and Life Sciences, University of Lübeck, Wallstraße 40, 23560 Lübeck, Germany
e-mail: goebel@math.uni-luebeck.de

D. Langemann
Institute Computational Mathematics, Technical University Braunschweig, Pockelsstraße 14, 38106 Braunschweig, Germany

Introduction

The systemic investigation of biological systems confronts mathematicians with two major difficulties. Firstly, there is an enormous number of mechanisms which are sufficiently relevant to be considered in the constitutive equations. Secondly, most of these mechanisms are not sufficiently quantified to be used in mathematical models determined to realistically reproduce experimental measurements.

Models of the human energy metabolism face these two difficulties. The two traditional concepts called glucostatic theory (Mayer 1953), which is still presented in medical text books, and lipostatic theory (Kennedy 1953), which is presently boosted by the recovery of the hormone leptin (Zhang et al. 1994), handle the named difficulties by postulating regulatory mechanisms without quantitative specification. Without any doubt, the regulatory mechanisms exist, and they are formed by numerous redundant but quantitatively not specified sub-mechanisms. Both theories work with very abstract constitutive equations combining the sub-mechanisms, and thus they are early systemic approaches to the human energy metabolism.

A new concept, the Selfish-Brain theory, includes regulatory mechanisms of both, the glucostatic and the

lipostatic theory, and extends them by the administrative position of the brain in the regulatory hierarchy (Peters et al. 2004). It could be shown that a mathematical model within the Selfish-Brain theory (Peters and Langemann 2009) can qualitatively reproduce medical observations like the energy contents of different organs in periods of inanition inanition (Krieger 1921) and the development of metabolic diseases as diabetes mellitus. This is not possible by means of the classical glucostatic or lipostatic theory (Peters et al. 2007).

In the present paper, we investigate a further mathematical model in the area of the Selfish-Brain theory, which deals with abstract energy contents in periphery, blood, and brain and which additionally focusses on signaling paths via insulin, ingestion, and appetite in the lateral hypothalamus (Morton et al. 2006). The energy exchange between the compartments as well as the activation of the signaling paths are again realized by a number of redundant sub-mechanisms, whose quantitative specification is only partly known. We overcome this uncertainty by robust modeling and by use of simple representative constitutive equations.

There exist various mathematical models describing interactions of the involved main determinants of the human energy metabolism. Several models are based either on the glucostatic or the lipostatic theory in which blood glucose or lipids are the regulated quantities. Exemplarily, one could mention the well-known Ackerman (1964) or Minimal Model (Bergman et al. 1981). Nevertheless, recent mathematical models support central aspects of the Selfish-Brain theory (Conrad et al. 2009; Langemann 2007; Langemann and Peters 2008). Furthermore, the impact of brain energy on pathological conditions such as ischemia is emphasized by means of detailed modeling of the brain energy metabolism (Vatov et al. 2006). The investigated dynamical system (Göbel et al. 2010) is a further development of former mathematical models including the brain as major controller and heavy consumer, cf. (Peters and Langemann 2009). As one novel characteristic, insulin is regarded as central feedback signal of the brain.

After introducing a mathematical model of the human whole-body energy metabolism in "Brain-centered energy metabolism model" section, and distinguishing between a short-term model containing the circadian ingestive behavior and a long-term model integrating over the daily cycle, we move on to the linearization of selected constitutive equations in "Linearization" section. It turns out that there is a class of constitutive equations which can be replaced by linearized versions without loss in the qualitative system behavior. However, the nonlinearity of a second class of constitutive equations is indispensable for the qualitative system behavior. This observation is supported by the simulation results in "Simulation results" section. In "Exogenous perturbations" section, we investigate how the linearization error is influenced by exogenous perturbations via parameter and initial value perturbation. Finally, in "Model analysis" section, the stability behavior of the presented brain-centered energy metabolism model is examined and a bifurcation analysis is performed.

The detection of the relations in the second class of constitutive equations is a central point in the systemic understanding of biological systems on a large scale, cf. (Langemann and Peters 2008). The detection focusses on the mathematical analysis of restricted sub-systems like supply chains (Langemann 2007). In this sense, we hope that the present paper with its sensitivity analysis of modified constitutive equations is a major step towards a systemic understanding of the human energy metabolism and towards a robust mathematical description and interpretation of qualitative models in systems biology.

Brain-centered energy metabolism model

Short-term model

The considered mathematical model of the energy metabolism consists on the one hand of energy fluxes between compartments and on the other hand of signals directing the energy fluxes within the organism, see Fig. 1. We consider the brain as superior regulatory instance (Peters et al. 2004) and as heavy energy consumer since the brain uses about 25% of the total body glucose utilization (Clark and Sokoloff 1999). The model contains several energy metabolites in separated compartments. The brain energy

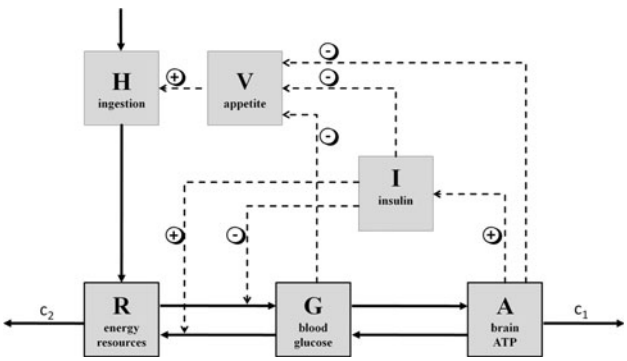

Fig. 1 Energy fluxes between compartments (*solid*) and control signals directing the energy fluxes in the organism (*dashed*). Energy supply chain of periphery R, blood G, and brain A. The ingested energy H passes the resources and the blood and is transported into the brain as final consumer. Energy is consumed by the brain (c_1) and the periphery (c_2). While the appetite V affected by A, G, and I controls the ingestion H, insulin controls the allocation to the brain via control of the blood glucose flux

content is denoted by A. It might be identified as the amount of high-energy phosphates in the brain like adenosine triphosphate (ATP) which is the universal form of immediately available energy in every body cell. The energy level in the blood is G consisting mostly of glucose and lactate. The energy resources in the body are called R which might be interpreted as available energy reserves in especially the muscle and fat tissue, liver, and gastrointestinal tract manifesting as glucose, glycogen etc. In addition to energy metabolites, the model contains control signals like plasma insulin denoted by I, the ingestion of energy H, and the appetite V.

The fluxes and signals in the abstract compartment model are not quantified but the direction of the dependencies is known. We model inductive influences as proportional relations, and prohibitive influences are described by anti-proportional relations. Thus, the glucose flux crossing the blood brain barrier by facilitated diffusion is proportional to G/A. The blood energy level G enforces the glucose flux across the blood brain barrier, whereas a high cerebral energy level A damps it. Likewise, the insulin-dependent glucose flux from the blood compartment into the resources is proportional to GI because the blood glucose level G needs to be high and the hormone insulin I needs to be available in the blood at the same time. Furthermore, the flux from the resources into the blood, which is composed of several sub-mechanisms, is modeled proportionally to R/G. Moreover, we assume that the resources are filled proportionally to the ingestion H because the resources compartment comprises the gastrointestinal tract amongst others. The energy consumption of the brain and that of the periphery are called c_1 and c_2 respectively. So, $c = c_1 + c_2$ is the total energy consumption of the organism.

The activation of the control signal insulin is a central new element in the presented model. Studies suggest that the allocation mechanism of the brain governs the production of the hormone insulin (Peters et al. 2004). The brain may supply itself with energy by dropping the insulin level. In this way, the insulin-dependent glucose flux into the body periphery is suppressed. The available blood glucose is assimilated into the brain since the glucose flux across the blood brain barrier is insulin-independent. Therefore, the model features an insulin production term proportional to the brain energy content A. This term reflects the competition for energy between brain and body periphery. The degradation of insulin is supposed to be of first order. Due to the close relation between the blood glucose level G and the fine deviations in the cerebral energy content A, a dependency of I on G can be observed in the simulation results, cf. "Simulation results" section, which is redundant in the constitutive model equations.

With low cerebral energy, blood glucose, and insulin level the appetite rises. Hence, in this model the appetite V anti-proportionally depends on brain energy A, energy content of the blood G, and insulin I. The ingestion H increases monotonously but strictly nonlinearly with the appetite V, the dependency is contained in a function f.

After parameter reduction by scaling, the brain-centered model of the energy metabolism is given by the system of nonlinear ordinary differential equations

$$\dot{A} = \frac{G}{A} - c_1, \tag{1a}$$

$$\dot{G} = -\frac{G}{A} - GI + p_1\frac{R}{G}, \tag{1b}$$

$$\dot{I} = p_2 A - I, \tag{1c}$$

$$\dot{R} = GI - p_1\frac{R}{G} + H - c_2, \tag{1d}$$

$$\dot{H} = p_5(p_3 f(V) - H) \tag{1e}$$

$$\text{with } V = \frac{p_4}{AGI} \tag{1f}$$

and with positive time-dependent functions A, G, I, R, H, V, and c_1, c_2 (Göbel et al. 2010). Likewise, the positiveness of the parameters $p_1, \ldots, p_5$ assures the monotonicity behavior of the effects described above. Figure 1 visualizes the different energy fluxes and signals of model (1).

Until now, the function f is monotonously increasing and saturated. That means $f{:}[0, \infty) \to [0, f_{\max}]$ with $f'(V) \geq 0$ for all V and $\lim_{V\to\infty} f(V) = f_{\max}$. Furthermore, the assumption of not more than one inflection point seems natural, and we get $f'(V) > 0$ for all V with $0 < f(V) < f_{\max}$. Since we have in mind that a small appetite induces a nearly vanishing ingestion, we call a function f fulfilling these conditions sigmoidal.

Long-term model

In the dynamical system (1), the parameter p_5 reflects the sensitivity of the organism to food intake consistent with its need for energy. A low value of p_5 indicates a slow adaption to the body's energy needs while a rather high value corresponds to a fast adaption to the energy needs of the body. For further increasing p_5 the ingestion is strongly regulated so that the energy uptake immediately satisfies the needs of the organism.

It is well known that food intake is mildly regulated on a short-time scale so that the daily ingestion regulation corresponds to a slow adaption to the body's energy needs. However, on a long-time scale extending over months or years we observe a strong regulation of food intake, i.e., an adaption to the organism's energy needs which is fast with respect to the long-time scale (Stanley et al. 2005).

The transition $p_5 \to \infty$ in system (1), i.e., an increasingly strong regulation of ingestion H, leads to $\lim_{p_5 \to \infty} H = p_3 f(V)$ (Walter 1970). Therefore, with $p_5 \to \infty$ we obtain the lower-dimensional system

$$\dot{A} = \frac{G}{A} - c_1, \tag{2a}$$

$$\dot{G} = -\frac{G}{A} - GI + p_1 \frac{R}{G}, \tag{2b}$$

$$\dot{I} = p_2 A - I, \tag{2c}$$

$$\dot{R} = GI - p_1 \frac{R}{G} + p_3 f\left(\frac{p_4}{AGI}\right) - c_2. \tag{2d}$$

While the ingestion is dynamically regulated in system (1) and oscillates around $p_3 f(V)$ on a short-time scale, this circadian oscillation is negligible on a long-time scale. The mean regulation of H to $p_3 f(V)$ becomes more and more important. Thus, system (2) is regarded as the related long-term model of the human energy metabolism which will give an inside into the long-term behavior of the model.

Stationary points

This subsection deals with the existence and uniqueness of stationary points of the dynamical systems (1) and (2) in the case of constant consumptions c_1 and c_2.

Proposition 1 *If f is sigmoidal and $c < p_3 f_{\max}$ holds true, then the dynamical system* (1) *has exactly one stationary point* $x^{\mathrm{s}}_{\infty} = \left(A_\infty, G_\infty, I_\infty, R_\infty, H_\infty\right)^\top$.

Proof The stationary condition $\dot{A} = \dot{G} = \dot{I} = \dot{R} = \dot{H} = 0$ and addition of (1a), (1b), and (1d) result in $H_\infty = c = c_1 + c_2$. Equation (1e) yields $p_3 f(V_\infty) = c$. Due to the preconditions, we find a unique $V_\infty = f^{-1}(c/p_3)$. Equations (1a) and (1c) give $G_\infty = c_1 A_\infty$ and $I_\infty = p_2 A_\infty$, and (1f) leads to $A_\infty G_\infty I_\infty = p_4/V_\infty$ implying

$$A_\infty = \sqrt[3]{\frac{p_4}{c_1 p_2 V_\infty}} = \sqrt[3]{\frac{p_4}{c_1 p_2 f^{-1}(c/p_3)}}.$$

Finally, (1b) provides

$$R_\infty = \frac{c_1^2 A_\infty}{p_1}\left(1 + p_2 A_\infty^2\right).$$

Thus, the stationary point is unique. □

Proposition 2 *If f is sigmoidal and $c < p_3 f_{\max}$ holds true, then the system of differential equations* (2) *has the unique stationary point* $x^{\mathrm{l}}_{\infty} = (A_\infty, G_\infty, I_\infty, R_\infty)^\top$ *with the notations from Proposition 1.*

Proof Proof is provided by analogous straight-forward calculation starting with system (2). □

Hence, the stationary point of system (2) is a projection of the stationary point of system (1). Thus, both stationary points coincide in the occurring quantities. The condition $c < p_3 f_{\max}$ is metabolically reasonable, the ability to ingest the consumed energy is a necessary prerequisite for the existence of stationary states of the organism.

Linearization

In "Brain-centered energy metabolism model" section, we have introduced the systems of nonlinear differential equations (1) and (2) describing the human energy metabolism on different time scales. The used terms in the constitutive equations are representatives from the class of feasible relations, i.e., from the class of functions with known monotonicity behavior. We study the robustness of our models against the choice of the representative relations, and we replace the terms G/A, GI, and R/G by their linearizations. We show that this replacement does not change the qualitative system behavior. However, the sigmoidal shape of the function f is essential for the system behavior. Therefore, the description of the appetite-dependent ingestion activation f and of the appetite V are retained.

We set $A = A_\infty + \Delta A$, $G = G_\infty + \Delta G$, $I = I_\infty + \Delta I$, and $R = R_\infty + \Delta R$ with the deviations ΔA, etc., from the stationary state. The linearizations of the terms G/A, GI, and R/G in the systems (1) and (2) are

$$\begin{aligned} GI &= (G_\infty + \Delta G)(I_\infty + \Delta I) \\ &= GI_\infty + IG_\infty - G_\infty I_\infty + \mathcal{O}(\Delta G + \Delta I)^2, \\ G/A &= (G_\infty + \Delta G)(1 - \Delta A/A_\infty)/A_\infty \\ &= G/A_\infty - (G_\infty/A_\infty^2)A + G_\infty/A_\infty + \mathcal{O}(\Delta G + \Delta A)^2, \\ R/G &= R/G_\infty - (R_\infty/G_\infty^2)G + R_\infty/G_\infty + \mathcal{O}(\Delta R + \Delta G)^2. \end{aligned} \tag{3}$$

If the terms G/A, GI, and R/G in the models (1) and (2) are replaced by these first-order Taylor approximations, then we get systems which are called linearizations of the models (1) and (2) in this paper, although they still contain nonlinear elements in the activation function f.

The question arises to what extent the terms $\mathcal{O}(\Delta G + \Delta I)^2$, etc., are negligible. Near the stationary point the behavior of the nonlinear system is controlled by the linear approximation. The analysis of the linear case provides some information about the local behavior of the nonlinear system. The solutions of a system of nonlinear differential equations look like those of its linearization near the stationary point, if all eigenvalues of the Jacobian in the stationary point have a nonzero real part (Hubbard and West 1995). In this general proposition, the term "look

like" means rather different things for different nonlinear systems but it surely contains the qualitative behavior of the solutions. In particular, the Theorem of Grobman and Hartmann assures the existence of a continuous bijective homeomorphism which locally maps the trajectories of the nonlinear system to the trajectories of the linearized system (Perko 2001). Several properties of the linearized set of equations are passed to the nonlinear system near the stationary point. In the following, we will demonstrate the effect of the linearization by numerical simulations of the systems (1) and (2).

Simulation results

In this section, we examine the behavior of our model (1) including the ingestion dynamic. We simulate the short-term regulation of the human whole-body energy metabolism. Furthermore, we are interested in the long-term behavior of our model metabolism. Therefore, we additionally examine mean ingestion on a long-time scale with our model (2). Moreover, we want to investigate the behavior of the nonlinear models in comparison to their linearizations.

For the numerical simulations we exemplarily use the sigmoidal function

$$f(V) = \frac{1}{2} + \frac{1}{\pi}\arctan\left(\frac{V - p_6}{p_7}\right) \tag{4}$$

describing the stimulus on food intake depending on the appetite V. Here, the parameter $p_6 > 0$ gives a loose threshold while $p_7 > 0$ controls the sensitivity of the ingestion stimulus. Since $f(V) \in [0, 1]$, the ingestion is modeled with maximal intake $f_{\max} = 1$.

We choose the parameter values p_j, $j = 1, \ldots, 7$, and the energy consumptions c_1, c_2 which assure that the stationary values are close to 1. The numerical calculations are made with $p = (p_j)_{j=1}^{7} = (2, 1, 4.8, 0.8, 1, 0.5, 0.001)^\top$, $c_1 = 0.8$, and $c_2 = 1.6$. These parameter values result in the stationary points $x_\infty^{\mathrm{s}} = (1.26, 1.01, 1.26, 1.04, 2.40)^\top$ with $V_\infty = 0.50$ and $x_\infty^{\mathrm{l}} = (1.26, 1.01, 1.26, 1.04)^\top$.

The trajectory of system (1) is called $x(t) = (A(t), G(t), I(t), R(t), H(t))^\top$. The disturbed stationary point $x(0) = x_\infty^{\mathrm{s}}(1 + \alpha)$ is used as initial value. The parameter α indicates the deviation from the stationary point in a selected direction. First, we choose $\alpha = 0.1$.

Figure 2 shows the simulation results of system (1) in comparison to its linearization (3). Both show a realistic qualitative behavior of the energy metabolism except in the sleep period, which is not included in the model. The short-term model (1) reproduces the circadian ingestive behavior which leads to oscillating energy contents in the compartments.

The simulation results reflect both mechanisms to provide the brain with sufficient energy, allocation, and ingestion. First, when the brain energy A decreases, the brain protects its energy supply via allocation. The insulin level I drops in order to reduce the glucose uptake into the resources and to strengthen the glucose flow across the blood brain barrier from the blood into the brain. Secondly, when the brain energy A, the insulin I, and the blood glucose G are low, the allocation mechanism does not suffice to adequately supply the brain with energy, thus increasing the ingestion H. Hereafter, the energy contents R, G, and A increase, and the increase starts in the energy resources R since they include the gastrointestinal tract. Then, the ingested energy attains to the blood and to the brain. Furthermore, the insulin I increases governed by the brain energy A as the hormone is required to abolish excess glucose from the blood.

Thus, model (1) and its linearization reproduce the physiological periodic appetite generation, cf. (Langemann and Peters 2008), and both generate oscillating energy contents in the compartments with the typical blood glucose and insulin variations. In particular, the frequencies of the oscillations are very similar.

Figure 3 depicts the two-dimensional phase plot (A, G) of model (1). It reflects that the nonlinear dynamical system as well as the linearization settle to a periodic orbit.

We use two error measures to evaluate the difference between the solution of (1) and of its linearization. The trajectory of the linearization is denoted by $x^{\mathrm{L}}(t)$. The maximum relative error between the trajectory $x(t)$ and the solution $x^{\mathrm{L}}(t)$ of the linearized short-term model in the time interval T is the vector

$$\delta x^{\mathrm{s}} = \left(\max_{t \in T} \frac{|x_j^{\mathrm{L}}(t) - x_j(t)|}{x_j(t)}\right)_{j=1}^{5}. \tag{5}$$

The example above with $T = [20, 40]$, i.e., after the transient phase, yields $\delta x^{\mathrm{s}} = (0.0281, 0.0766, 0.0161, 0.2882, 0.8331)^\top$.The last components are relatively large because the denominator in (5) is small, see Fig. 2 for the smallness of the difference between $x(t)$ and $x^{\mathrm{L}}(t)$.

The second error measure is the Hausdorff distance δ_{H} of the trajectory $x(t)$ to the solution $x^{\mathrm{L}}(t)$ of the linearized system in the phase plot (Barnsley 1993)

$$\delta_{\mathrm{H}} x^{\mathrm{s}} = \sup_{t_2 \in T} \inf_{t_1 \in T} \left\| x^{\mathrm{L}}(t_1) - x(t_2) \right\|_2. \tag{6}$$

This measure idealizes from possible phase shifts in the oscillating solutions. In our example with $T = [20, 40]$, we find the Hausdorff distance $\delta_{\mathrm{H}} x^{\mathrm{s}} = 0.0906$. The Hausdorff distance has the same order of magnitude as the maximum

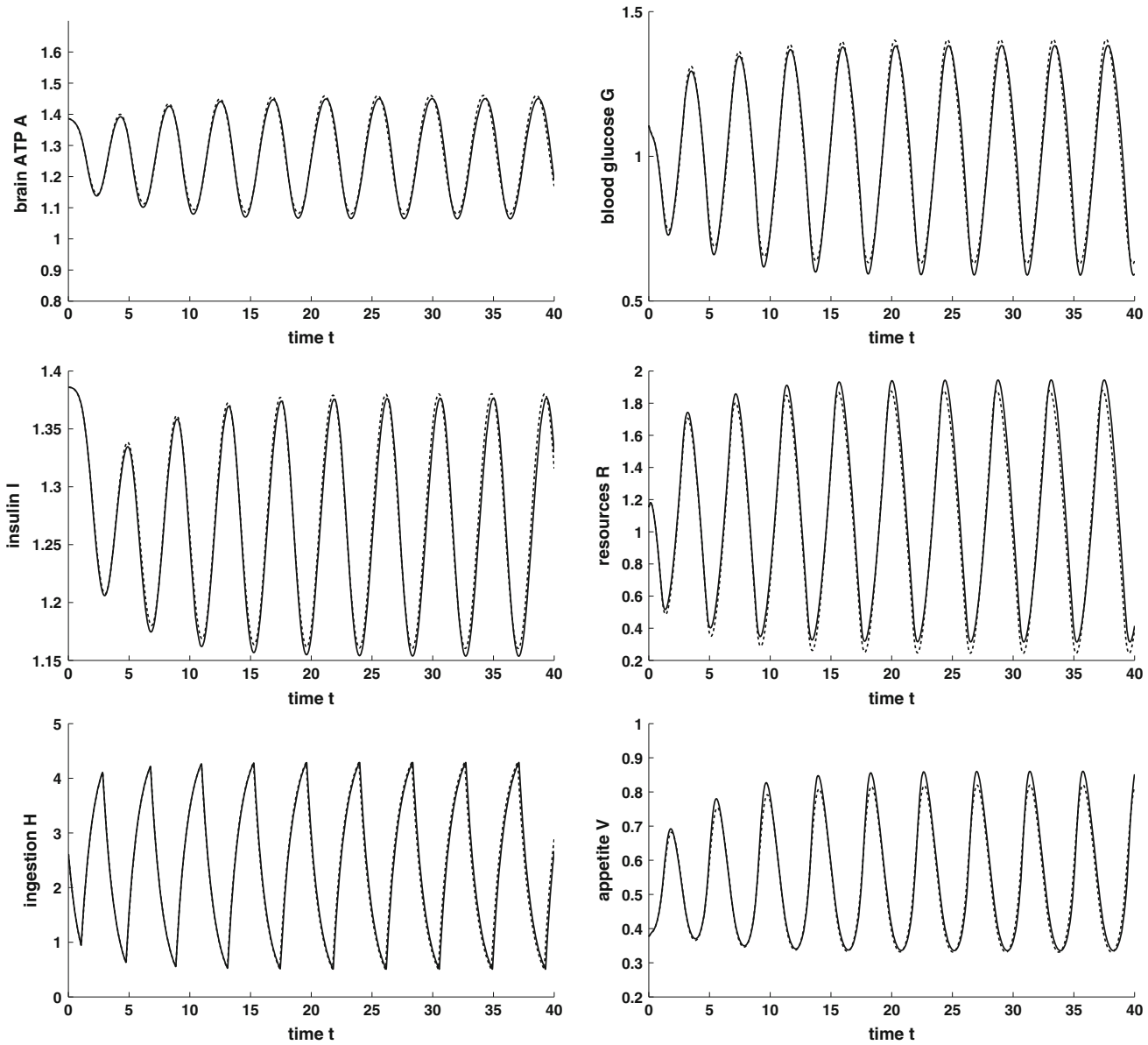

Fig. 2 Brain energy A, blood glucose G, insulin level I, energy resources in the body R, ingestion H, and appetite V in the short-term model. Simulation results of model (1) in *solid lines* compared to the simulation results of the linearized short-term model in *dashed lines*

relative error indicating that the phase is at most slightly shifted.

Long-term effects in the energy metabolism are simulated by model (2). Figure 4 shows the simulation results of the nonlinear dynamical system (2) in comparison to its linearization. We observe stable energy contents. These results underline that the energy metabolism is homeostatically regulated on a long-time scale.

Regarding the simulation results of system (2) in comparison to its linearization, we see that the trajectories of the nonlinear and the linearized system are almost indiscernible since the solutions quickly settle to the stationary values over time. The error measures δx^{l} and $\delta_{\mathrm{H}} x^{\mathrm{l}}$ for the long-term model (2) are formed analogously to δx^{s} in (5) and $\delta_{\mathrm{H}} x^{\mathrm{s}}$ in (6) but with four components only. With $T = [1, 5]$, we find $\delta x^{\mathrm{l}} = (0.0025, 0.0129, 0.0015, 0.1465)^{\top}$, again with a relatively large last component, and the Hausdorff distance is $\delta_{\mathrm{H}} x^{\mathrm{l}} = 0.0169$.

Therefore, the solutions of the systems of nonlinear differential equations (1), (2) and of their linearizations feature the same qualitative behavior. Hence, one cannot decide if the solution of the nonlinear dynamical system or the solution of its linearization is appropriate.

Exogenous perturbations

In this section, we investigate the influence of exogenous perturbations on the difference between linearized and nonlinear system (1). The results are similar for the dynamical system (2).

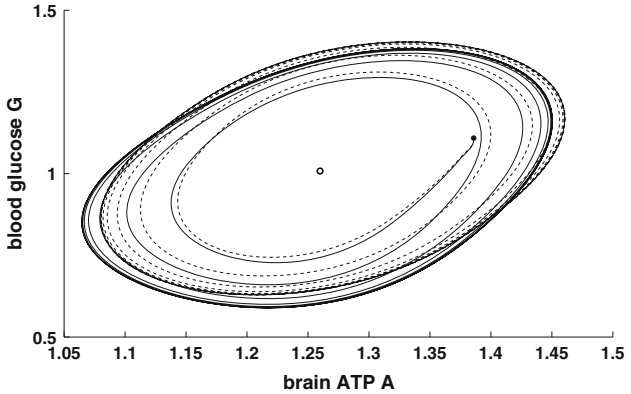

Fig. 3 Two-dimensional intersection of the phase plot of system (1) (*solid*) and of its linearization (*dashed*). Additionally, the initial value (*dotted*) and the stationary state x^s_∞ (*circle*)

Parameter perturbation

We investigate how the perturbation of parameter values influences the deviation between system (1) and its linearization. Exemplarily, we simulate a temporary increase in peripheral energy consumption c_2. The rise in peripheral energy consumption is an external load on the dynamical system. It can be regarded as a change in the environmental conditions, as a disease of the organism causing a higher energy need for identical actions or even as physical exercise. Shortly, this intervention combines all influences leading to a higher energy consumption of the muscle tissue.

Figure 5 shows the simulation results of the nonlinear dynamical system (1) in comparison to its linearization with temporarily increased energy consumption in the body periphery c_2. Since more energy is consumed by the body during the external load to the system, the energy resources in the body R are reduced, and the blood glucose level G is decreased as compared to the resting state. The energy flux across the blood brain barrier is slightly reduced since less glucose is available in the blood. This slightly decreases the brain energy level A. The reduced brain energy content activates the allocation via reduction of the insulin level I to assure the energy supply of the brain. This behavior

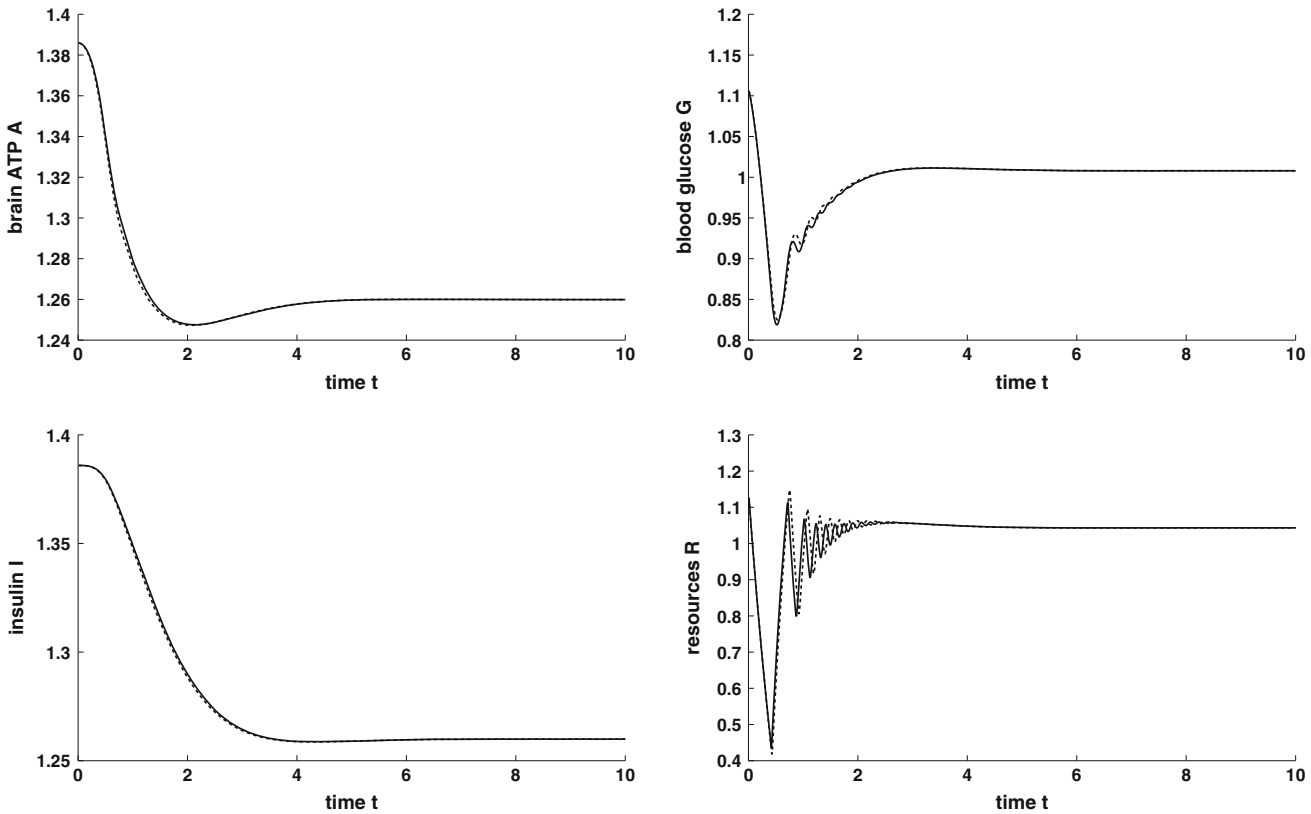

Fig. 4 Brain energy A, blood glucose G, insulin I, and energy resources in the body R in the long-term model. The simulation results of model (2) are depicted in *solid lines*, its linearization is shown in *dashed lines*

corresponds to experimental observations (Reilly et al. 1990). In order to satisfy the energy demand and to assure the energy supply of the organism during the increased need, the appetite V is increased, as expected, and more energy H is ingested.

Figure 6 depicts the maximum relative error δx^s in (5) and the Hausdorff distance $\delta_H x^s$ in (6) depending on the percentage increase in the peripheral energy consumption c_2. With rising parameter perturbation, we observe an increase in the components of δx^s as well as in $\delta_H x^s$. This corresponds to the simulation results shown in Figure 5. We see that the difference between $x(t)$ and $x^L(t)$ increases with the temporary increase in peripheral energy consumption c_2. A stronger perturbation means a larger deviation from the stationary point, and consequently the influence of the higher-order terms in the Taylor approximations (3) grows.

Initial value perturbation

Now, we investigate the linearization error of the dynamical system (1) depending on α which quantifies the deviation of the initial value from the stationary state. Figure 7 shows components of the maximum relative error δx^s and

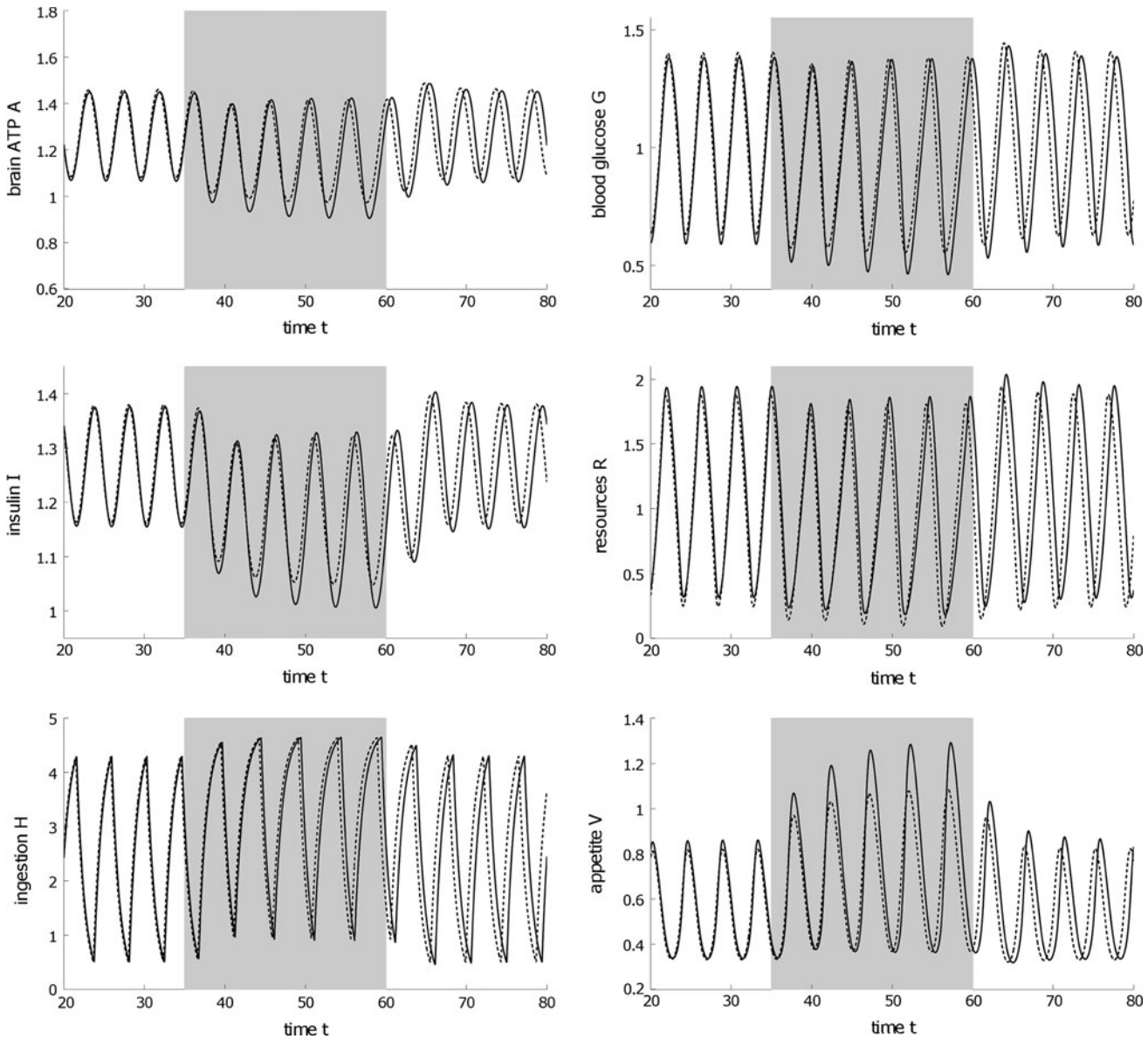

Fig. 5 Brain energy A, blood glucose G, insulin level I, energy resources in the body R, ingestion H, and appetite V in the short-time model. Simulation results of model (1) are given in *solid lines* in comparison to the simulation results of the linearized short-term model in *dashed lines*. During the external load the peripheral energy consumption c_2 is increased by 50%. The *gray background* marks the intervention interval [35,60]

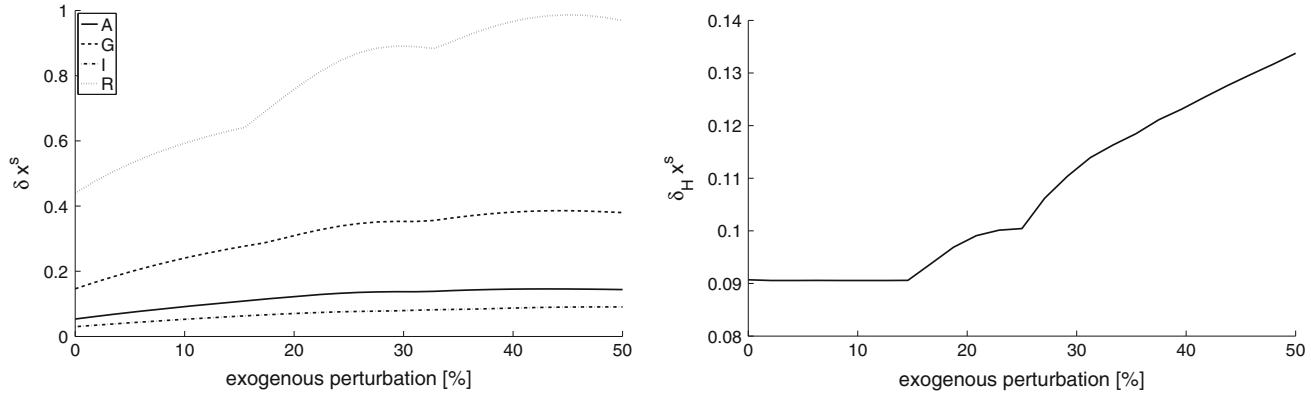

Fig. 6 Components of the error δx^s between the short-term model (1) and its linearization (*left plot*) as well as the Hausdorff distance $\delta_H x^s$ (*right plot*) with $T = [20, 80]$ depending on percentage increase in peripheral energy consumption c_2. Note that the fifth component of δx^s quantitatively behaves identically

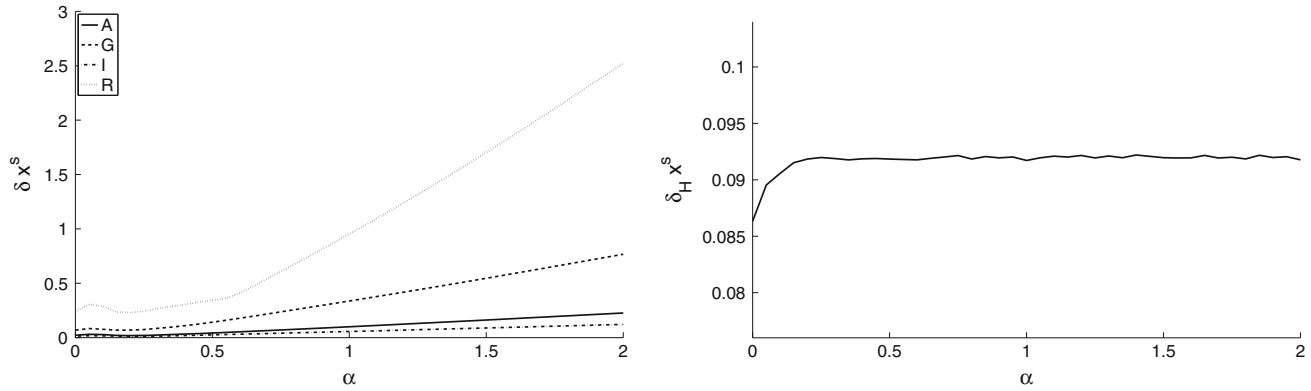

Fig. 7 Components of the error δx^s (*left plot*) and Hausdorff distance $\delta_H x^s$ (*right plot*) with $T = [20, 40]$ depending on the deviation α of the initial value from the stationary point. Note that the quantitative behavior of the fifth component of δx^s is identical

the Hausdorff distance $\delta_H x^s$ depending on α. We observe that the components of δx^s nearly linearly increase with α where astonishingly $\delta_H x^s$ remains almost unchanged. This can be explained by the fact that larger perturbations evoke a phase shift in the solutions from which is idealized in the Hausdorff distance. Hence, the qualitative system behavior remains unchanged.

Repeated parameter perturbation

The dynamical system (1) is not created and not appropriate to simulate the effects of long-term training, of the metabolic memory or of an evolutionary selection process. But it may serve as core in an extended model. Here, we present a model extension by an abstract memory term which influences the insulin metabolism and the energy allocation mechanism of the brain.

In order to simulate repeated external loads on the energy need, we introduce a metabolic memory M into system (1). The memory M increases during the training process, i.e., it remembers periods of increased energy needs which are periods of slightly decreased energy supply into the brain (Maren 1999). The center of metabolic learning may be located in the amygdala (Langemann et al. 2008). From the physiological point of view, the repeated increase in peripheral energy consumption can be regarded as regular physical exercise. During the learning process, the insulin production is diminished due to enhanced insulin sensitivity (Bobbert et al. 2007) and thereby the allocation is strengthened. Then, the extended dynamical system reads

$$\dot{A} = (1 + \beta M)\frac{G}{A} - c_1, \tag{7a}$$

$$\dot{G} = -(1 + \beta M)\frac{G}{A} - GI + p_1\frac{R}{G}, \tag{7b}$$

$$\dot{I} = (1 - \gamma M)p_2 A - I, \tag{7c}$$

$$\dot{R} = GI - p_1\frac{R}{G} + H - c_2, \tag{7d}$$

$$\dot{H} = p_5\left(p_3 f\left(\frac{p_4}{AGI}\right) - H\right), \tag{7e}$$

$$\dot{M} = \mu(\tilde{c}_2(t) - c_2). \tag{7f}$$

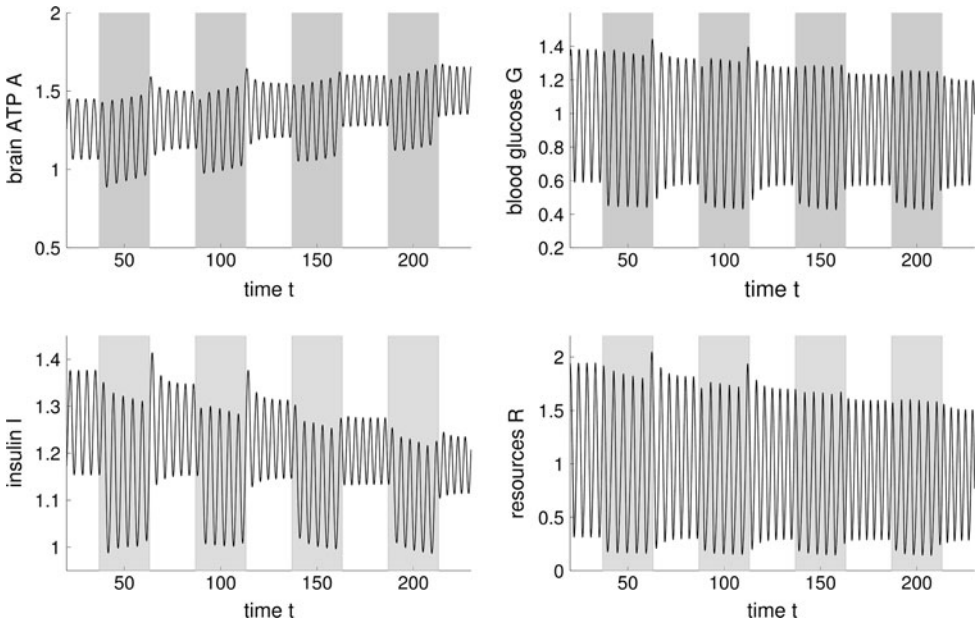

Fig. 8 Brain energy A, blood glucose G, insulin level I, and energy resources in the body R. The simulation results of model (7) are given with repeated external load on the energy need. During load the peripheral energy consumption c_2 is increased by 50%. The *gray background* marks the intervention intervals

Here, $\tilde{c}_2(t)$ denotes the time-dependent peripheral energy consumption, whereas c_2 is a constant. We choose the parameter values as before and, additionally, we set $\beta = 0.4$, $\gamma = 0.3$, and $\mu = 0.01$ for the simulations.

Figure 8 shows the simulation results of system (7) with repeated external load. Simulations without any load are shown at $t \in [20, 40]$ before the first intervention interval. During the interventions, the simulations coincide with the results in "Parameter perturbation" section. During the training process with repeated external load, the brain energy level A increases, thus assuring an appropriate energy supply of the brain with increased need after training. The insulin level I drops during the learning process. Experiments prove that trained subjects have a lower insulin level than untrained persons (Bobbert et al. 2007). This observation supports our simulation results. During the training process, as expected, the blood glucose level G and the energy resources in the body R are reduced compared to the untrained state. Note that the resources compartment comprises muscle as well as fat tissue, thus applying to the total mass of energy stores rather than to changes in the ratio of muscle to fat tissue. Ingestion H and appetite V are almost unaffected by the training process. Merely the ravenous appetite which occurs with increased energy need before the learning period slightly decreases. This demonstrates that system (1) can be used as core in a model hierarchy including metabolic memory or further regulatory mechanisms like stress, evolutionary selection, etc.

With the transition $p_5 \to \infty$ in system (7), we obtain a lower-dimensional dynamical system which describes the long-term behavior of model (7) (compare "Long-term model" section). The simulation results show a stable behavior. With increasing number of completed learning periods, cerebral ATP A stepwise increases, whereas the insulin level I, blood glucose G, and energy resources R decline with decreasing extent. Therefore, the model behaves as system (7), merely the circadian oscillation is neglected.

Model analysis

Stability analysis

In this section, we investigate the stability of the stationary point x^s_∞ of system (1). For now, we assume the cerebral energy consumption c_1 as well as the peripheral energy consumption c_2 to be constant.

The following proposition shows that a smooth or soft appetite activation leads to a constant, permanent food intake and hence, it is not appropriate to simulate the circadian rhythm of food intake. Consequently, Proposition 3 proves that a steep, sensitive appetite activation is indispensable for an energy metabolism model.

Proposition 3 *On condition of a sufficiently small derivative* $f'(V_\infty)$ *the stationary point* x^s_∞ *of system* (1) *is asymptotically stable.*

Proof The Jacobian of the dynamical system (1) is given by

$$J^{\mathrm{s}} = \begin{pmatrix} -G/A^2 & 1/A & 0 & 0 & 0 \\ G/A^2 & -1/A - I - p_1 R/G^2 & -G & p_1/G & 0 \\ p_2 & 0 & -1 & 0 & 0 \\ 0 & I + p_1 R/G^2 & G & -p_1/G & 1 \\ -uf'(V)/A & -uf'(V)/G & -uf'(V)/I & 0 & -p_5 \end{pmatrix}$$

with $u = (p_3 p_4 p_5)/(AGI) > 0$. Since $G_\infty = c_1 A_\infty$, $I_\infty = p_2 A_\infty$, and $p_1 R_\infty / G_\infty^2 = p_2 A_\infty + A_\infty^{-1}$, the Jacobian evaluated in the stationary point x_∞^{s} reads

$$J_\infty^{\mathrm{s}} = \begin{pmatrix} -c_1/A_\infty & 1/A_\infty & 0 & 0 & 0 \\ c_1/A_\infty & -2/A_\infty - 2p_2 A_\infty & -c_1 A_\infty & p_1/(c_1 A_\infty) & 0 \\ p_2 & 0 & -1 & 0 & 0 \\ 0 & 1/A_\infty + 2p_2 A_\infty & c_1 A_\infty & -p_1/(c_1 A_\infty) & 1 \\ -vf'(V_\infty) & -vf'(V_\infty)/c_1 & -vf'(V_\infty)/p_2 & 0 & -p_5 \end{pmatrix}$$

where $v = (p_3 p_4 p_5)/(c_1 p_2 A_\infty^4)$.

We will show that J_∞^{s} has eigenvalues with negative real parts only. The characteristic polynomial reads

$$\det(\lambda E - J_\infty^{\mathrm{s}}) = a_5\lambda^5 + a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$$

with the coefficients

$$\begin{aligned}
a_5 &= 1, \\
a_4 &= (c_1^2 + p_1 + c_1(2 + A_\infty + 2A_\infty^2 p_2 + A_\infty p_5))/(A_\infty c_1), \\
a_3 &= (c_1^2 + p_1 + c_1 p_1 + A_\infty(2c_1 + c_1^2 + p_1)(1 + p_5) \\
&\quad + 2A_\infty^3 c_1 p_2(1 + p_5) + A_\infty^2 c_1(2c_1 p_2 + p_5))/(A_\infty^2 c_1), \\
a_2 &= (c_1 p_1(1 + p_5 + A_\infty p_5) + c_1^2(p_1 + 2A_\infty p_5 + p_1 p_5 \\
&\quad + 2A_\infty^3 p_2 p_5) + c_1^3(1 + p_5 + A_\infty p_5 + A_\infty^2 p_2(3 + 2p_5)) \\
&\quad + A_\infty f'(V_\infty) p_1 v)/(A_\infty^2 c_1^2), \\
a_1 &= (c_1^2 p_1 p_5 + c_1^3(p_5 + 3A_\infty^2 p_2 p_5) + A_\infty f'(V_\infty) p_1 v \\
&\quad + c_1 p_1(p_5 + 2f'(V_\infty)v))/(A_\infty^2 c_1^2), \\
a_0 &= (3f'(V_\infty) p_1 v)/(A_\infty^2 c_1).
\end{aligned}$$

Since the coefficients $a_0, \ldots, a_5$ are positive for all parameters, the necessary condition for negative real parts holds true. Following the Hurwitz criterion, we investigate the minors $\mathscr{H}_1, \ldots, \mathscr{H}_5$ of the Hurwitz matrix (Khalil 2002). It is $\mathscr{H}_1 = a_4 > 0$. Since $\mathscr{H}_5 = a_0 \mathscr{H}_4$ holds true, $\mathscr{H}_5 > 0$ if and only if $\mathscr{H}_4 > 0$. Therefore, we have to investigate the positivity of the critical terms $\mathscr{H}_2$, $\mathscr{H}_3$, and $\mathscr{H}_4$. Since $\mathscr{H}_2$ is linear in $z = f'(V_\infty)$, $\mathscr{H}_3$ is quadratic in z, and $\mathscr{H}_4$ is cubic in z. These minors can be seen as functions of z with the Taylor expansions

$$\begin{aligned}
\mathscr{H}_2(z) &= \mathscr{H}_2(0) + z\mathscr{H}_2'(0), \\
\mathscr{H}_3(z) &= \mathscr{H}_3(0) + z\mathscr{H}_3'(0) + z^2\mathscr{H}_3''(0)/2, \\
\mathscr{H}_4(z) &= \mathscr{H}_4(0) + z\mathscr{H}_4'(0) + z^2\mathscr{H}_4''(0)/2 + z^3\mathscr{H}_4'''(0)/6.
\end{aligned}$$

Since $\mathscr{H}_2(0)$, $\mathscr{H}_3(0)$, and $\mathscr{H}_4(0)$ are constructed by positive terms only, it follows that $\mathscr{H}_2(0) > 0$, $\mathscr{H}_3(0) > 0$, and $\mathscr{H}_4(0) > 0$. Therefore, sufficient small $z = f'(V_\infty)$ always assures asymptotical stability of the stationary point x_∞^{s}. □

Proposition 3 says that a gradual ingestion activation results in stable behavior which is of course localized to the vicinity of the stationary point. A steep, i.e., more sensitive, appetite-dependent food intake activation may lead to periodic ingestive behavior, cf. (Langemann and Peters 2008), where the necessity of a steep appetite activation is proven. Since the matrix J_∞^{s} is rather filled with nontrivial terms, the explicit eigenvalues or the Hurwitz criterion lead to very long expressions. A rigorous analysis would give a lower bound of $f'(V_\infty)$ for the negativity of the named minors. All slopes exceeding the bound may lead to oscillating behavior in the short-term model (1), while the long-term model (2) still has a stable stationary point.

The numerical calculation of the eigenvalues of J_∞^{s} for $p = (2, 1, 4.8, 0.8, 1, 0.5, 0.001)^\top$, as above, results in positive real parts except in a small stability range where $c \approx p_3 f_{\max}$. This means that the short-term model oscillates except in the rare situation that the permanent total energy consumption is close to the maximal energy intake. By the way, this rare situation corresponds to a rather small slope $f'(V_\infty)$ because $V_\infty = f^{-1}(c/p_3)$ is large and the

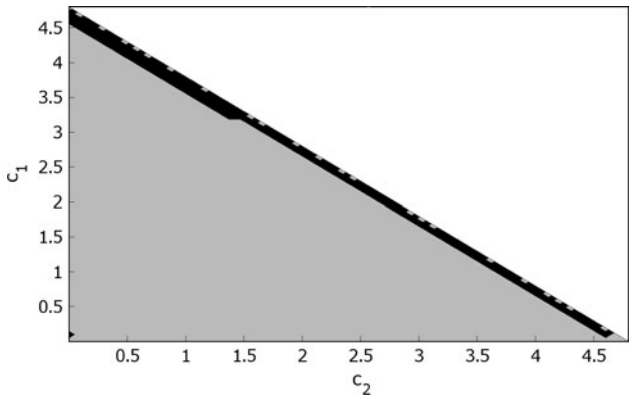

Fig. 9 Stability ranges of system (1) depending on cerebral energy consumption c_1 and peripheral energy consumption c_2. Stable ranges are *black*, whereas parameter combinations which lead to an instable system behavior are colored *gray*

appetite V is permanently high. Thus, Proposition 3 is found in the numerical results. Figure 9 shows the small stability range depending on (c_1, c_2).

Limit cycle and bifurcations

Proposition 3 proves that for increasing $f'(V_\infty)$ the stability properties of the unique stationary point of system (1) change and the stationary point becomes instable. The steepness of the sigmoidal function f is determined by the parameter p_7. Therefore, Proposition 3 implies that for small parameter values p_7 system (1) is not asymptotically stable concerning the stability of the stationary point. Hence, small parameter values p_7 are a necessary condition for oscillating behavior describing periodic ingestive behavior. Our results show that this holds true for the short-term model (1) as well as for its incomplete linearization (3).

We perform a numerical bifurcation analysis of system (1) and its incomplete linearization (3), and we consider the steepness parameter p_7 of the sigmoidal function f as a bifurcation parameter. The direct proof of the existence of limit cycles via Poincaré maps is very technical due to the dimension of the investigated dynamical system and the numerousness of system parameters.

For the bifurcation analysis, we use the initial values $p = (2, 1, 4.8, 0.8, 1, 0.5, 0.001)^\top, c_1 = 0.8, c_2 = 1.6$, as above, and the system parameter p_7 is varied. Figure 10 shows the results of the bifurcation analysis in (p_7, A, G)-space for system (1) (left plot) and its incomplete linearization (right plot). We observe a Hopf bifurcation point, i.e., a local bifurcation in which the unique stationary point of the dynamical system loses stability, at $p_7 = 0.1042$ for system (1) and at $p_7 = 0.1045$ for its incomplete linearization. Under reasonably generic assumptions about the dynamical system, a limit cycle branches from the stable stationary point in the neighborhood of the Hopf bifurcation. In the second step, we compute a branch of limit cycles starting from the Hopf point. The limit cycles oscillate around the stationary points with increasing amplitude.

We again observe that the qualitative behavior of system (1) and its linearization is very similar. Note that nonlinearity of the ingestion activation function f and the appetite V is indispensable for the qualitative system behavior. Without these nonlinear elements no bifurcations occur.

Bifurcation analysis using the First Lyapunov Value permits to decide whether the transition over the bifurcation point provokes either stability or instability (Guckenheimer and Holmes 2002; Jost 2005). The limit cycle is orbitally stable if the First Lyapunov Value L_1 at the bifurcation point is negative. We obtain the First Lyapunov Value $L_1 = -0.20 < 0$ for system (1) and $L_1 = -0.18 < 0$ for its linearization. Hence, in case of a transition over the bifurcation point a stable limit cycle (self-oscillations) emerges.

Figure 11 shows the eigenvalues of the Jacobian J^s_∞ in the stationary point of system (1) in the complex plane for varying steepness parameter p_7. It supports the results of

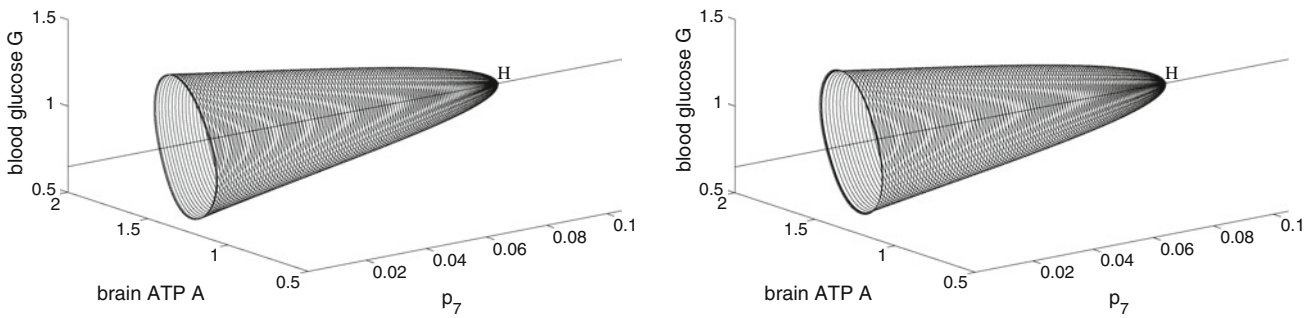

Fig. 10 Stationary points and limit cycles in (p_7, A, G)-space for system (1) (*left plot*) and its linearization (*right plot*). The points H undergo a Hopf bifurcation

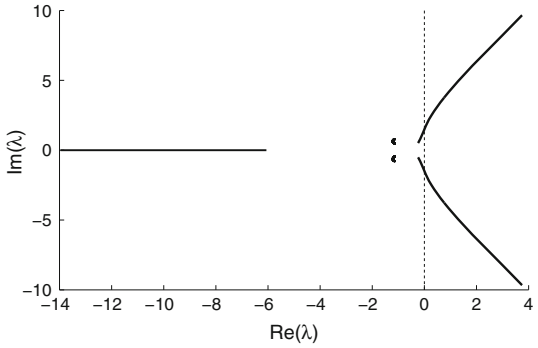

Fig. 11 Eigenvalues of the Jacobian J^s_∞ in the stationary point of system (1) in the complex plane for $p_7 \in [0.001, 1]$. In the Hopf bifurcation point, a pair of complex conjugate, purely imaginary eigenvalues crosses the imaginary axis

the bifurcation analysis. In the Hopf bifurcation point at $p_7 = 0.1042$, we obtain the eigenvalues $\lambda = (-6.32, 1.50i, -1.50i, -1.20 + 0.70i, -1.20 - 0.70i)^\top$, and hence a pair of complex conjugate, purely imaginary eigenvalues crosses the imaginary axis there.

The bifurcation analysis yields good agreement with our former findings. For small parameter values p_7, i.e., a steep ingestion activation function f, we observe oscillating behavior of system (1) and its linearization, whereas for bigger parameter values p_7 we obtain an asymptotically stable stationary point in both cases. Therefore, it exists a limit cycle, at least for parameter values p_7 which are slightly smaller than the Hopf bifurcation point.

Conclusion

The mathematical investigation of the human energy metabolism including the particular role of the brain has here led to a short-term model comprising abstract energy contents in selected compartments and the signaling pathways insulin, appetite, and ingestion. The short-term model is integrated into a long-term model by a strong adaption of the ingestion to the body's energy need, what is valid on a long-time scale. Both models reproduce the qualitative behavior of the human energy metabolism. Modeling the appetite regulation on a short-time scale yields the physiological periodic food intake and oscillating energy levels in the compartments. Therefore, the model describes the circadian ingestive behavior with the typical blood glucose and insulin variations. However, examining a mean ingestion on a long-time scale results in stable respectively homeostatic energy levels. Additionally, both models realistically reflect selected exogenous influences. The short-term model reproduces a single increase in energy need, and both models are able to reflect repeated load such as regular physical exercise.

This paper focusses on the sensitivity of the mathematical models to the particular choice of the constitutive equations which describe the energy fluxes and control signals. Thus, the simulation results of a nonlinear and a linearized version of the constitutive equations have been compared. We have found that the fluxes between the compartments do not sensitively influence the qualitative behavior of the model. Furthermore, even the quantitative influence of changes in the constitutive relations is small.

Moreover, we have conducted parameter as well as initial value perturbations. These systemic investigations provide further new aspects regarding the robustness of the model behavior. We have found that the qualitative system behavior remains unchanged for initial value perturbations as well as for moderate parameter perturbations.

These observations correspond to evolutionary stability. This means that the evolutionary selection process might have generated organisms with robust redundant regulatory mechanisms, the qualitative behavior of which is not affected by physiologically feasible exogenous changes. A future programme is the investigation of robust mathematical methods for the qualitative understanding of systems with uncertain constitutive relations in life sciences.

In forthcoming considerations, the investigated dynamical system shall be discussed in its interactions to other regulatory systems such as the stress axis (Conrad et al. 2009) or metabolic memory (Langemann et al. 2008). "Repeated parameter perturbation" section is a first approach to include metabolic learning in the model. The described dynamical system shall be expanded by further sub-compartments. For instance, the resources compartment comprises muscle and fat tissue as well as liver and gastrointestinal tract in our model in order to assure its compactness. We want to subdivide the resources compartment allowing differentiation of its components. Then, changes in the ratio of muscle to fat tissue during a learning period with repeated increase in energy need will be represented. The nonlinear dynamical system (Göbel et al. 2010) which is investigated in this paper and the linear model (Peters and Langemann 2009) both describe the human energy metabolism regarding the priority of the brain energy supply. Hence, they are representatives of different modeling approaches describing similar aspects. In particular, they represent the indispensable role of the brain as anergy consumer and as regulatory administration and try to contribute to the systemic understanding of the human energy metabolism, its adaption to exogenous changes, and its pathologies.

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