

# Selfish-brain theory: challenges in the top-down analysis of metabolic supply chains

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## Abstract

The Selfish-brain theory has created the theoretical basis for the systemic analysis of the energy metabolism in terms of a supply chain. The energy in form of glucose equivalents is transported from the exterior environment into the brain where it is finally consumed as ATP in the neurons. The transport process is governed by the brain itself as regulatory authority.

We discuss general supply chains and certain components to understand regulatory mechanisms in metabolic supply chains. Push and pull mechanisms are distinguished and discussed in detail. The dynamical systems describing supply chains are related to partial differential equations and they inherit their properties.

Furthermore, certain components like side compartments are regarded which act as short-time store. Examples are glycogen in the glycolysis or the fat compartment in the individual metabolism. Similar supply chains and regulatory mechanisms can be identified at different levels.

Due to the large amount of regulative substances and hormones involved in the regulation and the lack of quantitative knowledge, a bottom-up modelling fails and minimal models can provide a qualitative understanding. There are several observations and experimental results, from which certain properties of the supply chains can be deduced. A top-down analysis identifies crucial elements and allows a virtual pre-selection of experiments.

Finally, we present hierarchically ordered regulatory loops for the allocation, the appetite and the exploration for the simulation of daily cyclic behaviour and its development on a medium-term time-scale. Metabolic diseases can be understood as disturbances or congestions in the supply chain.

*Keywords:* Selfish-brain theory, supply chains, hierarchical regulatory loops, allocation, appetite, exploration.

## 1 Introduction

The delivery of nutrients or energy into organs consuming the nutrients or the energy is organized by supply chains. Within the supply chain, the transported matter is transformed. That motivates the

investigation of general supply chains and the discussion of their typical behaviour.

After two introductory examples in Sec. 1, which are the glycolysis known from textbook literature (Berg et al. 2002, Löffler et al. 2007) and the individual energy supply chain respective to the Selfish-brain theory (Peters et al. 2004), Sec. 2 discusses the example at the molecular level in more detail, and Sec. 3 deals with general supply chains. In particular, the role of push and pull components and the influence to the behaviour of the supply chain as a whole is investigated. The following Sec. 4 puts metabolic supply chains at the individual level in concrete terms. In particular, a minimal model for the appetite regulation is created. Necessary elements of the minimal model are deduced from general observations. This top-down approach leads to hierarchically ordered regulatory loops for allocation, appetite and exploration. The paper finishes with a conclusion and open questions.

Our example at the molecular level is the glycolysis. Here, glucose is transformed into pyruvate and finally into lactate in the mitochondria. Lactate is further transformed into ATP in the citric acid cycle. Although, glucose itself is not delivered within the glycolysis, there is a central linear pathway of transformation. It follows the transformation process from glucose via glucose-6-phosphate (G6P) to fructose-6-phosphate (F6P) and so on. In the first step, glucose is enriched by the reaction with a phosphate group from ATP. Nevertheless, glucose is transformed into G6P, and the influence of ATP is subordinate. Glucose is the supplier and pyruvate is the recipient of the transformation process.

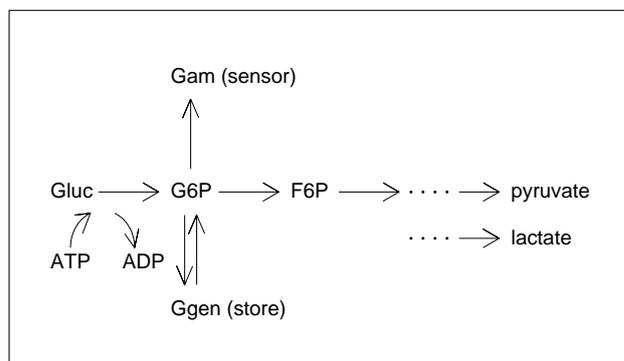


Figure 1: First steps of the glycolysis: glucose (Gluc) is energetically enriched to glucose-6-phosphate (G6P). Glycogen (Ggen) is a side compartment which acts as short-term energy store. Glucosamine (Gam) is a sensor which indicates the fullness of the store. G6P is further transformed into fructose-6-phosphate (F6P) and finally to 2 molecules of pyruvate and then into lactate by a gain of 34 ATP.

Fig. 1 presents the first steps of the glycolysis, (Berg et al. 2002). Additional to the central pathway formed by glucose, G6P, F6P etc., there is a sideways represented by glycogen. It increases if G6P is abundant and it decreases if G6P lies under a reference level. Glycogen acts as short-term store, it damps oscillations and assures a permanent and nearly constant supply of pyruvate.

Additionally, there is a secondary branch or side-way of glucosamine, which is increased if G6P is abundant and the glycogen store is full. The concentration of glucosamine acts as sensor, which indicates complete abundance in the supply with glucose. The functionality of sideways is discussed in Sec. 3, and the role of sensors is dealt with in Sec. 4.

A next example is the metabolic supply chain at the individual level. Fig. 2 sketches the transport of energy from the near environment into the brain. The traditional glycostatic approach proposes that the energy level in the body is regulated and the supply of the brain is a secondary consequence. Oppositely, the Selfish-brain theory (Peters et al. 2004) assumes that the energy supply of the brain has the priority over all other organs. This approach intends to explain obesity, diabetes and other metabolic diseases as disturbance or congestion within the supply chain (Peters et al. 2007).

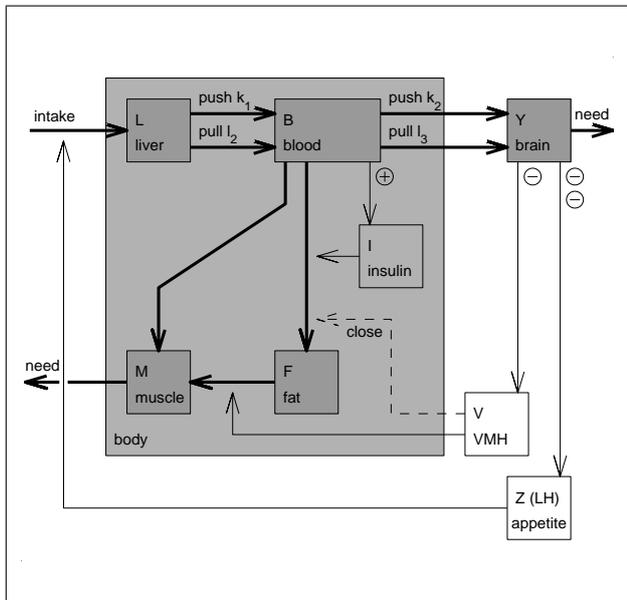


Figure 2: Details of the energy supply chain at individual level: The brain competes with the body periphery for energy. The inner loop marks the allocation process, induced by an activation of the ventromedial hypothalamus (VMH), which opens the fat compartment as alternative energy resource for the muscle. That assures sufficient blood glucose for the energy supply into the brain. The outer loop is appetite, generated in the lateral hypothalamus (LH), governing the ingestive behaviour. There are further loops like explorative behaviour organizing food from the exterior into the near environment, cf. Fig. 5. The model will be discussed in Sec. 4.

The central supply chain reaches from the exterior via the near environment to the intake of the individual, where it continues via the stomach, the liver, the blood glucose into the brain glucose and finally into ATP in the neurons. There, it serves the need of the activated neurons.

This supply chain has a second consumer, which is muscle activity. The sideways into the fat compartment, which is insulin induced in abundance of

blood glucose, has no direct path back into the central supply chain. Rather, fat is the alternative energy supplier for an augmented need of the muscles. The necessary signal is allocation, which is generated in the ventromedial hypothalamus (VMH) (Peters et al. 2004). Further signals are appetite and exploration. The regulatory role of such signals acting on remote parts of the supply chain, is discussed in Sec. 4.

We distinguish between two functionalities of the brain. First, the brain is an important energy consumer, which needs approximately half the energy of the whole human. Second, it is the regulatory authority, which governs the supply chain and the delivery of energy to the different organs.

Of course, the dynamical system sketched in Fig. 2 is a rough model. There are much more regulatory mechanisms, e.g. the leptin feedback of the fat compartment to the brain (Morton et al. 2006). Nevertheless, it may serve to explain the interaction between the two functionalities of the brain, the role of the sideways into the fat compartment and other aspects. On the other hand, we have to remark that this dynamical system is already too complex for a detailed mathematical analysis. That becomes aggravated by the lack or the uncertainty of the necessary parameters.

Therefore, Sec. 4.3 discusses a top-down analysis of the appetite regulation starting with a minimal model consisting of the compartments brain and body and the appetite only. We will find the necessity of a push component, which reflects the small push component at the molecular level (Vannucci et al. 1997). The strong push component called *energy on demand* (Magistretti et al. 1999) exists at the individual level, too.

This kind of self-similarity of the supply chains at different levels gives the hope that the investigation of such supply chains will deepen the overall understanding of delivery processes of energy or nutrients.

## 2 Linearized kinetics in the steady state

As a general example, we regard the first reaction of the glycolysis, Fig. 1, which is



and which is – as most of biochemical reactions – theoretically bilateral although it is observed only as a transformation of glucose into glucose-6-phosphate in the glycolysis.

We denote the concentration of glucose by  $c_{\text{Gluc}}$ , the one of G6P by  $c_{\text{G6P}}$  and so on. Neglecting more sophisticated kinetics the reaction turnover or the flux is

$$j = k_{\text{Gluc}}c_{\text{Gluc}}c_{\text{ATP}} - \ell_{\text{G6P}}c_{\text{G6P}}c_{\text{ADP}}. \quad (2)$$

The first summand in Eq. (2) is called the *push* component because the educts pushes the transformed matter in the direction of the supply chain. The second summand is the *pull* component because the products pull the transformed matter.

Now, the change of the concentration of the educts is given by the derivatives with respect to the time  $t$ , which is

$$\dot{c}_{\text{Gluc}} = \dot{c}_{\text{ATP}} = -j,$$

and the change of the products is

$$\dot{c}_{\text{G6P}} = \dot{c}_{\text{ADP}} = j.$$

Hence, a positive flux  $j$  expresses a transformation from the left-hand side to the right-hand side, or a flux in the direction of the supply chain.

Next, ADT and ATP are much smaller molecules and they are permanently produced respectively consumed in the steady state process of the glycolysis. Therefore, it can be assumed that  $c_{\text{ADP/ATP}} > c_{\text{Gluc/G6P}}$ , and the concentration of ADP and ATP can be regarded as nearly constant. In particular, it is sparsely influenced by the reaction (1).

If now,  $c_{\text{Gluc}}^*$ ,  $c_{\text{G6P}}^*$  etc. denote the steady state concentrations or another set of concentrations fulfilling the condition

$$0 = k_{\text{Gluc}} c_{\text{Gluc}}^* c_{\text{ATP}}^* - \ell_{\text{G6P}} c_{\text{G6P}}^* c_{\text{ADP}}^* \quad (3)$$

then  $c_{\text{Gluc}} = c_{\text{Gluc}}^* + \Delta c_{\text{Gluc}}$  etc. and  $k = k_{\text{Gluc}} c_{\text{ATP}}^*$  as well as  $\ell = \ell_{\text{G6P}} c_{\text{ADT}}^*$  provide the linear relation

$$j \approx k \Delta c_{\text{Gluc}} - \ell \Delta c_{\text{G6P}}. \quad (4)$$

Eq. (4) can be seen as a linearization of Eq. (2) near the equilibrium state. In case that no equilibrium state exists, the flux can be linearized with respect to a mean state or a general reference state, and of course a linearization is possible for more general or more realistic reaction kinetics.

### 3 Supply chains

We describe supply chains and discuss their behaviour. The assumptions of Sec. 2 leading to the linear relation (4) motivate to begin with linear supply chains. The results can be transferred for supply chains with realistic non-linearities (Liu & Michel 1994).

#### 3.1 Linear set-up

We regard a supply chain with  $n$  compartments and  $u_i$ ,  $i = 1, \dots, n$  denotes the deviation of the fullness of the  $i$ -th compartment from a reference state, e.g. the steady state. If fullness describes a concentration of the substance  $S_i$  like in Sec. 2, then  $u_i = \Delta c_{S_i}$ .

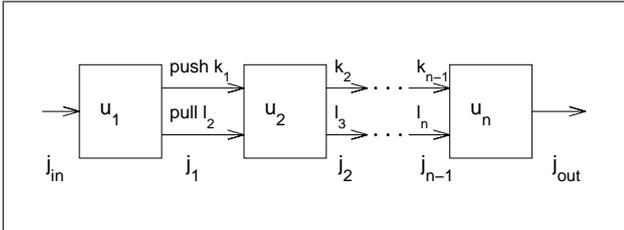


Figure 3: Supply chain:  $u_i$  is the deviation of the fullness of the  $i$ -th compartment from a reference state. The flux  $j_i$  from the  $i$ -th to the  $(i+1)$ -th compartment is composed by a push ( $k_i u_i$ ) and by a pull ( $-\ell_{i+1} u_{i+1}$ ) component. Finally, there are the inflow  $j_{\text{in}}$  and the outflow  $j_{\text{out}}$ .

The flux  $j_i$ ,  $i = 1, \dots, n-1$  links the  $i$ -th compartment with the  $(i+1)$ -th compartment. It is composed by a push component determined by  $u_i$  and a pull component determined by  $u_{i+1}$ . That yields

$$j_i = k_i u_i - \ell_{i+1} u_{i+1}. \quad (5)$$

Furthermore, an inflow  $j_{\text{in}}$  enters the first compartment, and an outflow  $j_{\text{out}}$  leaves the last compartment, cf. Fig. 3. The outflow is used by the final consumer of the supply chain.

We set  $j_0 = j_{\text{in}}$  and  $j_n = j_{\text{out}}$ , and we get

$$\dot{u}_i = j_{i-1} - j_i \quad (6)$$

for  $i = 1, \dots, n$ . Let us remark that the reaction constants  $k_i$ ,  $i = 1, \dots, n-1$  and  $\ell_i$ ,  $i = 2, \dots, n$  are non-negative, and so do  $j_{\text{in}}$  and  $j_{\text{out}}$ . The transported matter moves from the first compartment to the  $n$ -th compartment, which determines the direction of the supply chain.

The equations (6) form a system of ordinary differential equations, which is written in matrix notation with  $\mathbf{u} = (u_1, \dots, u_n)^T \in \mathbb{R}^n$  and  $\mathbf{j} = (j_1, \dots, j_{n-1})^T \in \mathbb{R}^{n-1}$ . It holds

$$\mathbf{j} = \mathbf{K}\mathbf{u} - \mathbf{L}\mathbf{u} \quad (7)$$

with

$$\mathbf{K} = \begin{pmatrix} k_1 & & 0 \\ & \ddots & \vdots \\ & & k_{n-1} & 0 \end{pmatrix} \in \mathbb{R}^{(n-1) \times n}$$

and

$$\mathbf{L} = \begin{pmatrix} 0 & \ell_2 & & \\ \vdots & & \ddots & \\ 0 & & & \ell_n \end{pmatrix} \in \mathbb{R}^{(n-1) \times n}.$$

The time-derivative  $\dot{\mathbf{u}}$  is found by

$$\dot{\mathbf{u}} = \mathbf{A}\mathbf{u} + \mathbf{a} = \mathbf{D}(\mathbf{K} - \mathbf{L})\mathbf{u} + \mathbf{a} \quad (8)$$

with  $\mathbf{a} = (j_{\text{in}}, 0, \dots, -j_{\text{out}})^T \in \mathbb{R}^n$  and

$$\mathbf{D} = \begin{pmatrix} -1 & & & \\ 1 & \ddots & & \\ & \ddots & -1 & \\ & & & 1 \end{pmatrix} \in \mathbb{R}^{n \times (n-1)}.$$

The inflow and the outflow may depend on the time  $t$ . The system (8) is completed by initial conditions  $\mathbf{u}(0) = \mathbf{u}_0$ , which are of less interest in the investigation of the general behaviour of supply chains.

The system (8) reads in detail as

$$\begin{aligned} \dot{u}_1 &= j_{\text{in}} - k_1 u_1 + \ell_2 u_2, \\ \dot{u}_i &= k_{i-1} u_{i-1} - (k_i + \ell_i) u_i + \ell_{i+1} u_{i+1}, \\ &\vdots \\ \dot{u}_n &= k_{n-1} u_{n-1} - \ell_n u_n - j_{\text{out}} \end{aligned}$$

with  $i = 2, \dots, n-1$ . The right-hand of this system obeys a weak column-sum criterion, and it resembles the discretization of a second-order differential operator because  $\dot{u}_i$  is expressed as weighted second difference of the triple  $[u_{i-1} \ u_i \ u_{i+1}]$  (Ames 1992).

As deviation from a reference state,  $u_i$  may be negative. Realistically, the flux always has the direction of the supply chain. But, the system (8) allows negative fluxes. We show in the following theorem that a sufficiently large inflow and outflow assures non-negative fluxes  $j_i \geq 0$  for all  $i = 1, \dots, n-1$ .

**Theorem 1** *Let be  $\mathbf{u}(t)$  a solution of Eq. (8) for  $t \in [0, T]$ . Then, there is a constant  $c$  and a solution  $\mathbf{v}(t)$  of  $\dot{\mathbf{v}} = \mathbf{A}\mathbf{v} + \mathbf{a} + \mathbf{b}$  with  $\mathbf{b} = (c, 0, \dots, -c)^T \in \mathbb{R}^n$  with a component-wise non-negative flux vector  $\mathbf{j}_{\mathbf{v}} = (\mathbf{K} - \mathbf{L})\mathbf{v}$ .*

**Proof:** Let be  $\mathbf{z} \in \mathbb{R}^n$  a solution of the underdetermined system  $\mathbf{1} = (\mathbf{K} - \mathbf{L})\mathbf{z}$  with  $\mathbf{1} = (1, \dots, 1)^T \in \mathbb{R}^{n-1}$ , which is not unique but surely existent because  $\mathbf{K} - \mathbf{L}$  is a rank-deficite triangular matrix.

The solution  $\mathbf{u}(t)$  generated the flux  $\mathbf{j} = (\mathbf{K} - \mathbf{L})\mathbf{u}$ .  
With

$$c = - \min_{i=1, \dots, n-1} \min_{t \in [0, T]} j_i(t)$$

holds  $\mathbf{j} + c\mathbf{1} \geq 0$  component-wise for all  $t \in [0, T]$ , and thus

$$(\mathbf{K} - \mathbf{L})(\mathbf{u}(t) + c\mathbf{z}) \geq 0.$$

At the same time holds

$$\mathbf{D}(\mathbf{K} - \mathbf{L})\mathbf{z} = \mathbf{D} \cdot \mathbf{1} = (-1, 0, \dots, 1) \in \mathbb{R}^n,$$

and  $\mathbf{v}(t) = \mathbf{u}(t) + c\mathbf{z}$  obeys the required conditions.  $\square$

Theorem 1 shows that there are sufficiently large quantities for inflow and outflow, which yield non-negative fluxes between all compartment for any given set of constants  $k_i$  and  $\ell_i$ . Basing on the same idea, the following statement gives a criterion to check whether negative fluxes occur in the simulation or not.

**Theorem 2** *Let the inflow and the outflow be non-negative, i.e.  $j_{\text{in}} \geq 0$  and  $j_{\text{out}} \geq 0$ . If the initial condition  $\mathbf{u}_0$  yield non-negative fluxes  $(\mathbf{K} - \mathbf{L})\mathbf{u}_0 \geq 0$ , then the solution  $\mathbf{u}(t)$  does always so.*

**Proof:** Assume that  $t$  is the first time instant with  $j_i(t) = 0$  for a  $i = 1, \dots, n-1$ . Then the time-derivative of the flux  $j_i$  is

$$\frac{d}{dt} j_i(t) = k_i \dot{u}_i - \ell_{i+1} \dot{u}_{i+1}$$

by Eq. (5). Due to Eq. (6) together with the assumption, we get

$$\begin{aligned} \frac{d}{dt} j_i(t) &= k_i(j_{i-1} - j_i) - \ell_{i+1}(j_i - j_{i+1}) \\ &= k_i j_{i-1}(t) + \ell_{i+1} j_{i+1}(t) \geq 0 \end{aligned}$$

because  $t$  was the first time instant when any flux vanishes. Hence, the neighbouring fluxes  $j_{i-1}(t)$  and  $j_{i+1}(t)$  are non-negative. Finally, no flux component can pass zero and the assertion holds.  $\square$

### 3.2 Properties of pure push systems

We regard a pure push system, i.e. all pull components vanish and  $\mathbf{L} = \mathbf{0}$ . Necessary, the push components must not permanently vanish, and it holds  $k_i > 0$ ,  $i = 1, \dots, n-1$ . The matrix  $\mathbf{A} = \mathbf{D}\mathbf{K}$  reads now

$$\mathbf{A} = \begin{pmatrix} -k_1 & & & 0 \\ k_1 & -k_2 & & \vdots \\ & k_2 & \ddots & \\ & & \ddots & -k_{n-1} \\ & & & k_{n-1} & 0 \end{pmatrix}.$$

The system (8) gets reducible and attractive with respect to the first  $n-1$  components of  $\mathbf{u}$  because the eigenvalues of the triangular matrix  $\mathbf{A}$  are  $-k_i < 0$  and 0.

Let be  $\mathbf{y}$  a disturbance of the solution  $\mathbf{u}$  of Eq. (8). It fulfils the homogeneous differential equation

$$\dot{\mathbf{y}} = \mathbf{A}\mathbf{y} \quad (9)$$

or in detail  $\dot{y}_1 = -k_1 y_1$ ,  $\dot{y}_2 = k_1 y_1 - k_2 y_2$  and so on. Thus, the component  $z_i$  is influenced only by the components  $z_m$  with  $m < i$ . Any disturbance propagates forward in the direction of the supply chain, and a time dependent inflow determines whole the behaviour of the supply chain.

Eq. (9) can be regarded as a naive semi-discretization (Ames 1992) of the transport equation, (Smoller 1983),

$$\frac{\partial}{\partial t} y(x, t) = - \frac{\partial}{\partial x} [\kappa(x)y(x, t)] \quad (10)$$

with the grid-points  $x_i = i$ ,  $i = 1, \dots, n$  and  $\kappa(x_i) = k_i$ .

The generalized characteristics  $\xi(t)$  of Eq. (10) are the curves where

$$\kappa(\xi(t))y(\xi(t), t) = \text{const.}$$

holds. Differentiation of the last expression yields

$$\kappa'(\xi)\xi'(t)y + \kappa(y, x\xi'(t) + y, t) = 0$$

and thus

$$(\kappa'y + \kappa y, x)\xi'(t) + \kappa y, t = 0.$$

Finally, we find

$$\xi'(t) = -\kappa \frac{y, t}{(\kappa y), x} = \kappa(\xi(t)) > 0. \quad (11)$$

The first-order partial differential equation (10) inherits the properties of the system of ordinary differential equations (9), e.g. Eq. (11) contains the property that all initial disturbances, which are given as initial values  $y(x, 0)$  of Eq. (10), propagate in the direction of the supply chain.

### 3.3 Properties of pure pull systems

A pure pull system behaves oppositely. Since the pull components is seen as the dominant one in the Selfish-brain theory (Peters et al. 2007), cf. Sec. 1, it is discussed in some more detail.

It holds  $\mathbf{K} = \mathbf{0}$  and  $\mathbf{A} = -\mathbf{D}\mathbf{L}$  with

$$\mathbf{A} = \begin{pmatrix} 0 & \ell_2 & & & \\ \vdots & -\ell_2 & \ell_3 & & \\ & & -\ell_3 & \ddots & \\ & & & \ddots & \ell_n \\ 0 & & & & -\ell_n \end{pmatrix}.$$

The system (8) again gets reducible, and it is attractive with respect to the last  $n-1$  components. All disturbances, which obey Eq. (9) with the respective matrix  $\mathbf{A} = -\mathbf{D}\mathbf{L}$ , are backward, i.e. opposite to the direction of the supply chain.

If the pull coefficients form an increasing sequence  $\ell_2 \leq \dots \leq \ell_n$ , then the last compartment has the strongest regulation, since the eigenvalue  $-\ell_n$  belonging to the eigenvector  $\mathbf{e}_n = (0, \dots, 0, 1)^T$  is the one of the largest modulus. Any disturbance in damped out most efficiently in the last compartment. The fullness  $u_n(t)$  is the strongestly regulated one under all  $u_i$ ,  $i = 1, \dots, n$ . This observation will be interesting in the seek for minimal models of the energy metabolism in Sec. 4.

Analogously to the discussion of the pure push systems, the dynamical system  $\dot{\mathbf{y}} = \mathbf{A}\mathbf{y}$  for the disturbance of a pure pull system can be seen as a naive discretization of the first-order transport equation

$$\frac{\partial}{\partial t} y(x, t) = \frac{\partial}{\partial x} [\lambda(x)y(x, t)] \quad (12)$$

with the grid-points  $x_i = i$ ,  $i = 1, \dots, n$  and  $\lambda(x_i) = \ell_i$ . Then, we expect  $z_i(z) \approx y(x_i, t)$  for the components  $z_i$  of the vector  $\mathbf{z}$ .

Again, the generalized characteristics  $\xi(t)$  of Eq. (12) are defined by

$$\lambda(\xi(t))y(\xi(t), t) = \text{const.}, \quad (13)$$

and they fulfil

$$\xi'(t) = -\lambda(\xi(t)) < 0. \quad (14)$$

Here, the characteristics propagate backwards like the disturbances of the dynamical system do.

We again regard the case that the pull component increases in the direction of the supply chain, i.e.  $\lambda$  is increasing in  $x$ . Due to condition (13),  $\lambda$  decreases during the backward propagation of the disturbance, and the modulus of  $y$  is increasing. This is the equivalent behaviour, we have detected in the system of ordinary differential equations. The larger  $x$  that stronger regulated is  $y$ , and very small oscillations in the outflow may result in large oscillation at the beginning of the supply chain what is a known behaviour in logistics, cf. the beer distribution game (Sterman 1989), and in sociodynamics, cf. traffic simulation (Helbing 1995).

Pure pull supply chains react on the outflow, only. The outflow can be interpreted as a need or a demand, and the system supplies on demand.

### 3.4 Side compartment

We consider a side compartment, which is located at the  $i$ -th compartment, cf. Fig. 4. Its deviation of a reference fullness is denoted by  $s$ .

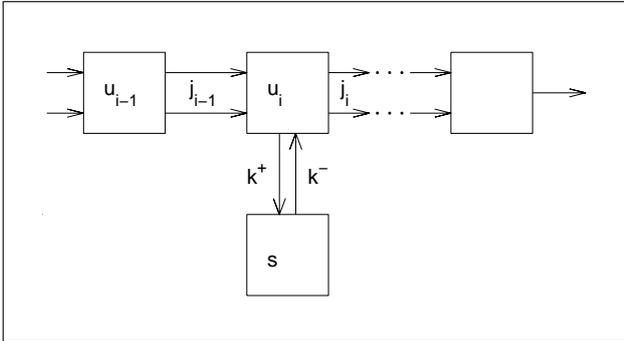


Figure 4: Side compartment at the  $i$ -th compartment in the supply chain acts as short-term store.

The dynamical system (8) modifies by

$$\begin{aligned} \dot{u}_i &= j_{i-1} - j_i - k^+ u_i + k^- s, \\ \dot{s} &= k^+ u_i - k^- s. \end{aligned}$$

Clearly, the side compartment has a damping and a time-delaying effect. In a period of an abundance in the  $i$ -th compartment, the store is filled, and there is an outflow out of the store when the fullness in the  $i$ -th compartment is small, i.e.  $u_i$  is negative, and when the store is full.

The effect becomes strengthened for very small  $k^-$ . That means the store itself is nearly passive. Then, the term  $-k^+ u_i$  is a pure damping of the  $i$ -th compartment. The propagation of any disturbance is effectively damped.

Examples of side compartments in supply chains are the glycogen in the glycolysis, cf. Fig. 1, and the fat compartment in the individual metabolic supply chain, cf. Fig. 2. In both cases, there are sensors indicating an abundance in the side compartment like glucosamine in the glycolysis or leptin in the individual metabolism.

## 4 Energy supply chains

The energy supply chain reaches from the exterior, where food is explored into the near environment, via the near environment, the body into the brain. Again, energy is transported in different material appearances like food, glucose, lactate and finally ATP. Nevertheless it follows a central pathway from the supplier, which is the exterior, to the final recipients and consumers, which is first brain – and in particular the activated neurons – and subordinate the body periphery with the muscles (Peters et al. 2004, 2007).

### 4.1 Brain as regulatory authority

Until now, we have emphasized the role of the brain as the final consumer. But on the other hand, it is the regulatory authority which manages the signals from sensors. Fig. 5 shows the central pathway of the energy supply chain from the exterior via the near environment over the body periphery to the final recipient, which is the brain as consumer.

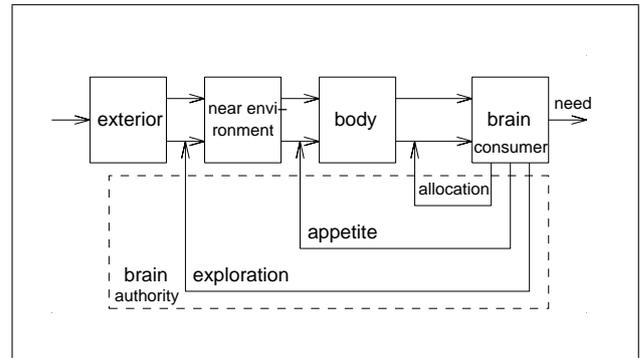


Figure 5: Simplified individual metabolic supply chain: On the one hand, the brain is an important energy consumer. On the other hand, it governs the metabolic supply chain by supervising the regulatory mechanisms allocation, appetite and exploration as authority. The Selfish-brain theory claims the priority of the energy supply of the brain.

There are three hierarchically ordered loops. First, the allocation mechanism contains the competition of the brain and the body for energy. A small energy deficit in the brain generates the activation of the ventromedial hypothalamus (VMH) (Peters et al. 2004). The activated VMH directs the energy demand of the muscles from the blood glucose to the fat compartment, cf. Fig. 2. In the simplified set-up in Fig. 5, this is modelled by an energy pull of the brain from the body periphery.

Second, the appetite which is induced by the activated lateral hypothalamus (LH) regulates the flux from the near environment into the body periphery. This regulatory mechanism is not covered by the investigations in Sec. 3 because it acts in a remote part of the energy supply chain. Sec. 4.3 will discuss the functionality of such remote loops. A crucial question is whether the appetite is generated by an energy deficit in the body, which would only be messaged by the brain, or by an energy deficit in the brain. The first idea of a purely messaging brain can be rejected because in that case, appetite would be a transport mechanism in the sense of Sec. 3 and would not generate any cyclic food intake like observed in healthy adult persons.

Third, there is the exploration loop. Explorative behaviour contains the transport of energy equivalents from the exterior environment into the near environment. The rather psychological question of the

regulatory mechanisms for explorative behaviour is reduced in Fig. 5 to an abstract outer feedback loop.

These additional loops assure the permanent energy supply to the brain, and the energy level is observed to be constant (Oltmanns et al. 2005) even in situations of additional need. The analogon is not observed in the muscles where the ATP level decreases under spontaneous additional need (Oltmanns et al. 2005). The strong regulation of the energy level in the brain leads to the thesis that the energy supply chain has a dominant push component, cf. Sec. 3.3.

## 4.2 Mistuning and congestion

Within the selfish-brain theory, metabolic diseases like obesity and diabetes are interpreted as a mistuning in the energy supply chain (Peters et al. 2007). A defect in the allocative behaviour, i.e. either a defect in the generation of the signal in the VMH or a defect in the application of this signal, leads to a diminished energy supply to the brain. Consequently, the appetite signal is activated and the food intake increases. The body periphery becomes thickened. Then, the body compartment has abundant energy, and the brain needs less competitive allocative behaviour to cover its energy needs. The supply chain has a bottleneck between the body and the brain, and the necessary congestion before the bottleneck is the obese body.

This effect is dramatically enforced by a side-compartment like fat, cf. Fig. 2. It stores the additional intake. The medium-term feedback of the fat, e.g. by leptin (Morton et al. 2006), transfers the supply chain into a new modified reference state, which is referred to as obesity. The situation sketched in Fig. 6 shows the body compartment in a minimum of the daily cycle, but the fat compartment has already stored additional intake.

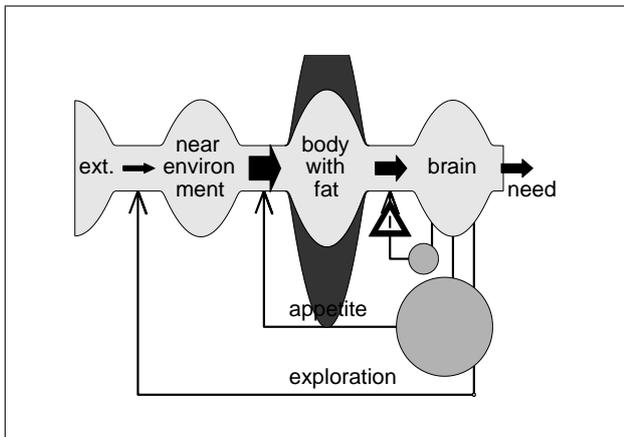


Figure 6: Defect in the allocative behaviour (attention sign) leads to an enforced appetite and thus an enforced ingestive behaviour. The additional intake is stored in the fat compartment (dark grey). Its growth represent the congestion before the bottleneck.

Otherwise, a defect in the appetite behaviour, again caused by a lacking appetite signal, by defect in the application or by a defect in the ingestion of the food, is a bottleneck between the near environment and the body. In this case, the congestion is observed in the near environment, and the energy supply of the body is at a low level. Such situations lead to an enforced explorative behaviour (Peters et al. 2004). Fig. 7 presents a sketch out of the simulation of that case.

The effects of defects are closely related to the effects of bottlenecks in traffic dynamics and general

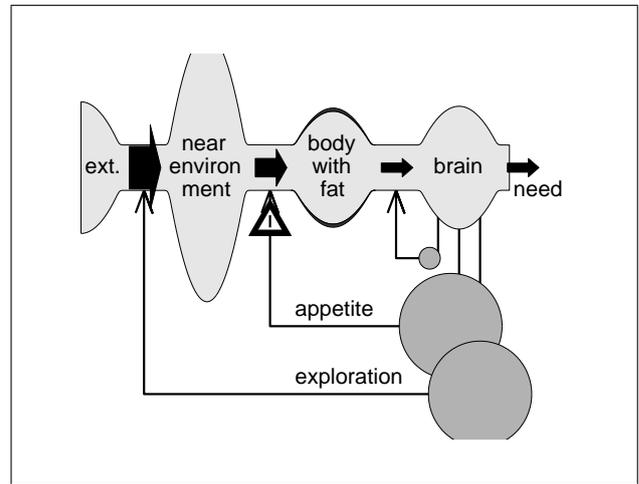


Figure 7: Defect in the ingestive behaviour (attention sign) leads to an enforced explorative behaviour. The congestion before the bottleneck is found in the the growth of the near-environment compartment.

sociodynamics (Helbing 1995, Helbing et al. 2000). Thus, the investigation of mistunings or metabolic supply chains can be based on the quantitative sociodynamical theory.

## 4.3 Minimal model of appetite regulation

A central aspect in the energy supply chain is the appetite activation what about a manifold physiological knowledge exists (Berthoud 2004, Morton et al. 2006, Nery et al. 2004). The appetite signal, generated in the lateral hypothalamus, cf. Fig. 2, acts on a remote part of the supply chain, namely the ingestive behaviour, cf. Fig. 5. We want to study the role of such sensor induced signals, and therefore we investigate a rather simple model for the daily appetite regulation consisting of the two compartments body periphery and brain in the energy supply chain and as a third one, the appetite activation.

We identify certain indispensable components in the model. From the general observation of a cyclic ingestive behaviour, we deduce the necessity of a push component in the energy transport from the body into the brain which is physiologically described in (Vannucci et al. 1997). Furthermore, we show that a strong pull component in this transport leads to a nearly constant energy level in the brain. The biological correspondent is the energy-on-demand-concept in (Magistretti et al. 1999).

As next deductive result, we get the condition of a sensitive appetite activation for a cyclic food intake. This condition is mirrored in the appetite amplifying resp. diminishing neuropeptides NPY and  $\alpha$ -MSH which become incorporated in the appetite-regulating neural network shortly after the birth (Bouret et al. 2004). This incorporation represents a more sensitive appetite activation and marks the change from the permanent umbilical energy uptake of the foetus into the cyclic ingestive behaviour in later life.

### 4.3.1 Appetite model set-up

We investigate a model formed by three compartments, first the body periphery, second the brain and third the appetite regulation in the lateral hypothalamus. Here, the fullness of the body compartment is the theoretical energy supply state within the body periphery, which is named  $X$  and which might be measured e.g. in mol glucose. The energy supply state in the brain is denoted by  $Y$ . The appetite activation in

the lateral hypothalamus is called  $Z$ . It is handled as a normalised value  $Z \in [0, 1]$ .

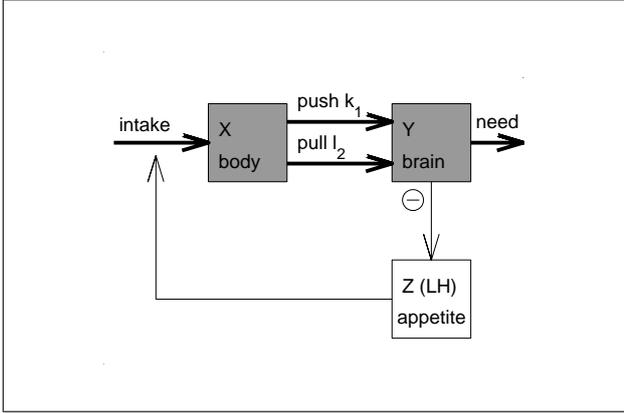


Figure 8: Energy supply chain of the body periphery and the brain. An appetite-regulated food intake passes the periphery and is transported by a push/pull-mechanism into the brain as final consumer.

Additionally, we assume a constant energy need  $S > 0$  of the brain and a constant energy offer  $R > S$ . The energy intake requires the appetite activation, and thus its influx is  $RZ \geq 0$ . The transport between the body and the brain is composed of a push component  $K_1(X - X_0)$  which delivers abundant energy from the body into the brain and of a pull component  $-L_2(Y - Y_0)$  which represents the pulling of the brain for energy on demand. Here,  $X_0$  and  $Y_0$  are the reference energy levels. Realistic transport regulation is non-linear, e.g. it contains a saturation (Liu & Michel 1994), but it is not yet quantified.

A crucial element in the model is the appetite activation  $F(X, Y)$  describing the increase of the appetite. Obviously, the appetite activation is decreasing with an increasing energy level in the brain as well as in the body. At the same time, the appetite is decayed proportionally. We get the dynamical system

$$\begin{aligned}\dot{X} &= -K_1(X - X_0) + L_2(Y - Y_0) + RZ, \\ \dot{Y} &= K_1(X - X_0) - L_2(Y - Y_0) - S, \\ \dot{Z} &= P(F(X, Y) - Z).\end{aligned}\quad (15)$$

with the time  $T$ , the energy level  $X = X(T)$ , its time derivative  $\dot{X} = dX/dT$  etc. and

$$K_1, L_2, P \in \mathbb{R}^+, K_1^2 + L_2^2 > 0 \quad (16)$$

as well as

$$F(X, Y) \in [0, 1] \text{ and } F_{,X} \leq 0, F_{,Y} \leq 0.$$

Here, we denote  $\mathbb{R}^+ = \{u \in \mathbb{R} : u \geq 0\}$ . Furthermore, we claim that the appetite activation does not have extrema or saddle points except it is saturated, i.e.

$$F_{,X}^2 + F_{,Y}^2 = 0 \Leftrightarrow F \in \{0, 1\}. \quad (17)$$

Even if we have not fixed the appetite activation  $F$ , Eq. (17) seems to be physiologically reasonable.

Additionally we assume, that the lateral hypothalamus which is the appetite centre in the brain reacts at least on extremal supply states of the brain, which is mathematically formulated by

$$\lim_{Y \rightarrow -\infty} F(X, Y) = 1, \lim_{Y \rightarrow \infty} F(X, Y) = 0 \quad (18)$$

for all  $X \in \mathbb{R}$ .

### 4.3.2 Push component

Sec. 4.1 deals with the important role of the pull component in the metabolic supply chain. Now, we ask whether the push component can be omitted in a minimal model without losing central properties like the cyclic food intake. Therefore, we investigate the case  $K_1 = 0$ , and we get the system (15) in the form

$$\begin{aligned}\dot{X} &= L_2(Y - Y_0) + RZ, \\ \dot{Y} &= -L_2(Y - Y_0) - S, \\ \dot{Z} &= P(F(X, Y) - Z).\end{aligned}\quad (19)$$

We know that  $L_2 > 0$  by Eq. (16) which expresses the fact that the energy flow from the body into the brain is not permanently vanishing. We ask for the system properties of Eq. (19) beginning by the existence of stationary points followed by the investigation of their stability.

**Theorem 3** *If  $F_{,X}(X, Y) < 0$  for all  $X, Y$  with  $F(X, Y) = S/R$ , then the system (19) has exactly one stationary point.*

**Proof:** The stationary point is denoted by  $Q^* = (X^*, Y^*, Z^*)^T$ , and the first two equations of the regarded system with  $\dot{X} = \dot{Y} = \dot{Z} = 0$  yield the unique solution

$$Y^* = Y_0 - \frac{S}{L_2} \text{ and } Z^* = \frac{S}{R} \in (0, 1).$$

Now, the appetite activation  $F$  is monotonously decreasing in the neighbourhood of  $F(X, Y) = Z^*$ , and  $X^*$  is unique.  $\square$

We see from the proof, that  $F_{,X} = 0$  would allow ambiguities. They concern the total amount of  $X$  which does not occur anymore on the right-hand side of Eq. (19), and we will recover the ambiguities in the following theorem about the stability of  $Q^*$ .

**Theorem 4** *If  $Q^*$  is unique in Eq. (19), then it is asymptotically stable.*

**Proof:** We consider the Jacobian of the right-hand side of Eq. (19) in  $Q^*$  and its eigenvalues  $\lambda_j$ ,  $j \in \{1, 2, 3\}$ , and we get

$$J = \begin{pmatrix} 0 & L_2 & R \\ 0 & -L_2 & 0 \\ PF_{,X} & PF_{,Y} & -P \end{pmatrix}$$

with

$$\lambda_1 = -L_2, \lambda_{2,3} = -\frac{P}{2} \pm \sqrt{PRF_{,X} + \frac{P^2}{4}}.$$

Now, if  $F_{,X}(X^*, Y^*) < 0$ , then the real parts of all eigenvalues are negative, and  $Q^*$  is asymptotically stable. If otherwise  $F_{,X}(X^*, Y^*) = 0$ , then it needs to be negative in a neighbourhood of  $Q^*$ , and  $Q^*$  is stable, too.  $\square$

In the case that the stationary point is not unique, then  $F_{,X} = 0$  holds at least in a certain domain, and the energy level  $X$  is arbitrary. The lasting system of  $Y$  and  $Z$  yields a single stationary and asymptotically stable point.

Hence, we have shown that a cyclic behaviour of the system (15) implies a push component from the body into the brain, i.e.

$$K_1 > 0. \quad (20)$$

Hence, the push component, which is found in molecular supply chains (Vannucci et al. 1997) is necessary at the individual level, too. We have shown that it cannot be omitted while preserving the property of cyclic food intake.

### 4.3.3 Dimensionless formulation

Here, we give a dimensionless formulation of system (15) under condition (20). The first step is setting the reference level to zero as it has been done in Eq. 4 without any loss of generality. But, the number of parameters in Eq. 15 can be further reduced. We apply a transformation of coordinates by

$$x = \frac{K_1}{S} \Delta X, \quad y = \frac{K_1}{S} \Delta Y, \quad z = \frac{R}{S} Z, \quad t = K_1 T. \quad (21)$$

with  $\Delta X = X - X_0$  and  $\Delta Y = Y - Y_0$ . With the renamed  $\dot{x} = dx/dt$  etc., we find

$$\begin{aligned} \dot{x} &= -x + \ell y + z, \\ \dot{y} &= x - \ell y - 1, \\ \dot{z} &= p(f(x, y) - z). \end{aligned} \quad (22)$$

with

$$\ell = \frac{L_2}{K_1}, \quad p = \frac{P}{K_1} \quad \text{and} \quad f(x, y) = \frac{R}{S} F(X, Y).$$

We call Eq. (22) the dimensionless formulation. Now, it holds

$$f(x, y) \in [0, f_{\max}] \quad \text{with} \quad f_{\max} = \frac{R}{S} > 1.$$

In the following, we use the dimensionless formulation for an investigation of necessary conditions implied by the general observation of cyclic food intake.

### 4.3.4 Stationary points

**Theorem 5** *The system (22) with an appetite activation  $f$  fulfilling the conditions (16), (17) and (18) has exactly one stationary point  $q^* = (x^*, y^*, z^*)^T$ .*

**Proof:** The stationarity condition  $\dot{x} = \dot{y} = \dot{z} = 0$  leads to  $z^* = 1$ . Now, we regard the system of equations

$$x - \ell y = 1 \quad \text{and} \quad f(x, y) = 1. \quad (23)$$

In the case  $\ell > 0$ , the first equation in Eq. (23) is a monotonously increasing linear function  $y_\ell = y_\ell(x)$ , and the second equation describes a level line  $y_f = y_f(x)$  of  $f$ . By Eq. (16),  $y_f(x)$  is monotonously decreasing in  $x$ . Thus, there is exactly one intersection point.

In the case  $\ell = 0$ , we find  $x^* = 1$  and we get  $f(1, y) = 1$ . We use the condition (18) which now has the form

$$\lim_{y \rightarrow -\infty} f(1, y) = 0 \quad \text{and} \quad \lim_{y \rightarrow \infty} f(1, y) = f_{\max} > 1$$

after the coordinate transformation (21), and the assertion is shown.  $\square$

It is to remark that the proof needs condition (18) only in the unphysiological case  $\ell = 0$ , i.e. for a system without a pull component.

### 4.3.5 Stability

**Theorem 6** *The stationary point  $q^*$  is asymptotically stable if the condition*

$$(1 + \ell + p)(1 + \ell) - (1 + p)f_{,x} + f_{,y} > 0 \quad (24)$$

with the derivatives  $f_{,x} = f_{,x}(x^*, y^*)$  and  $f_{,y} = f_{,y}(x^*, y^*)$  at  $q^*$  is fulfilled.

**Proof:** The characteristic polynomial of the Jacobian  $J$  in the stationary point can be given in the form  $-\det(J - \lambda I) = \lambda(\lambda^2 + A\lambda + B) + C$  with positive  $A = 1 + \ell + p$ ,  $B = p(1 + \ell + f_{,x})$  and  $C = -p(\ell f_{,x} + f_{,y})$ .

Regarding  $C$  as a parameter,  $C = 0$  leads to the root 0 and two roots of  $\lambda^2 + A\lambda + B = 0$  with negative real parts. The polynomial  $-\det(J - \lambda I)$  has a positive slope at  $\lambda = 0$ , and thus a small  $C$  leads to three eigenvalues with negative real parts due to the continuity of the polynomial roots with respect to the coefficients.

If now, we ask for eigenvalues with positive real parts, first we are looking for two roots with vanishing real part. This ansatz yields after a comparison of coefficients to the specialised Hurwitz criterion  $AB - C > 0$  for roots with negative real parts which is just the condition (24).  $\square$

In the modelling of cyclic food intake, we are interested in situation when the unique stationary point is not stable, i.e. when the condition (24) is not fulfilled. The only negative term of the left-hand side is  $f_{,y} \leq 0$ . We see that  $f_{,y} < 0$  is a next necessary condition for cyclic food intake and that the appetite activation has to be sensitive, i.e. a comparatively large  $|f_{,y}|$  is needed which is even to increase with a growing pull component.

### 4.3.6 Boundedness

A physiological relevant model of the appetite regulation on a daily time scale should not allow an infinite increase or decrease of the trajectory. Here, we elementarily show that the solution is indeed bounded.

**Theorem 7** *The solution of the system (22) is bounded, i.e. for all initial values  $q(0) = (x(0), y(0), z(0))^T$  there is a bounded domain  $\Omega \subset \mathbb{R}^3$  so that  $q(t) \in \Omega$  holds for all  $t \geq 0$ .*

**Proof:** Since  $f \in [0, f_{\max}]$  holds, the assumption  $z \geq f_{\max}$  leads to  $\dot{z} \leq 0$  and  $z \leq 0$  leads to  $\dot{z} \geq 0$ . Hence, if  $z(0) \in [0, f_{\max}]$ , then  $z(t) \in [0, f_{\max}]$  for all  $t \geq 0$ . If  $z(0)$  is outside the named interval, then  $z(t)$  monotonously changes until  $z(t) \in [0, f_{\max}]$ . Next, the spectral transformation

$$\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} \ell & -1 \\ 1 & 1 \end{pmatrix} \begin{pmatrix} \xi \\ \eta \end{pmatrix}$$

transforms the first two equations of the system (22) into

$$\dot{\xi} = \frac{z-1}{\ell+1} \quad \text{and} \quad \dot{\eta} = -(\ell+1)\eta - \frac{z+\ell}{\ell+1}. \quad (25)$$

The differential equation for  $\eta$  in Eq. (25) shows that  $\eta(t)$  remains in the interval

$$\Theta = \left[ -\frac{f_{\max} + \ell}{(\ell+1)^2}, -\frac{\ell}{(\ell+1)^2} \right]$$

if it once is inside. Otherwise, the coordinate  $\eta$  monotonously changes until it is in  $\Theta$ . The interval  $\Theta$  for  $\eta$  describes a stripe in the  $(x, y)$ -plane which is not parallel to the  $x$ -axis.

Now, by Eqs. (16) and (18) there is a  $\xi_m$  so that  $f(\xi_m, \eta) < 1/2$  for all  $\eta \in \Theta$ . Since  $x$  and  $y$  are increasing with an increasing  $\xi$ , the relation  $f(\xi, \eta) < 1/2$  holds for all  $\xi \geq \xi_m$  and all  $\eta \in \Theta$ .

We regard a trajectory with  $\xi(t_0) = \xi_m$  and  $z(t_0) \in [0, f_{\max}]$ . As long as  $\xi(t) \geq \xi_m$ , it holds  $z(t) \leq \zeta(t)$  with a solution  $\zeta$  of

$$\dot{\zeta}(t) = p \left( \frac{1}{2} - \zeta(t) \right) \quad \text{and} \quad \zeta(t_0) = f_{\max}.$$

This initial-value problem can be solved in a closed form, and it follows

$$\xi(t) \leq \xi(t_0) + \int_{t_0}^t \frac{\zeta(\tau) - 1}{\ell + 1} d\tau = \dots \quad (26)$$

which is

$$\xi_m + \frac{2f_{\max} - 1 - pt - e^{-pt}(2f_{\max} - 1)}{2p(\ell + 1)}.$$

Hence, there is a time instant  $t_m$  when the trajectory again passes the line defined by  $\xi_m$ . The maximal deviation of  $\xi(t)$ ,  $t \in [t_0, t_m]$  is found by calculating the maximum of the right-hand side of Eq. (26) for  $t \geq 0$ . An analogous argumentation leads to a lower bound. With a decreasing  $\xi$ , the appetite activation increases and now, we get a positive  $\dot{\xi}$ .  $\square$

Let us mention that even the case  $\ell = 0$  without a stationary point leads to a bounded solution, i.e. a cyclic behaviour.

Fig. 9 shows a projection of the trajectory into the  $(x, y)$ -plane. The limit cycle is clearly visible, it is attractive and stable.

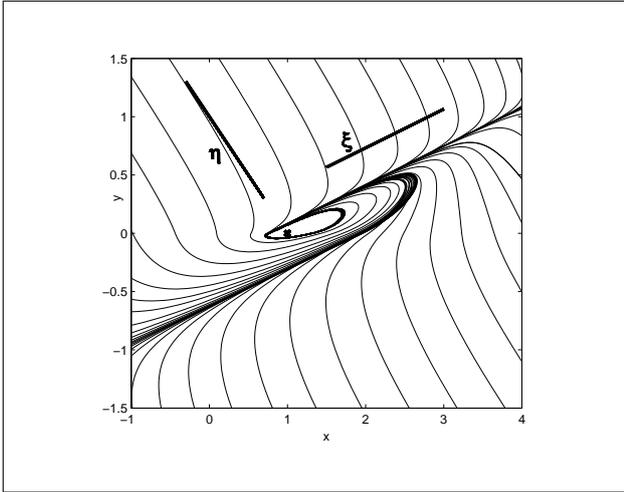


Figure 9: Projection of the trajectories in the minimal appetite regulation model into the  $(x, y)$ -plane showing the energy levels in the body and in the brain. The transformed coordinates  $(\xi, \eta)$  are given for comparison, cf. Eq. (25). The visible limit cycle is attractive, and the trajectories approach it very quick. The singular point marks the unstable stationary point  $q^*$ . Example from Sec. 4.3.7.

#### 4.3.7 Numerical example

In the numerical example calculation, we use the continuously differentiable appetite activation  $f = f_\varepsilon(y)$  depending on the parameter  $\varepsilon$  determining the slope in the stationary point. The function  $f_\varepsilon(y)$  is given by

$$f_\varepsilon(y) = \begin{cases} 0 & \text{if } y \geq \varepsilon, \\ (1 - \varepsilon^{-1}y)^2 & \text{if } y \in [0, \varepsilon], \\ 5 - (2 + \frac{1}{2}\varepsilon^{-1}y)^2 & \text{if } y \in [-4\varepsilon, 0], \\ 5 & \text{if } y \leq -4\varepsilon. \end{cases} \quad (27)$$

Now, the stationary solution is  $q^* = (1, 0, 1)^T$ , and the derivatives of  $f$  are  $f_{,x} = 0$  and  $f_{,y} = -2\varepsilon^{-1}$ . With  $\ell = 3$  and  $p = 2$ , the condition (24) reads  $\varepsilon > 1/12$  for a asymptotically stable stationary solution and

$\varepsilon < 1/12$  for an unstable one. We see that a steeper, i.e. more sensitive appetite activation leads to a cyclic behaviour, and the solution is still bounded. Numerical examples are shown in Figs. 10 and 11. The actual transport  $x - \ell y$  is always directed towards the brain.

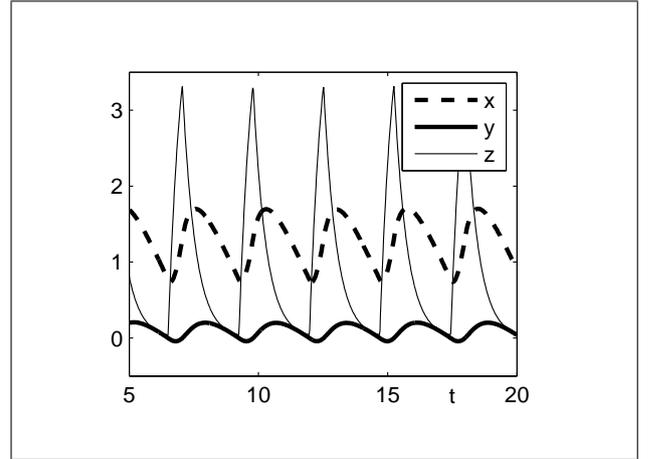


Figure 10: Cyclic ingestive behaviour with  $f$  of Eq. (27),  $\ell = 3$ ,  $p = 2$ ,  $\varepsilon = 0.001$ .

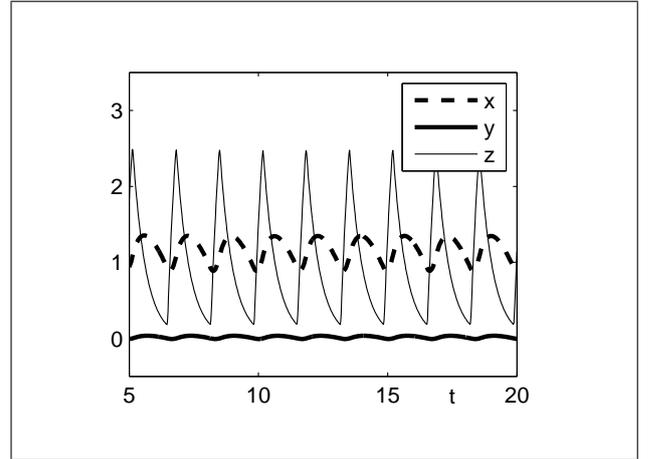


Figure 11: Stronger pull component: Solution for  $\ell = 10$ , cf. Fig. 10.

#### 4.3.8 Stable cyclic solutions and sensitive appetite activation

The general observation of a cyclic ingestive behaviour implies

1. a push component in the energy transport from the body into the brain,
2. the dependence of the appetite activation on the energy level in the brain,
3. and a very sensitive activation of the appetite close to an on/off-switch.

The first property is shown in Sec. 4.3.2 and it is found physiologically in (Vannucci et al. 1997) although a strong pull component is dominant (Magistretti et al. 1999). We can interpret the push component as an indicator of the body energy level for the brain.

The second property is shown in Theorem 6, where the derivative of the appetite activation  $f$  with respect to the brain energy level  $y$  is the only term contributing to a violated condition (24). Furthermore, a strong pull component requires a large  $|f_{,y}|$  close to a

jump in the function  $f$ . We find this property in the change from a permanent umbilical food intake to a cyclic ingestive behaviour in later life which is caused by the incorporation of the neurons NPY and POMC producing the appetite amplifying and suppressing neuro-peptides NPY and  $\alpha$ -MSH which reciprocally block each other (Bouret et al. 2004). Fig. 12 shows the transition from a permanent intake with a weak slope in the appetite activation to a postnatal cyclic intake.

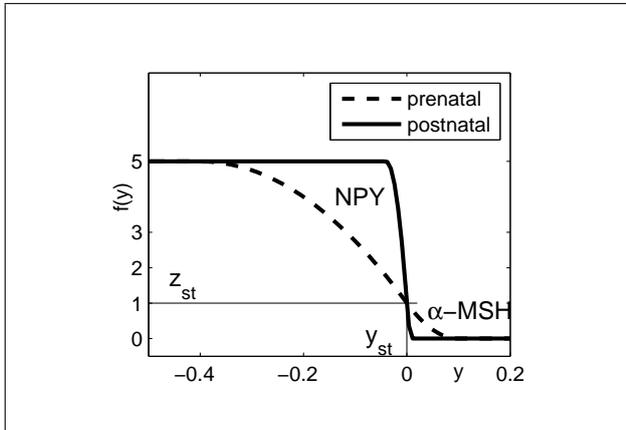


Figure 12: Transition from permanent to cyclic food intake: The dashed line describes a prenatal appetite activation  $f_\varepsilon$  with a relatively large  $\varepsilon$ , which leads to permanent food intake. The neuro-peptides NPY and  $\alpha$ -MSH amplify the appetite activation. They are expressed by the neurons NPY and POMC, which are incorporated after the birth. The appetite activation becomes more sensitive by a stronger slope. It is shown in the solid line with a smaller  $\varepsilon$ . Cyclic food intake occurs.

Figs. 10 and 11 show the cyclic ingestive behaviour for differently strong pull components. Let us remark, that the stronger the pull component the less variation occur in the cerebral energy level  $Y$ . The energy supply assures a constant delivery and a damping of the cyclic energy inflow. That underlines the highest rank of the brain in the hierarchy of energy supply (Peters et al. 2004, 2007).

## 5 Conclusion

### 5.1 Summarization

We have discussed a number of aspects of supply chains in the modelling of metabolic transport processes. Starting with the glycolysis, we have linearized the chemical reaction kinetics, we have shown the relation to general linear supply chains, and we have shortly investigated the functionality of side-compartments as short-term stores and of sensors acting to remote parts in the supply chain.

The same components could be found in metabolic supply chains at the individual level. In particular, these supply chains come into the focus of interest because the Selfish-brain theory assumes the highest priority for the energy supply of the brain and intends to explain metabolic diseases like obesity, diabetes etc. as mistuning or congestion in the metabolic supply chain (Peters et al. 2004).

Unfortunately, the choice of the relevant parameters among a tremendous amount of regulatory mechanisms known in the physiological literature and the identification of these parameters are difficult and time-expensive. For instance, a suitable parameter choice yield a quite realistic behaviour of the model

proposed in Fig. 2. Properties of the model like the constant energy level in the brain or the dependance of the cerebral need on the activity of the brain (Cox et al. 2002, Boyle et al. 1994) influence the model and the admissible parameter sets reproducing this properties. Presently, such investigations at the individual level are done (Oltmanns et al. 2005) and have already shown the central property that the energy level in the muscles is much more volatile under load than the energy level of the brain.

Nevertheless, the Selfish-brain theory offers a qualitative understanding of metabolic processes, and experimental investigations shall be focussed to answering central questions within the theory, e.g. the question whether the pull-component or the push-component is dominant in the energy supply of the brain. On the one hand, we have seen in Sec. 4.3 that the small push component cannot be neglected in the neglected if the model should reproduce daily cyclic behaviour in the food intake. But on the other hand, the metabolic system behaves like a supply chain with dominant and increasing pull component with the brain as final consumer.

Therefore, we have investigated general supply chains in Sec. 3. They are modelled by linear systems of ordinary differential equations. These high-dimensional systems can be interpreted as discretizations of partial differential equations. Central properties are found in the both types of equations.

If there are push- and pull components of similar strength all over the supply chain, then the partial differential equation is a heat conduction equation and then any disturbances or any changes within the supply chain are transported in both directions, i.e. forward and backward the supply chain. But, if the push-component is dominant, then the partial differential equation is a first order transport equation and then any changes move with the direction of the supply chain, and the behaviour of the supply chain is determined by the supplier or by the offer at the begin of the supply chain. Analogously, a dominant pull-component leads to a transport of any changes or disturbances against the direction of the supply chain. The final consumer determines the behaviour of the supply chain.

Within the Selfish-brain theory, the brain is the final consumer, its energy level is hold nearly constant, and the supply of the other organs is subordinate. The need of the brain determines allocation, appetite and exploration. That would suggest that the metabolic supply chain at the individual level is dominated by the pull component, and the push component would act as a sensor for the signals allocation, appetite and exploration. Such interpretations underlines the similarity to supply chains at the cellular and molecular level (Magistretti et al. 1999, Vannucci et al. 1997).

### 5.2 Open questions

A question, which is to be answered in the future, consists in the experimental evidence of the dominance of one component in supply chains at the individual level. Whereas, the experimental proof at the cellular or molecular level can be proceeded by the transport direction of any disturbances and by the relation between the predecessor and the successor compartment, the supply chains at the individual level are superposed by psychological effects, social preconditioning, cue-induced intake etc.

A next question consists in the transition from a microscopical knowledge of detailed supply processes to a macroscopical description. For instance, a detailed investigation of glucose feedback regulated by insulin yields much more information than used in

the more general description of the metabolic supply chain. The extraction of the central relations would build the bridge from the microscopical model to the macroscopical one. Here, the top-down analysis and the bottom-up modelling get into touch.

Furthermore, the metabolic system consists in more regulatory loops, like e.g. the stress axis (Peters & Conrad 2007). These regulatory loops are tuned to each other in healthy humans. On the one hand, food intake supplies the brain and body periphery with energy, on the other hand, it damps the activity of the stress axis. If both set-points mismatch, the intake exceeds the energy need. That finally leads to obesity, too (Peters et al. 2007).

The hierarchical separation of these regulatory loops is a crucial point in the analysis of metabolic supply chains. Is it possible to investigate and analyze partial systems and transfer the results to larger systems, which comprehend the partial systems?

Beside the named questions in modelling, the investigation of general supply chains raises problems, e.g. the influence of realistic nonlinearities in the push and pull component, the recognition of transient substances and reconstruction of reaction kinetics from experimental observations.

A realistic nonlinearity could consist in the influence of the fullness of the predecessor compartment to the reaction constant  $\ell_i = \ell_i(u_{i-1})$ . We expect, that  $\ell_i$  increases with increasing  $u_{i-1}$ , i.e. the transport is eased with the supply state of the supplying compartment. Such a dependency of the push component on the supply state can be interpreted as a weak push component, but it is not identical. Next, the dependency could act as a sensor, too. It is subject to further investigations.

Transient substances occur in chemical reaction chains, and it is to assume that even more complex reactions or reactions with non-linear kinetics are composed of second-order reactions, which are coupled by transient substance. The detection of such transient substances from macroscopical properties in the supply chain could focus experimental investigations into the interesting parts.

In comparison to (Peters & Conrad 2007) where biochemical rules for homeostatic systems and positive feedback have been stated, we would like to ask whether it is possible to extract simple rules for metabolic supply chains at the different levels.

A top-down analysis of supply chains will answer the named questions. In combination with a bottom-up modelling of the details in the transport systems of energy or nutrients, the Selfish-brain theory is creating a new qualitative and quantitative understanding of the human metabolism and the development of diseases like obesity and diabetes.

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