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ORIGINAL PAPER

Unbuffered and buffered supply chains in human metabolism

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Abstract The investigation of very complex dynamical systems like the human metabolism requires the comprehension of important subsystems. The present paper deals with energy supply chains as subsystems of the metabolism on the molecular, cellular, and individual levels. We form a mathematical model of ordinary differential equations and we show fundamental properties by Fourier techniques. The results are supported by a transition from a system of ordinary differential equations to a partial differential equation, namely, a transport equation. In particular, the behavior of supply chains with dominant pull components is discussed. A special focus lies on the role of buffer compartments.

Keywords Supply chains · Transport equation · Metabolism model · Buffer compartment · Selfish brain · Fourier techniques

1 Introduction

Energy supply plays a key important role in metabolic systems. A systemic understanding of the energy metabolism is the key to the investigation of obesity, diabetes, and other metabolic diseases [1].

A central element in metabolic systems is the supply chain, which is found on the molecular level, e.g., in glycolysis [2], on the cellular level, e.g., in the energy-on-demand mechanism of neurons [3], and on the individual level in the investigation of the

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development of obesity [4]. During the transport of energy, the supporting substances are transformed in a chain of biochemical reactions.

The consideration presented here introduces ideas established in logistics and sociodynamics into biomathematical investigations of the human metabolism. A very early discussion of general supply chains is found in [5], which focuses on industrial applications in logistics. Already there, the bullwhip effect is investigated, which means the retrograde propagation and amplification of perturbations in pull-dominated supply chains. Further applications are managerial science in [6] and sociodynamical applications in vehicle traffic and pedestrian behavior in [7, 8].

More modern literature on general supply chains like [9] considers life-science applications like metabolic networks and food webs. Biochemical pathways are interpreted as supply chains or more branched networks. Such large systems ask for an abstraction, which is, for example, found in [10], as well as in [7], where a large system of ordinary differential equations governing the system's behavior is transformed into a partial differential equation, i.e., a transport equation. Another aspect is the selection of reasonable submodels determining characteristic parts of the system's behavior, which includes a hierarchical order of submodels, cf. [11].

Supply chains in the context of metabolism models [12] are mathematically investigated in [13]. Furthermore, new systemic approaches like the energy-on-demand concept [3] encourage mathematical modeling and simulation in life-science applications.

The application of supply chains for the discussion and investigation of energy delivery in metabolism on the individual level is derived from the selfish-brain theory [1, 14], which was founded by Achim Peters. A mathematical core model of the human metabolism is presented in [12]. Furthermore, [15] introduces the technique of a deductive functional assignment of elements in the signaling system of appetite regulation. An aspect of this work is the determination of a set of dynamical systems within a fixed framework, which assures certain qualitative properties of the system independently of the particular shapes of the kinetics. Finally, [16] deals with related modeling in metabolic learning.

The present investigation is based on this research, and concentrates on the special role of buffer or side compartments in abstract supply chains. This particular focus gives a qualitative insight into the influence of buffers on the behavior of a supply chain.

On these levels, various supply chains are accompanied by buffers, which store energy for a relatively short time. These buffers are glycogen in glycolysis or phosphocreatine in ATP delivery in neurons. On the individual level, the liver is a buffer compartment, as well as the short-time fat storage compartment [1, 12]. In periods with abundant energy, energy enters these buffers, and in periods of energy deficiency, energy is pulled out of the buffers. Thus, the buffers act like dampers in the supply chain, and they assure a constant energy supply of the final consumers.

The brain has a very restricted storage ability, and it is supplied permanently and constantly by the metabolism [1] even if disturbances in energy needs or in the external availability of energy occur [17]. The energy supply mechanism is supported by numerous buffers, like, the liver, as a short-time buffer and the visceral fat compartment, as a long-term buffer on the individual level. The systemic understanding of this mechanism with its buffers is a central requirement in research on the causes of obesity and other metabolic diseases.

The present paper starts with a presentation of supply chains and respective buffer compartments in Section 2. Here, Subsection 2.1 mentions glycolysis on the molecular level, Subsection 2.2 briefly addresses the astrocyte–neuron lactate shuttle for the energy supply on the cellular level, and 2.3 deals with selected aspects of supply chains in the human metabolism. Before the mathematical considerations of supply chains are introduced, Subsection 2.4 gives some general remarks about tolerant and robust mathematical models in life-science applications.

Supply chains without buffer compartments are briefly discussed in Section 3. We will give a mathematical formulation of the problem, develop the dynamical system describing a supply chain and show central properties of pure push and pure pull systems. Furthermore, we will provide the transition from the system of ordinary differential equations to a partial differential equation while conserving the qualitative system behavior. A main result consists in the retrograde propagation of all perturbations in systems with a dominant pull component, which gives a hint of the mechanisms assuring a constant energy supply into the brain.

Section 4 focusses on the role of buffer compartments, and in particular on their damping property. Again, we present a dynamical system and discuss its behavior. First, a single compartment with a buffer is discussed by Fourier techniques, and filter functions are given explicitly. The properties found by Fourier techniques are again supported by the transformation of the ordinary differential equations into a general transport equation. This transport equation has two sets of characteristics representing transport in the supply chain itself and the interaction of the supply chain with the buffers. The supply chains conserve basic properties as a hierarchically subordinate model while the buffers are added.

The paper finishes with a conclusion in Section 5, where the qualitative mathematical results for general supply chains are set into the context of the examples mentioned above. The systemic understanding of supply chains as an important subsystem of metabolic networks opens a growing field of interdisciplinary research.

2 Buffer compartments on different levels

We present supply chains and respective buffers on the molecular, the cellular, and the individual level, and we illustrate the supply chains by an example for each level. These examples are glycolysis on the molecular level, the astrocyte–neuron lactate shuttle for the energy supply of the neuron on the cellular level, and integrated glucose metabolism as an example for a supply chain on the individual level.

The section finishes with general remarks on the mathematical modeling of supply chains, given in Subsection 2.4. Applications of the mathematical results are discussed in Section 5.

2.1 Molecular level—glycolysis

Glycolysis [2] is a supply chain on the molecular level [13]. It is buffered by glycogen. Glycogen is a glucose polymer that provides short-term energy storage in the cells of animals. It can be found mainly in the liver and in muscle, but also in astrocytes in the brain, cf. Subsection 2.2. The biochemical details of glycogen synthesis and breakdown are well known and can be found in textbooks like [18]. In times of energy abundance, characterized by high levels of glucose in the blood or ATP in the cell, glucose is converted to glycogen. If energy is needed, glycogen is used to generate glucose.

The starting point for the synthesis of glycogen is glucose, which is first converted to glucose 6-phosphate (G6P) and thereby trapped in the cell. G6P becomes glucose 1-

phosphate (G1P) in an intermediate reaction, which is activated with uridine triphosphate and becomes uridine diphosphate glucose. This compound can then be added to existing glycogen molecules.

In the breakdown of glycogen, single glucose molecules are removed from the glycogen chains and converted to G1P and eventually to G6P, which can be used as a starting point for glycolysis and thereby for the production of energy. In liver cells, G6P can also be converted to glucose and transported back into the blood. This is a mechanism that enables the liver to serve as an energy buffer for the whole body. Muscle cells lack the necessary enzymes; their use of glycogen is strictly local.

Due to their importance for the energy metabolism of the body, the glycogen pathways are under strong hormonal regulation by the insulin–glucagon system. However, allosteric mechanisms also play an important role on the single-cell level [19].

2.2 Cellular level—astrocyte–neuron lactate shuttle

Neurons have no direct contact with the blood vessels but are surrounded by glial cells, most which are being astrocytes. Since the middle of the last decade, there has been evidence that the astrocytes play a major role in regulating the energy supply of neurons [3].

The basic idea behind the astrocyte–neuron lactate shuttle theory is that neuronal activity leads to increased glycolysis and glycogenolysis activity in astrocytes. One of the products is lactate, which is used as fuel by the neurons [20]. By this mechanism, active neurons stimulate their supply of energy, which is called energy on demand. Astrocytes are even able to increase perfusion locally in regions with high activity to meet the needs of the neurons [21], which supports the idea of a strong pull component in the energy metabolism of neurons.

As mentioned before, glycogen is used in astrocytes as a storage molecule [22]. Although the absolute content of glycogen is not as high in the brain as in the liver or in muscle, it is an important source of glucose and, thereby, of lactate. In particular, it enables astrocytes to buffer times with very high activity and low glucose blood levels and it ensures the supply of neurons with energy.

2.3 Individual level—metabolism

On the individual level, the human energy metabolism is a prominent example of a supply chain. Energy enters the individual by cyclic food intake, and the brain and the muscles permanently consume energy [1, 14]. The question of how the brain regulates its constant energy level is of great importance for the systemic understanding of human metabolism and the development of metabolic diseases [4]

The main compartments of the individual metabolic supply chain are the stomach, the liver, the blood glucose, the brain, and the body periphery including the muscles. Of course, a large number of intermediate states can be regarded as separate compartments. Buffers in this metabolic supply chain are the stomach and the liver, which change the cyclic food intake into an oscillating but still permanent supply. In particular, the liver is able to store energy in the form of glycogen and to transform it back into blood glucose. It is the prototype of a buffer compartment.

But the most interesting buffer or side compartment is the body fat, occurring in various forms and in various locations. Energy enters and leaves the body fat via different pathways and in different forms, but in the following, we abstract to the deviation from an assumed flux balance.

All fluxes between the different compartments are regulated by a considerable number of partly redundant signaling mechanisms. In the present paper, we concentrate on the role of buffer compartments for the energy supply of the final consumers, here the brain and the body periphery. A more detailed model is found in [23].

2.4 Modeling remarks

It is a very general and comprehensive question whether rather simple mathematical models can describe processes in biochemical and other life-science applications, where, of course, saturated kinetics and stronger non-linearities, as well as network-like structures, occur.

The present investigation aims for qualitative results, which hold true for a large variety of supply chains and which, in particular, provide a systemic understanding of the role of buffer compartments. On the one hand, the evolutionary selection has generated robust and redundant mechanisms, which cannot be too sensitive against perturbations either in the parameters or in the kinetics. We think that mechanisms, the qualitative behavior of which is sensitively changed by exogenous influences, have not survived. On the other hand, it is very unlikely that a complete analysis and quantification of the interaction of all redundant submechanisms might be possible within the near future. Furthermore, the network of specific supply mechanisms often is not completely analyzed, not even qualitatively. For instance, the role of lactate described in Subsection 2.2 is under strong discussion, cf. [24] and [20], while there seems to be accordance about the importance of the astrocyte for the energy supply of the neurons.

Therefore, here we investigate abstract simplified supply chains and buffers, which can be used as components in more complex biochemical or metabolic networks. In particular, we assume an immediate effect of each cause, since any time delay found by measurements is affected by subordinate mechanisms as well. Next, we linearize the kinetics near the equilibrium or working point. Thus, we are aware that the results formally hold true only for small perturbations. Due to evolutionary stability, the validity range is not restricted to infinitesimally small perturbations, although it does not include extremal situations.

3 Supply chains

3.1 Model set-up

Let us consider a supply chain of n compartments with the time-dependent energy contents $u_\nu = u_\nu(t)$, $\nu = 1, \ldots, n$. The energy contents are independent of the particular manifestation of the energy or the energy-supporting substance. They are measured as deviations from an equilibrium content u_ν^*. Hence, the total energy in the νth compartment is $u_\nu^* + u_\nu(t)$.

The flux from the compartment ν into the compartment $\nu + 1$ is named $j_\nu(t) + j^*$, $\nu = 1, \ldots, n-1$, where j^* is the flux in the equilibrium of the supply chain. If the supply chain remains in the equilibrium, then all fluxes between neighboring compartments, as well as the inflow and the outflow of the supply chain, are identical to j^*.

The time-dependent inflow into the first compartment of the supply chain is called $j_{\text{in}}(t) + j^* = j_0(t) + j^*$ and the outflow from the nth compartment is $j_{\text{out}}(t) + j^* = j_n(t) +$

j^*, as shown in Fig. 1. The fluxes $j_\nu(t)$, $\nu = 0, \ldots, n$ are deviations from the equilibrated situation. In the absence of other sources and sinks in the supply chain, the continuity equation reads

$$\dot{u}_\nu(t) = \frac{\mathrm{d}}{\mathrm{d}t}(u_\nu^* + u_\nu(t)) = [j_{\nu-1}(t) + j^*] - [j_\nu(t) - j^*] = j_{\nu-1}(t) - j_\nu(t) \tag{1}$$

for $\nu = 1, \ldots, n$. An assumption about the constitutive equations is the smooth dependency of the total flow $j^* + j_\nu = J_\nu(u_\nu^* + u_\nu, u_{\nu+1}^* + u_{\nu+1})$, $\nu = 1, \ldots, n-1$ on the energy contents in the linked compartments, cf. Subsection 2.4. We have already mentioned that $J_\nu(u_\nu^*, u_{\nu+1}^*) = j^*$, and we find

$$j_\nu = \frac{\partial J_\nu}{\partial u_\nu}(u_\nu^*, u_{\nu+1}^*)\, u_\nu + \frac{\partial J_\nu}{\partial u_{\nu+1}}(u_\nu^*, u_{\nu+1}^*)\, u_{\nu+1} + \mathcal{O}(u_\nu, u_{\nu+1})^2.$$

Since it seems natural that the flow from compartment ν into compartment $\nu+1$ increases with u_ν and decreases with $u_{\nu+1}$, we denote the push factor $k_\nu \geq 0$ describing the dependency of j_ν on the content u_ν of the supplier or preceding compartment, and the pull factor $\ell_{\nu+1} \geq 0$ describing the dependency of j_ν on the content $u_{\nu+1}$ of the receiver or succeeding compartment, by

$$k_\nu = \frac{\partial}{\partial u_\nu} J_\nu(u_\nu^*, u_{\nu+1}^*) \;\text{ and }\; \ell_{\nu+1} = -\frac{\partial}{\partial u_{\nu+1}} J_\nu(u_\nu^*, u_{\nu+1}^*).$$

The constitutive equations for the balance law (1) are approximated by

$$j_\nu = k_\nu u_\nu - \ell_{\nu+1} u_{\nu+1} \;\text{ for }\; \nu = 1, \ldots, n-1 \tag{2}$$

for sufficiently small deviations u_ν, $\nu = 1, \ldots, n$. The linearized dynamical system (1,2) reads in detail as

$$\begin{aligned} \dot{u}_1 &= j_{\text{in}}(t) - k_1 u_1 + \ell_2 u_2\,, \\ \dot{u}_\nu &= k_{\nu-1} u_{\nu-1} - (k_\nu + \ell_\nu) u_\nu + \ell_{\nu+1} u_{\nu+1}\,, \\ &\;\vdots \\ \dot{u}_n &= k_{n-1} u_{n-1} - \ell_n u_n - j_{\text{out}}(t) \end{aligned} \tag{3}$$

with $\nu = 2, \ldots, n-1$.

Let us remark that a metabolic supply chain usually has a definite transport direction. Although negative values of j_ν occur in the presented model equations, a sufficiently large j^* assures positive total fluxes. Furthermore, it is easy to see that initial conditions with

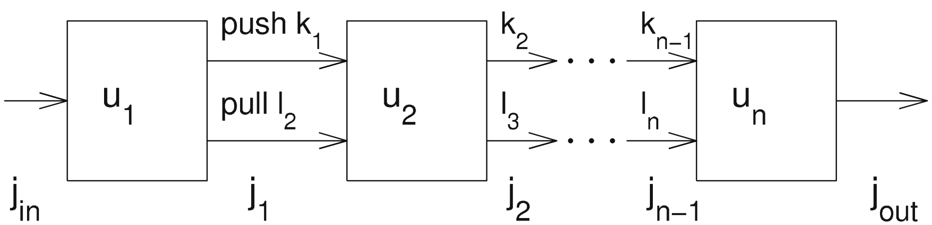


Fig. 1 Abstract supply chain with energy contents u_ν in the n compartments and the linking fluxes j_ν, $\nu = 0, \ldots, n$ composed of a linear push and a linear pull component

positive fluxes assure positive fluxes for all time instants if inflow and outflow are always positive [13].

In the particular case of a pure pull system, the push components k_ν are vanishing, and every flux j_ν is governed by the succeeding compartment $u_{\nu+1}$ alone. Hence, any disturbance propagates backwards in the supply chain because the energy content in the compartment ν does not influence the energy contents u_γ with $\gamma > \nu$. Then, the need $j_{\text{out}}(t)$ dominates the supply chain, and the dynamical system (3) describes a retrograde wave or retrograde information transport, while the actual energy transport is still forward due to $j^* > 0$. An analogous consideration holds true for pure push systems, where the information is transported in the forward direction.

3.2 Transition to the transport equation

The dynamical system (3) resembles a naive semidiscretization of a partial differential equation in $v = v(t, x)$, where the position x is associated with the course of the supply chain. That evokes the idea to consider a partial differential equation instead, and to discuss the systems's qualitative behavior by means of a single equation.

This transition is furthermore supported by the observation that most of the supply chains in life-science applications are continuous, and that the n compartments are part of the mathematical model—and not necessarily of the modeled mechanism. For instance, a tremendous number of intermediate products are found in a reaction chain like glycolysis. Also, ATP delivery in the neuron is a continuous transport process, and energy is continuously transported in human metabolism on the individual level, too.

Hence, on the one hand, the description of a supply chain by a partial differential equation is a formal step, which starts with the system of ordinary equations, but on the other hand, it is a compartment-free model of a continuous supply chain. Now, the question occurs of which partial differential equation yields a suitable model of a continuous supply chain.

The position is defined as $x \in [0, n+1]$, and the energy level at the points $x_\nu = \nu \in \mathbb{N}$ may be $u_\nu(t) \approx v(t, \nu)$. The push components are $\kappa(x) \geq 0$ with $\kappa(\nu) = k_\nu$, and the pull components are $\lambda(x) \geq 0$ with $\lambda(\nu) = \ell_\nu$. Due to the different directions of the information transport in (3), the first-order upwind scheme in the semidiscretization gives

$$\frac{\partial}{\partial x}[\kappa(x_\nu)v(t, x_\nu)] \approx k_\nu u_\nu(t) - k_{\nu-1}u_{\nu-1}(t)$$

and

$$\frac{\partial}{\partial x}[\lambda(x_\nu)v(t, x_\nu)] \approx \ell_{\nu+1}u_{\nu+1}(t) - \ell_\nu u_\nu(t).$$

Equation 3 reads now as the formal first-order semidiscretization of the transport equation

$$\frac{\partial}{\partial t}v(t, x) = -\frac{\partial}{\partial x}[\kappa(x)v(t, x)] + \frac{\partial}{\partial x}[\lambda(x)v(t, x)]. \tag{4}$$

Suitable boundary conditions depend on the wave direction [25].

Let us remark that (3) can be interpreted as a semidiscretization of a second-order differential equation, too [26]. But in general, an absolute term $\gamma(x)u(x)$ is needed in addition to the diffusion term and the convection term. Furthermore, the biochemical interpretation of a diffusion term in a supply chain is questionable because most biochemical reactions have a distinct direction under physiological conditions.

We now show a fundamental property of pure pull systems.

Theorem 3.1 *In the case $\kappa(x) = 0$, the waves in (4) with $\lambda(x) > 0$ propagate backwards.*

Proof Equation 4 can be written as $v_t - [\lambda(x)v]_x = 0$ with $\lambda(x) > 0$. The characteristics $\xi = \xi(t)$ with the starting point $(0, x_0)$ obey the initial-value problem

$$\xi'(t) = -\lambda(\xi(t)) < 0 \ \text{ with } \ \xi(0) = x_0.$$

Thus, $\lambda(x)v(t, x)$ is constant in t, and particularly, it is

$$\lambda(\xi(t))v(t, \xi(t)) = \lambda(x_0)v(0, x_0), \tag{5}$$

and any wave with the initial values $v(0, x)$ propagates backwards with the characteristic $\xi(t)$ because $\xi'(t) < 0$. □

The analogous result holds true for a pure push system, where the waves propagate in the direction of the supply chain. Forward waves can serve as a signal about the energy contents in the preceding compartments to the final consumer [15].

The following corollary contains the increase of the perturbations during their retrograde propagation, as illustrated in Fig. 2. It is related to the observation that the brain as final consumer enjoys a nearly constant energy content [1, 17].

Corollary 3.2 *If $\lambda(x)$ is monotonously increasing, then in (4) with $\kappa(x) = 0$, the amplitudes of the waves increase while propagating backwards.*

Proof Equation 5 gives the expression

$$v(t, \xi(t)) = \frac{\lambda(x_0)}{\lambda(\xi(t))} v(0, x_0),$$

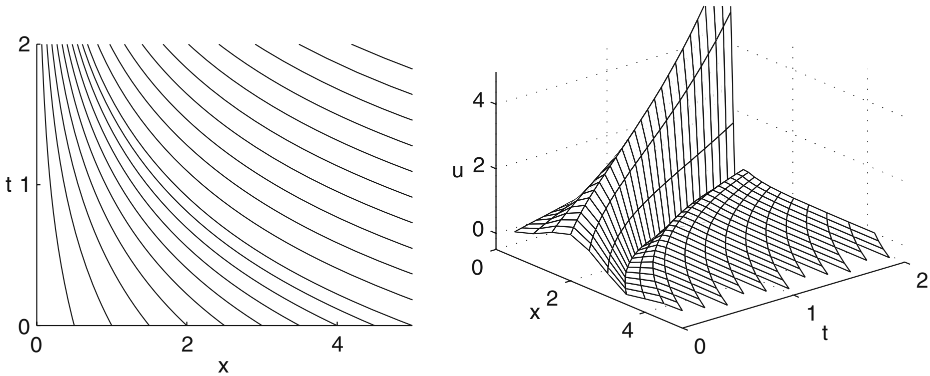


Fig. 2 *Left*: characteristics moving backwards in a pure pull system with $\lambda(x) = x$. *Right*: example solution with an initial wave, which amplifies while moving backwards

and the assertion follows from the fact that $\xi(t)$ is decreasing and, hence, $\lambda(\xi(t))$ is decreasing in t for every characteristic, too. $\square$

A serious problem in the transition from (3) to (4) results from the situation that the push and pull terms can be combined in the transport equation to

$$\frac{\partial}{\partial t}v(t,x) = \frac{\partial}{\partial x}[(\lambda(x) - \kappa(x))v(t,x)].$$

Thus, the qualitative behavior of a supply chain containing push and pull components is modeled by a transport equation, the wave direction of which depends only on the sign of $\alpha(x) = \lambda(x) - \kappa(x)$. So, all supply chains with identical differences $\lambda(x) - \kappa(x)$ are modeled by the same transport (4). In particular, small push components $\kappa(x) \ll \lambda(x)$, $x \in [0, n+1]$ have no influence on the qualitative behavior of the pull system in (4). However, the push components play an important role if signaling components like appetite are considered [15] because the push components provide information about the energy contents in preceding compartments to the final consumer.

4 Buffers in supply chains

We now consider a supply chain with a buffer attached to each compartment, as shown in Fig. 3. We use the same approach as in Section 3 to get a straightforward extension of the dynamical system (3). The deviation of the content of the νth buffer from its reference value y_ν^* is denoted by $y_\nu = y_\nu(t)$. We introduce the flux $s_\nu = s_\nu(t)$ from the chain compartment into its buffer. Assuming that s_ν depends smoothly on u_ν and y_ν, a linearization gives

$$s_\nu = q_\nu u_\nu - r_\nu y_\nu, \quad \text{with} \quad q_\nu, r_\nu > 0. \tag{6}$$

In the equilibrium, the contents of the buffer compartments do not change, and therefore, the flux must vanish. Therefore, the reference flux s^* is zero.

The continuity equations for u_ν and y_ν are given by

$$\begin{aligned} \dot{u}_\nu &= j_{\nu-1} - j_\nu - s_\nu, \\ \dot{y}_\nu &= s_\nu \end{aligned}$$

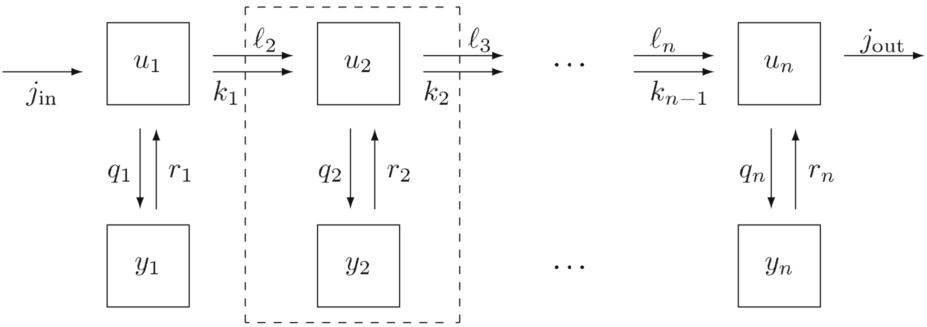


Fig. 3 Extended supply chain with buffers. The *dashed box* indicates one element. The in- and outflow of the element ν consists of one part that depends on u_ν and one part that does not. The parameters k_ν and ℓ_ν belong to the dependent part, whereas $k_{\nu-1}$ and $\ell_{\nu+1}$ belong to the independent part

for $\nu = 1, 2, \ldots, n$. With (2) and (6), the dynamical system reads

$$\begin{aligned}
\dot{u}_1 &= j_{\text{in}}(t) - k_1 u_1 + \ell_2 u_2 - q_1 u_1 + r_1 y_1,\\
\dot{u}_\nu &= k_{\nu-1} u_{\nu-1} - (k_\nu + \ell_\nu) u_\nu + \ell_{\nu+1} u_{\nu+1} - q_\nu u_\nu + r_\nu y_\nu,\\
\dot{u}_n &= k_{n-1} u_{n-1} - \ell_n u_n - q_n u_n + r_n y_n - j_{\text{out}}(t),\\
\dot{y}_\gamma &= q_\gamma u_\gamma - r_\gamma y_\gamma
\end{aligned} \tag{7}$$

for $\nu = 2, \ldots, n-1$ and $\gamma = 1, \ldots, n$. Hence, (7) extends (3) by the buffers.

4.1 Single buffered compartment

The supply chain is built of n identical elements, each consisting of one chain compartment and its buffer, as illustrated in Fig. 3. The coefficients k_ν and ℓ_ν, etc., are denoted without the index in the discussion of a single compartment here, although they are still regarded as dependent on ν. We find the system

$$\begin{aligned}
\dot{u} &= -(k+\ell)u - qu + ry + f(t), \qquad (8)\\
\dot{y} &= qu - ry,
\end{aligned}$$

with non-negative parameters k, ℓ, q, and r for the contents $u(t)$ and $y(t)$ of the chain compartment and the attached buffer. The existence of the buffer is assured by $q > 0$. Furthermore, we assume $k + \ell > 0$ because the compartment is active in the supply chain. The time-dependent function $f(t)$ represents the external in- or outflow due to the push or pull activity of the neighboring compartments or the more general in- or outflow of the compartments at the ends of the supply chain.

Now, our aim is the analysis of the response of the element to the input function $f(t)$. We are especially interested in how the contents of the main compartment and of the buffer are influenced by $f(t)$. Since the system (8) is linear, periodic steady states can be analyzed by the Fourier transform. This technique, widely used in engineering and signal processing, converts the differentiation with respect to t in the time domain to a multiplication with $\mathrm{i}\omega$ in the frequency domain. For reference, we define the Fourier transform $\hat{f}$ of a function f as

$$\hat{f}(\omega) = \int_{-\infty}^{\infty} f(t)\mathrm{e}^{\mathrm{i}\omega t}\,\mathrm{d}t.$$

The question of the existence of the Fourier transform refers to the usage of appropriate function spaces and is not of practical interest for the investigation of physiological supply chains.

Theorem 4.1 *Let $\hat{f}$ be the Fourier transform of f in (8). Then, the Fourier transforms $\hat{u}$ and $\hat{y}$ of u and y, respectively, are $\hat{u}(\omega) = H(\omega)\hat{f}(\omega)$ and $\hat{y}(\omega) = G(\omega)\hat{f}(\omega)$ with the filter functions*

$$H(\omega) = \frac{r + \mathrm{i}\omega}{\eta} \quad \text{and} \quad G(\omega) = \frac{q}{\eta},$$

with the common denominator $\eta = (k+\ell)r - \omega^2 + \mathrm{i}\omega(k+\ell+q+r)$.

Proof The application of the Fourier transform to (8) gives the linear algebraic system

$$\mathrm{i}\omega \begin{pmatrix} \hat{u} \\ \hat{y} \end{pmatrix} = \begin{pmatrix} -(k+\ell+q) & r \\ q & -r \end{pmatrix} \begin{pmatrix} \hat{u} \\ \hat{y} \end{pmatrix} + \begin{pmatrix} \hat{f} \\ 0 \end{pmatrix}$$

in the frequency domain. Its solution $\hat{u}$ and $\hat{y}$ yields the desired result. □

So, if f is purely harmonic in a single frequency ω, then u and y are scaled and phase-shifted versions of f. Of course, the response of the system, i.e., the scaling and the shift, depends on the frequency ω. To investigate the dependency on the frequency ω, we regard the modulus of the filter functions

$$|H(\omega)| = \frac{\sqrt{r^2+\omega^2}}{|\eta|} \quad \text{and} \quad |G(\omega)| = \frac{q}{|\eta|}.$$

The common denominator fulfills $|\eta| \neq 0$ for all real ω because

$$|\eta|^2 = (k+\ell)^2 r^2 + \omega^4 + \omega^2 \left[(k+\ell)^2 + (q+r)^2 + 2q(k+\ell)\right]. \tag{9}$$

Thus, independently from the input f, no resonance effect occurs. The reason lies in the compensating flux $-(k+\ell)u$, which drives u back to zero and, consequently, y, too. This is reflected on the frequency side by the fact that $(k+\ell)r$ is the only term in the denominator η of the filter functions that is not multiplied by $\mathrm{i}\omega$. Some properties of the modulus $|H(\omega)|$ and $|G(\omega)|$ will be highlighted.

Theorem 4.2 *The moduli $|H(\omega)|$ and $|G(\omega)|$ of the filter functions reach their global maximum at $\omega = 0$ and decrease monotonously to zero for $\omega \to \pm\infty$.*

Proof Since $\eta = \mathcal{O}(\omega^2)$ for $\omega \to \pm\infty$, we have

$$\lim_{\omega\to\pm\infty} |H(\omega)| = \lim_{\omega\to\pm\infty} |G(\omega)| = 0.$$

Next, we differentiate $|H(\omega)|^2$ and $|G(\omega)|^2$ since both filter functions are positive for all ω. We find

$$\frac{\mathrm{d}}{\mathrm{d}\omega}|H(\omega)|^2 = -\frac{2\omega[(\omega^2+r^2)^2 + qr^2(2k+2\ell+q+2r)]}{|\eta|^4}$$

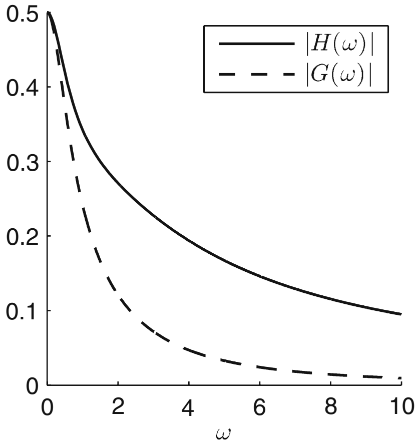
and

$$\frac{\mathrm{d}}{\mathrm{d}\omega}|G(\omega)|^2 = -\frac{2q^2\omega[2\omega^2 + r^2 + 2qr + (k+\ell+q)^2]}{|\eta|^4}.$$

Each derivative has exactly one zero at $\omega = 0$, and both derivatives are positive for $\omega < 0$ and negative for $\omega > 0$ because all parameters are positive. That proves the maximum and monotonicity property. □

The result of the preceding theorem can be regarded as a lowpass property of the system composed of a single compartment and a buffer. High frequencies contained in $f(t)$ are damped more strongly by the system than low frequencies, as illustrated in Fig. 4.

By looking at the influence of the parameters in $|H(\omega)|$ and $|G(\omega)|$, we can state some rough estimates. The modulus of H decreases with increasing k, ℓ, and q, and the damping



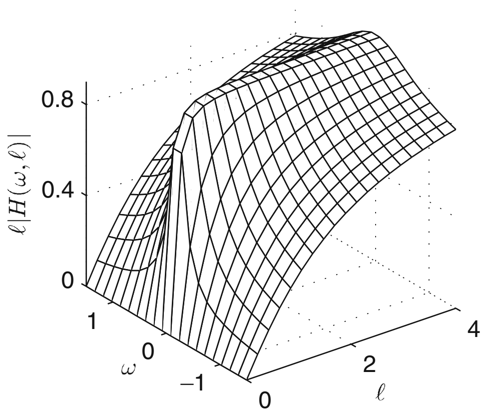


Fig. 4 *Left*: modulus of the filter functions $H(\omega)$ and $G(\omega)$ for $k = \ell = q = r = 1$. *Right*: $\ell|H(\omega)|$ in the pure pull system for $q = r = 1$

effect on u is then enforced. Increasing parameters k, ℓ, and r enhances the damping of y, too.

In general, only the push and pull components k and ℓ will enlarge the damping in both compartments. This underlines their importance also in the buffered case. The damping and the lowpass properties are critical for the application to metabolic supply chains because the brain relies heavily on a constant energy content and, thus, on a sufficient inflow of energy.

Let us now examine the influence of the buffer on the damping of $f(t)$. By setting $q = r = 0$ in (8), we find the solutions for the compartment without buffer. The content of the chain compartment in the case without buffer is denoted by $u_{\mathrm{no}}(t)$ with the Fourier transform $\hat{u}_{\mathrm{no}}(\omega)$.

Theorem 4.3 *The absolute values of the filter functions* $|H(\omega)|$ *and* $|H_{\mathrm{no}}(\omega)|$ *in the cases with and without buffer fulfill*

$$|H(0)| = |H_{\mathrm{no}}(0)| \;\; \textit{and} \;\; |H(\omega)| < |H_{\mathrm{no}}(\omega)| \;\; \textit{for } \omega \neq 0.$$

Proof The identity for $\omega = 0$ follows from $\lim_{\omega \to 0} |H(\omega)| = 1/(k + \ell)$ for all non-negative parameters with $k + \ell > 0$.

For $\omega \neq 0$, we again consider the squared functions. Expanding $|H_{\mathrm{no}}(\omega)|^2$ with ω yields

$$|H_{\mathrm{no}}(\omega)|^2 = \frac{\omega^2}{(k+\ell)^2\omega^2 + \omega^4}.$$

Adding different positive terms to the numerator and denominator in the above equation gives $|H(\omega)|$. It holds true for general $c_1, c_2, d_1, d_2 > 0$ that

$$\frac{c_1}{c_2} > \frac{c_1 + d_1}{c_2 + d_2} \;\; \text{is equivalent to} \;\; d_2 > \frac{c_2 d_1}{c_1}, \tag{10}$$

and $c_1 = \omega^2$, $c_2 = (k+\ell)^2\omega^2 + \omega^4$, $d_1 = r^2$, and $d_2 = (k+\ell)^2 r^2 + \omega^2[(q+r)^2 + 2q(k+\ell)]$, cf. (9), yield the property in (10) since $\omega^2[2q(k+\ell+r) + r^2] > 0$ with non-negative parameters and with $k + \ell > 0$. □

Hence, the damping effect of the element is always enhanced by the buffer. The qualitative property of damping enhancement is independent of the input $f(t)$ and of the particular parameters. This emphasizes the relevance of buffer compartments. They diminish the influences of disturbances on the contents of the compartments in the supply chain and help to assure a more constant delivery of energy.

4.2 Pure pull supply chain

We now assemble the supply chain of length n from single elements to find expressions for the solution in the frequency domain. In particular, we deal with pure pull supply chains in this subsection. These are supply chains without push components, i.e., $k_\nu = 0$ for all $\nu = 1, \dots, n-1$. Then, the behavior of the supply chain is governed by the receivers, only. The hierarchically ordered receivers are all compartments $i = 2, \dots, n$ in retrograde order.

Theorem 4.4 *Let $j_{\mathrm{in}} = j_{\mathrm{in}}(t)$ and $j_{\mathrm{out}} = j_{\mathrm{out}}(t)$ be Fourier transformable functions with the transforms $\hat{j}_{\mathrm{in}}$ and $\hat{j}_{\mathrm{out}}$. Then, it holds true that*

$$\begin{aligned}
\hat{u}_1 &= H_1(\omega)(\hat{j}_{\mathrm{in}} + \ell_2 \hat{u}_2),\\
\hat{u}_\nu &= H_\nu(\omega)(k_{\nu-1}\hat{u}_{\nu-1} + \ell_{\nu+1}\hat{u}_{\nu+1}),\\
\hat{u}_n &= H_n(\omega)(k_{n-1}\hat{u}_{n-1} - \hat{j}_{\mathrm{out}}),
\end{aligned}$$

and

$$\begin{aligned}
\hat{y}_1 &= G_1(\omega)(\hat{j}_{\mathrm{in}} + \ell_2 \hat{u}_2),\\
\hat{y}_\nu &= G_\nu(\omega)(k_{\nu-1}\hat{u}_{\nu-1} + \ell_{\nu+1}\hat{u}_{\nu+1}),\\
\hat{y}_n &= G_n(\omega)(k_{n-1}\hat{u}_{n-1} - \hat{j}_{\mathrm{out}}),
\end{aligned}$$

for $\nu = 2, 3, \dots, n-1$ with

$$H_\nu(\omega) = \frac{r_\nu + \mathrm{i}\omega}{\eta_\nu}, \quad G_\nu(\omega) = \frac{q_\nu}{\eta_\nu}$$

and $\eta_\nu = (k_\nu + \ell_\nu) r_\nu - \omega^2 + \mathrm{i}\omega(k_\nu + \ell_\nu + q_\nu + r_\nu)$ for $\nu = 1, 2 \dots, n$.

Proof We define the time-dependent exogenous excitations f_ν of each compartment/buffer pair by $f_1(t) = j_{\mathrm{in}}(t) + \ell_2 u_2(t)$, by $f_\nu(t) = k_{\nu-1}u_{\nu-1}(t) + \ell_{\nu+1}u_{\nu+1}(t)$ for $\nu = 2, 3, \dots, n-1$, and by $f_n(t) = k_{n-1}u_{n-1}(t) - j_{\mathrm{out}}(t)$. After inserting that into (8), we have the structure of a single element for all pairs of u_ν and y_ν. We use Theorem 4.1, and we obtain the result. □

Corollary 4.5 *In a pure pull chain, i.e., $k_\nu = 0$ for all ν in (7), it holds true that*

$$\hat{u}_\nu = -H_\nu \prod_{\gamma=\nu+1}^{n} \ell_\gamma H_\gamma \cdot \hat{j}_{\mathrm{out}} \ \ \textit{and} \ \ \hat{y}_\nu = -G_\nu \prod_{\gamma=\nu+1}^{n} \ell_\gamma H_\gamma \cdot \hat{j}_{\mathrm{out}}$$

for $\nu = 2, \dots, n$ and

$$\hat{u}_1 = H_1\left(\hat{j}_{\mathrm{in}} - \prod_{\gamma=2}^{n} \ell_\gamma H_\gamma \cdot \hat{j}_{\mathrm{out}}\right) \ \textit{and}\ \hat{y}_1 = G_1\left(\hat{j}_{\mathrm{in}} - \prod_{\gamma=2}^{n} \ell_\gamma H_\gamma \cdot \hat{j}_{\mathrm{out}}\right).$$

Proof For $k_\nu = 0$, the tridiagonal system in Theorem 4.4 reduces to an upper triangular system, and the solution can be calculated by backward substitution. □

A similar solution can be found in the case of the respective pure push chain by forward substituting.

The particular role of the first compartment results from the fact that its content is governed by the inflow j_{in} and by the second compartment as receiver, whereas all other compartments only depend on the succeeding compartment or the outflow j_{out}, respectively.

The general structure found for one compartment with buffer is conserved in the pull chain. The disturbance is now the prefiltered version of j_{out}, which travels backwards in the supply chain as already indicated in Section 3. The solution for $\nu = 2, 3, \ldots, n$ involves only the transform of j_{out}. For the first compartment, the independent flux is modified by j_{in}, which only affects the first compartment. All information transport is retrograde.

Each element in the chain possesses the lowpass property on its own. The strength of the lowpass depends just on the parameters present at the individual element. We can already conclude from the subsequent product that this lowpass property is enforced as the disturbance travels in the supply chain. Next, there is also a damping effect of the transport along the chain.

Since a pure pull chain is characterized by $j_{\nu-1} = -\ell_\nu u_\nu$, the filter function H_ν for the content of the compartment ν implies the filter function $\ell_\nu H_\nu$ for the flux. The following Theorem 4.6 shows a relation between the damping of the compartment contents and the damping of the transport in the linking fluxes.

Since the filter functions H_ν are direct equivalents of H for the particular compartments, the following property is noted without the index ν.

Theorem 4.5 *For $\ell > 0$ and $|H(\omega)|$ from the pure pull chain, it holds true that $\ell|H(0)| = 1$ and $\ell|H(\omega)| < 1$ for all $\omega \neq 0$. Moreover, it is true that $\lim\limits_{\ell\to\infty} \ell|H(\omega)| = 1$.*

Proof Obviously, $\ell|H(0)| = 1$, and we find

$$\ell|H(\omega)| = \frac{\ell\sqrt{r^2+\omega^2}}{\sqrt{(\ell^2+\omega^2)r^2 + (2qr + (\ell+q)^2)\omega^2 + \omega^4}} < 1$$

for all $\omega \neq 0$ because additional positive terms occur in the denominator. At the same time, these expressions show $\lim\limits_{\ell\to\infty} \ell|H(\omega)| = 1$ and, thus, the decreasing behavior of $H(\omega)$ with respect to ℓ. □

Therefore, it holds true that the product over some $\ell_\nu|H_\nu(\omega)|$ is smaller than 1 for $\omega \neq 0$, and it is ever-decreasing the more terms are involved in the product. That means, the further away in terms of the number of compartments a compartment lies from the end of the pull chain, the weaker the signal $j_{\text{out}}(t)$ arrives at that compartment, i.e., the signal suffers a damping while traveling along the supply chain. Although the specific size of the damping depends on the parameters, the effect itself does not. Generally speaking, the more compartments we have in a supply chain, the more strongly disturbances are damped out by the transport process.

The second part of Theorem 4.6 shows, on the other hand, that large ℓ_ν weaken the damping in the fluxes, as shown in Fig. 4. This is consistent with our previous statement that increasing ℓ decreases the magnitude of $|H(\omega)|$.

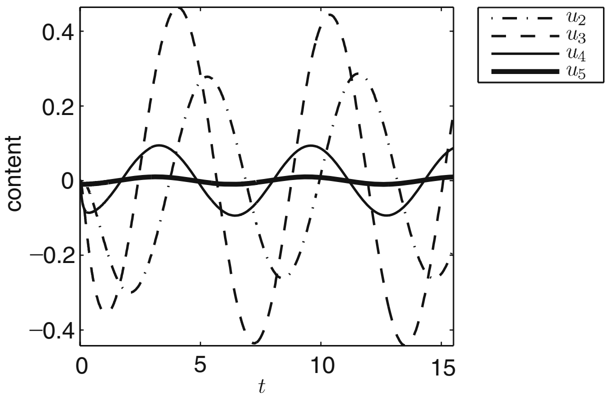


Fig. 5 Numerical example for the pure pull chain with five compartments. The parameters were $q_\nu = r_\nu = 1$ for $\nu = 1, 2, \dots, 5$ and $\ell_2 = 0.1$, $\ell_3 = 1$, $\ell_4 = 10$, and $\ell_5 = 100$. The outflow at the right boundary was $j_{\text{out}} = \cos t$

Large pull parameters ℓ_ν lead to a strong damping on the individual level of the content of the νth compartment but, therefore, decrease the damping of disturbances along the supply chain. The signal just passes through, nearly without being changed in its amplitude, and that requires variable fluxes j_ν, which strongly adapt to the needs in the pull components.

That means that the content of the compartments at the end of the chain is regulated, i.e., damped, the most in the case of a pull-dominated supply chain with increasing pull components, as found in metabolic applications. Therefore, a constant delivery of energy is guaranteed. The fluctuation in the need at the right boundary is passed up to the beginning, where it signals the energy demand, as shown in Fig. 5. Similar observations are made in logistic supply chains [6, 27].

4.3 Continuous setting

This section deals with a continuous representation of the supply chain with buffers. As in Section 3, we consider the function $v(t, x)$ for the energy level in the chain itself and we introduce $z(t, x)$ for the energy level in the buffer. We take $u_\nu \approx v(t, \nu)$ and $y_\nu \approx z(t, \nu)$ with $\nu \in \mathbb{N}$. We find the straightforward extension of (4) to be the system

$$\begin{aligned} v_t &= -(\kappa v)_x + (\lambda v)_x - \mu v + \rho z, \\ z_t &= \mu v - \rho z. \end{aligned} \tag{11}$$

Again, the push and pull components are $\kappa(x) \geq 0$ and $\lambda(x) \geq 0$ and the flux between the supply chain and the buffer is parameterized by $\mu(x) > 0$ and $\rho(x) > 0$ with $\mu(\nu) = q_\nu$ and $\rho(\nu) = r_\nu$.

We put $\alpha(x) = \lambda(x) - \kappa(x)$, and we write (11) as

$$\frac{\partial}{\partial t}\begin{pmatrix} v \\ z \end{pmatrix} = \frac{\partial}{\partial x}\left[\begin{pmatrix} \alpha(x) & 0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} v \\ z \end{pmatrix}\right] + \begin{pmatrix} -\mu v + \rho z \\ \mu v - \rho z \end{pmatrix}.$$

Now, obviously, identical characteristics are found in the system and in the separated equations [28]. Along $\xi(t)' = -\alpha(\xi)$, we have

$$\frac{\mathrm{d}}{\mathrm{d}t} v(\xi(t), t) = \alpha'(\xi(t)) v(\xi(t), t) - \mu(\xi(t)) v(\xi(t), t) + \rho(\xi(t)) z(\xi(t), t),$$

while, along $\zeta(t)' = 0$, i.e., with a constant ζ, we have

$$\frac{\mathrm{d}}{\mathrm{d}t} z(\zeta(t), t) = \mu(\zeta(t))v(\zeta(t), t) - \rho(\zeta(t))z(\zeta(t), t).$$

The first set of characteristics ($\xi'(t) = \alpha(\xi)$) describes the transport of energy in the supply chain. These characteristics correspond with the characteristics that we found in the case without buffers. Therefore, again, the direction of the transport depends on the sign of $\alpha(x)$.

The characteristics for z are straight stationary lines. This is due to the fact that there is no transport along x in the buffers. Each point is just connected with its corresponding point in the supply chain. We had the same effect in the discrete model, where the solution for $Y_\nu(\omega)$ did not involve any filter functions from other buffers $Y_\gamma(\omega)$, $\gamma \neq \nu$.

Another approach to the system (11) is to differentiate the first equation with respect to t, which gives

$$v_{tt} = (\alpha v)_{xt} - \mu v_t + \rho z_t.$$

The sum of both equations in (11) is $z_t = (\alpha v)_x - v_t$. Together, we have

$$v_{tt} = (\alpha v)_{xt} - \mu v_t + \rho((\alpha v)_x - v_t),$$

a partial differential equation of second order for the energy level in the supply chain with buffers. This equations is hyperbolic for all x, because collecting terms yields

$$v_{tt} - \alpha v_{xt} = (\alpha'(x) - \mu - \rho)v_t + \rho(\alpha v)_x$$

and the discriminant $-\alpha^2/4$ is negative for all x. The equation describes the propagation of two waves along the two sets of characteristics. One of these waves corresponds with the transport in the supply chain and one with the exchange of energy between the chain and the respective buffers.

5 Conclusion

As expected, the investigation of supply chains as an important element in metabolic systems has shown that the dominance of strong pull components assures constant energy contents in the compartments near the final receiver in the chain, which is assumed to be the brain [1].

Furthermore, the retrograde propagation of disturbances is proven in supply chains with dominant pull components. Therefore, the system of differential equations with linearized constitutive functions was regarded as a discretization of a partial differential equation, namely, a transport equation. The qualitative behavior can be found in this continuous setting, too.

The continuous setting refers to metabolic supply chains, which are physiologically continuous and the compartments of which are a result of modeling. For instance, glycolysis, on the molecular level, consists of numerous intermediate products, the different states of which form a continuous transformation process from glucose to pyruvate or lactate.

Next, buffers enforce the damping property of the supply chain. In particular, all disturbances in the inflow are damped, which assures a more constant delivery with energy to the final consumer in the supply chain. The damping effect is enforced by high frequencies of the disturbance; buffer compartments act like lowpass filters. On the molecular level, buffers are found in side compartments like, e.g., glycogen. The liver and the fat compartment are buffers on the individual level. Independently from the quantitative specification of these transport processes on different levels, the properties of buffered supply chains are found in the qualitative behavior of glycolysis, the neuron–astrocyte lactate shuttle, and human metabolism.

Finally, the relation between the damping of the compartment contents and the damping of the fluxes is discussed. A strong damping in a compartment content requires an unchanged propagation of the respective flux. Hence, the constancy of the brain's energy content can only be assured by a strong brain pull, which leads to a flux from the periphery into the brain, which is perfectly adapted to the variable need of the brain, cf. the anticipated energy on demand in [3].

The retrograde propagation in a pull-dominated supply chain encourages the search for the cause of an effect in the transport direction. For instance, the different fat compartments are short-term and long-term buffers mainly filled by abundant blood glucose via insulin-dependent transport. The qualitative results for buffered supply chains motivate the search for the cause of a large fat compartment in the transport direction behind blood glucose, e.g., in the brain as discussed in [4]. This modified point of view might enrich the established glucostatic [29] and lipostatic theories [30], which are still taught in medicine.

Another interesting example in metabolic supply is foraging or hoarding behavior [31]. The external food storage resulting from foraging behavior can be interpreted as a buffer in the metabolic supply chain, too. Although the molecular mechanisms are complex [32], the systemic understanding of supply chains shows that the cause of hoarding behavior is in the transport direction, or vice versa, that hoarding behavior is a consequent effect of a disturbance in the food intake.

The principal behavior of the metabolic supply chain is reflected in the supply chains on lower levels, which serve the metabolic supply chain on the individual level and which support it by behaving in a redundant manner, cf. the evolutionary stability mentioned in Subsection 2.4.

The transition to a system of partial differential equations modeling the continuous buffered supply chain has shown that the properties of the unbuffered supply chain are mainly conserved, i.e., the characteristics of the transport equation in the unbuffered case are recognized. Furthermore, a subsequent set of characteristics is related to the added buffers.

We can regard the unbuffered supply chain as a component, which is augmented by the buffers as subsequent components. The added components expand and slightly modify the dynamical behavior of the supply-chain component to that of the composed system.

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