Deductive Functional Assignment of Elements in Appetite Regulation

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Abstract This paper presents a simple mathematical model for energy transport from the body into the brain and for appetite regulation. Particular properties in appetite regulation are deduced from the general observation of cyclic food intake. These particular properties are the importance of a push component, however small it may be, from the body into the brain, the dependence of the appetite activation on the energy supply level in the brain and a necessary condition for the sensitivity of this dependence. The dominant pull component in the energy transport is accompanied by a smaller push component managing this information transport. The properties listed above correspond to physiological observations. For instance, sensitivity is found in the postnatal development of projections between neuropeptide Y (NPY) neurons and pro-opiomelanocortin (POMC) neurons, which release, respectively, the appetite-amplifying and -reducing neuropeptides NPY and α -melanocyte-stimulating hormone at their nerve terminals. The development of these projections determines the change from the permanent feeding of the foetus into the cyclic ingestive behaviour in later life. The correspondence verifies the mathematically-deduced properties, justifies the simple model and supports the technique of the deductive functional assignment.

Keywords Dynamical system · Deductive approach · Appetite regulation · System identification · Metabolism · Energy allocation

1 Introduction

The systemic approach in the analysis of the human metabolism [1] explains obesity as a mistuning of the energy supply chain from the resources in the environment into the final

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adenosine tri-phosphate delivery into the brain [2]. A central aspect in the energy supply chain is appetite activation [3–5].

Here, we identify certain indispensable components of appetite regulation by deducing properties within a given model class from the external observation of cyclic food intake of healthy adult persons. This top-down analysis allows us to analyse fundamental properties of the models without knowing the processes in all detail as, e.g. in [6]. A physiological justification of deduced properties supports the model and the deductive approach itself.

From the 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 [7] and can be interpreted as an information transport mechanism. We remark 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 described in [8]. A further deductive result we obtain from this approach is the condition of a sensitive appetite activation of cyclic food intake.

This condition is mirrored in the appetite amplifying and diminishing neuropeptides neuropeptide Y (NPY) and α -melanocyte-stimulating hormone (MSH), respectively. Neurobiological research has recently revealed how the hypothalamic appetite-regulating neural network is organised [4]. The orexigenic neurons of the lateral hypothalamus (LH) are central in the control of appetite and food intake. Their activation generates appetite and promotes ingestive behaviour. These neurons have glucose sensors on their cell surface, which monitor glucose concentrations within the brain [9]. With glucose deprivation, the orexigenic neurons start firing.

The LH neurons also receive information about the energy stored in the body through a neuronal network located in the arcuate nucleus (ARC), Fig. 1. LH neurons are stimulated by NPY neurons and inhibited by pro-opiomelanocortin (POMC) neurons, which release the neuropeptide α -MSH. The hormones leptin and insulin, which indicate availability of energy in the body, inhibit NPY neurons, while they stimulate POMC neurons. There is

Fig. 1 Hypothalamic neurocircuits of appetite regulation. Orexigenic neurons of the lateral hypothalamus (LH) increase food intake when glucose concentrations fall. The arcuate nucleus (ARC) contains both NPY neurons, which are inhibited by insulin and leptin and which, when activated, stimulate food intake, and POMC neurons, which reduce food intake and are stimulated by insulin and leptin. Both neuronal subsets project to the adjacent lateral hypothalamus (LH), which contains neurons that stimulate food intake

experimental evidence that, in the fasting state, the LH neurons are activated by falling glucose concentrations; this activation is additionally enhanced by falling insulin and leptin concentrations [4]. In the fed state, LH neurons are suppressed by raising glucose concentrations; they are furthermore suppressed by the refilling of the body stores via the NPY/POMC network [4]. There is anatomical evidence for reciprocal inhibition between NPY and POMC neurons [10, 11], which would favour the predominant activation of NPY neurons in the fasting state and the predominance of POMC neurons in the fed state. A recent neuroanatomical study showed that, only 10 days after birth, NPY neurons and POMC neurons develop axonal connections to orexigenic neurons in the LH [12]. These observations show that the ARC network can be regarded as a leptin amplifier. The postnatal connection between ARC and LH 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.

The deductive approach determines the necessity of appetite generation depending on the brain energy level in contrast to the glucostatic theory [13], which cannot explain the old observation of nearly constant brain energy level during atrophic phases [14] nor new experimental results of the constant brain energy under cyclic intake and need [15], cf. Section 5. The deduction determines indispensable components within a model class. Its benefit is the selection of a small set of models within this large class. Hence, by nature, it does not disprove alternative theories outside the model class like the lipostatic theory [16], which is a nowadays scientific focus by the investigation of leptin. Nevertheless, the above observations are not clarified. Furthermore, we mention that the amount of ingested food is rather independent of physical restrictions like those shown in [17].

After the description of the model in Section 2, where the appetite regulation is included in a short supply chain, the system behaviour is investigated in Section 3 with elementary mathematical tools [18]. Necessary conditions are shown for a cyclic behaviour of the mathematical model. The physiological correspondents are discussed in Section 4. Section 5 deals with exogenic conditions like social and natural cycling for differently developed societies. In this context, the model's behaviour in atrophic phases is briefly discussed. The paper finishes with an outlook to extended models of the human metabolism including more aspects of ingestive behaviour and of the energy allocation from the body into the brain [1].

2 Supply Chain Model

2.1 Description of the Model

We investigate a model formed by three compartments: the body periphery, the brain, and appetite regulation in the LH. The theoretical energy supply state within the body periphery is denoted as X ; it might be measured, for example, in moles of glucose in the blood. The energy supply state in the brain is denoted by Y . The appetite activation in the LH is called Z . It is handled as a normalised value $Z \in [0, 1]$ (Fig. 2).

Additionally, we assume a constant energy need $S > 0$ of the brain and a constant energy availability $R > S$. The energy intake requires appetite activation, and thus, the 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 $K_2(Y - Y_0)$, which represents the pulling of the brain for energy on demand.

Fig. 2 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

Here, X_0 and Y_0 can be regarded as set-points for the energy levels. Realistic transport regulation is nonlinear, e.g. it contains a saturation, but it is not yet quantified. More general but still physiologically meaningful transport functions do not affect the qualitative behaviour of the model.

A crucial element in the model is the appetite activation $F(X, Y)$ describing the increase of the appetite. The appetite activation decreases with an increasing energy level in the brain as well as in the body. At the same time, the appetite diminishes proportionally. With energy level $X = X(T)$ and time T , we get the dynamical system

$$\begin{aligned}\dot{X} &= -K_1(X - X_0) + K_2(Y - Y_0) + RZ, \\ \dot{Y} &= K_1(X - X_0) - K_2(Y - Y_0) - S, \\ \dot{Z} &= P(F(X, Y) - Z),\end{aligned}\quad (1)$$

with $K_1 \geq 0$, $K_2 > 0$, $P > 0$, $F(X, Y) \in [0, 1]$ and the partial derivatives $F_{,X} \leq 0$, $F_{,Y} \leq 0$ with respect to X and Y .

2.2 Vanishing Push Component

Here, we ask whether the model allows cyclic food intake in the case of a vanishing push component of the transport from the body into the brain. Therefore, we investigate system (1) for $K_1 = 0$, which is

$$\begin{aligned}\dot{X} &= K_2(Y - Y_0) + RZ, \\ \dot{Y} &= -K_2(Y - Y_0) - S, \\ \dot{Z} &= P(F(X, Y) - Z).\end{aligned}\quad (2)$$

The energy flow from the body into the brain is not permanently vanishing, i.e. $K_2 > 0$. Now, we regard the existence and the stability of stationary points of (2).

Theorem 1 *If $F_{,X}(X, Y) < 0$ for all X, Y with $F(X, Y) = S/R$, then the system (2) has exactly one stationary point.*

Proof The stationary point $\underline{Q}^* = (X^*, Y^*, Z^*)^T$ is obtained by setting $\dot{X} = \dot{Y} = \dot{Z} = 0$, and we find $Y^* = Y_0 - S/K_2$ and $Z^* = S/R \in (0, 1)$. Now, the appetite activation F is monotonously decreasing in the neighbourhood of $F(X, Y) = Z^*$, and X^* is unique. $\square$

The proof shows that $F_X = 0$ would allow ambiguities concerning the total amount of X , which, however, do not occur in (2). We will resolve the ambiguities in the next theorem on the stability of Q^* .

Theorem 2 *If Q^* is unique in (2), then it is asymptotically stable.*

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

$$J = \begin{pmatrix} 0 & K_2 & R \\ 0 & -K_2 & 0 \\ PF_{,X} & PF_{,Y} & -P \end{pmatrix}, \quad \lambda_1 = -K_2, \quad \lambda_{2,3} = -\frac{P}{2} \pm \sqrt{PRF_{,X} + \frac{P^2}{4}}.$$

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 is negative in a neighbourhood of Q^* , and Q^* is stable, too. $\square$

If the stationary point is not unique, then $F_X = 0$ holds in a certain domain, and the energy level X is arbitrary. The reduced system of Y and Z yields a single stationary and asymptotically stable point. Hence, we have shown that a cyclic behaviour of the system (1) implies a push component from the body into the brain, i.e. $K_1 > 0$.

2.3 Dimensionless Formulation

With that condition, we apply a transformation of coordinates by

$$x = \frac{K_1}{S}(X - X_0), \quad y = \frac{K_1}{S}(Y - Y_0), \quad z = \frac{R}{S}Z \quad \text{and} \quad t = K_1 T, \quad (3)$$

and with the renamed $\dot{x} = dx/dt$ etc., we find

$$\begin{aligned} \dot{x} &= -x + ky + z, \\ \dot{y} &= x - ky - 1, \\ \dot{z} &= p(f(x, y) - z). \end{aligned} \quad (4)$$

with

$$k = \frac{K_2}{K_1} > 0, \quad p = \frac{P}{K_1} > 0 \quad \text{and} \quad f(x, y) = \frac{R}{S}F(X, Y).$$

We call (4) the dimensionless formulation. Now, it holds that $f(x, y) \in [0, f_{\max}]$ with $f_{\max} = R/S > 1$.

3 System Properties

3.1 Stationary Points

Theorem 3 *The system (4) 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

$$x - ky = 1 \quad \text{and} \quad f(x, y) = 1. \quad (5)$$

The first equation in (5) is a monotonously increasing linear function $y_k = y_k(x)$, and the second equation describes a level line $y_f = y_f(x)$ of f . By $f_x \leq 0$ and $f_y \leq 0$, $y_f(x)$ is monotonously decreasing in x . Thus, there is exactly one intersection point. $\square$

3.2 Stability

Theorem 4 *The stationary point q^* is asymptotically stable if*

$$(1 + k + p)(1 + k) - (1 + p)f_x(x^*, y^*) + f_y(x^*, y^*) > 0. \quad (6)$$

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 $A = 1 + k + p$, $B = p(1 + k + f_x)$ and $C = -p(kf_x + f_y)$. 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 we now ask for eigenvalues with positive real parts, we are looking for two roots with vanishing real parts. After a comparison of coefficients to the specialised Hurwitz criterion, this ansatz yields $AB - C > 0$ for roots with negative real parts, which is just the condition (6). $\square$

If the condition (6) is fulfilled, the ubiquitous attraction domain of the unique stationary point prevents the system from having cycling behaviour. On the other hand, the only negative term of the left-hand side is $f_y \leq 0$. Thus, $f_y < 0$ is a further prerequisite for cyclic food intake. Furthermore, the modulus $|f_y|$ needs to be large, i.e., the appetite activation has to be sufficiently sensitive. In other words, a rather soft regulation of the appetite by the orexigenic neuron, cf. Fig. 1, may not produce cyclic food intake, but the exaggerations by NPY and POMC do so. They cause an appetite regulation in the manner of an on/off switch.

3.3 Boundedness

A relevant appetite model on a daily time scale cannot have an infinitely increasing trajectory. Indeed, the solution of (4) is bounded.

The idea of the proof starts with the investigation of the last equation of system (4). The appetite z tends to the interval $[0, f_{\max}]$, and by the consequent change of x and y , it enters $[0, f_{\max}]$ and stays inside. A spectral transformation of the resting system in x and y shows a related property.

3.4 Numerical Example

In the numerical example calculation, we use the appetite activation

$$f = f_{\varepsilon}(y) = \begin{cases} 0 & \text{if } y \geq \varepsilon, \\ (1 - \varepsilon^{-1}y)^2 & \text{if } y \in [0, \varepsilon], \\ 5 - (2 + \frac{1}{2}\varepsilon^{-1}y)^2 & \text{if } y \in [-4\varepsilon, 0], \\ 5 & \text{if } y \leq -4\varepsilon. \end{cases} \quad (7)$$

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 $k = 3$ and $p = 2$, the condition (6) reads $\varepsilon > 1/12$ for an asymptotically stable stationary solution and $\varepsilon < 1/12$ for an unstable one. Hence, a steeper, i.e. more sensitive, appetite activation leads to cyclic ingestive behaviour. Figure 3, left, shows an example. The transport $x - ky$ is always directed towards the brain.

4 Physiological Representation

The general observation of a cyclic ingestive behaviour implies (1) an energy push component from the body into the brain, (2) an appetite activation depending on the brain energy level and (3) a very sensitive appetite activation close to an on/off switch. These indispensable properties indicate the necessary elements of appetite regulation.

Property 1 is shown in Section 2.2 and it is found physiologically in [7], although a strong pull component is dominant [8]. We can interpret the push component as an indicator of the body energy level for the brain, i.e. an information transport. Properties 2 and 3 are shown in Theorem 4, where the derivative of the appetite activation f_y with respect to the brain energy level is the only term contributing to a violated condition (6). Furthermore, a strong pull component requires a large $|f_y|$ close to an on/off switch 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 postnatal connection of NPY and POMC neurons, producing the appetite-amplifying and -suppressing neuropeptides NPY and α -MSH which display the ability to reciprocally inhibit each other [10, 11]; see Fig. 3,

Fig. 3 Left: Cyclic ingestive behaviour with f of (7), $k = 3$, $p = 2$, $\varepsilon = 0.001$. Right: Effect of the neuropeptides NPY and α -MSH on the appetite activation: The prenatal regulation (dashed) is mild. The connection of NPY and POMC neurons results in a sharper contrast, i.e. in a steeper activation function f (solid)

right. As an implication of the above considerations, NPY and POMC neurons regulate the periodicity of food intake rather than the amount of ingested food.

Let us remark that, the stronger the pull component, the less variation occurs 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 [1, 2].

Moreover, the influence of cues on the metabolic behaviour is a topic of medical discussion [1, 2]. The present model is too sparse to model the growth of the fat compartment or implications for the psyche, but we see that a cue-induced modification of the intake is damped down very quickly by the present dynamical system because the limit orbit of the cyclic food intake is stable; any disturbance like cue-induced additional intake is attenuated. A lasting change of energy levels enters the model only in the case of a permanent change of the appetite activation f or of the model parameters. Such changes are the object of metabolic learning in the cerebral hemispheres [17, 19].

5 Social and Natural Cycling in Food Availability

Until now, an abundant and permanent food availability has been a precondition of the investigated model class. Here, we discuss the influence of a cycling in food availability. First, we investigate social cycling, which summarises the socio-cultural context of food intake. Endogenic learned mechanisms interact with the adaption to exogenic rhythms. The needs and the social cycling of the food availability are not independent from each other. Rather, they form a feedback loop. Here, we model social cycling by an abundant but pulsed food availability. Second, we investigate a natural random cycling depending on the success of a hunter-gatherer society. Besides hunting and gathering success, the ability to store food is essential for the amount of available food.

The dynamical system in (4) oscillates with its stable eigenfrequency shown in Fig. 3. Any exogenously applied frequency governs the system behaviour, and we observe the exogenic frequency. Hence, the simulation shown in Fig. 3 does not explain a certain number of meals a day.

We modify (4) by a time-dependent food availability $a(t)$, and food intake is possible if the appetite z and the availability $a(t)$ are both positive. We get the system

$$\begin{aligned}\dot{x} &= -x + ky + a(t)z, \\ \dot{y} &= x - ky - 1, \\ \dot{z} &= p(f(x, y) - z).\end{aligned}\tag{8}$$

The time-dependent food availability $a(t)$ allows us to describe, for example, cues inducing an increased food intake induced by more psychological reasons. Within the given model class, cues lead to an increase of x and a smaller increase of the brain energy y , but their influence is damped out within a small number of oscillations of the system.

If now $a(t)$ is a periodic food availability, the system (8) oscillates with the exogenous frequency. A first example is $a(t) = a_{\max}$ whenever $t \bmod T \in [0, \Delta t]$ and, else, vanishing with the period T and a time window Δt of the available food $a_{\max}$. If the availability of food exceeds the need 1 of the brain, i.e. if $a_{\max} f_{\max} \Delta t > T$, then all parameter choices lead to a periodic system behaviour of (8). We observe that larger $a_{\max}$, corresponding to highly energetic food, may lead to longer cycles which are multiples of T . Then, the intake in the

Fig. 4 Social cycling. *Left:* Nearly similar food availability three times in the period $T = 20$, first intake in each period is the largest one. *Right:* Weighted food availability, similar availability for first and second meals. Nevertheless, the first intake is very small, cf. (8). For the legend, see Fig. 3; note the exaggerated oscillations of brain energy. Time T is shown on the horizontal axes

time windows in a cycle may be different. The more T differs from the eigen-period of the system, the stronger the oscillations are.

As known from technical mechanics, more complicated periodic excitations in $a(t)$ generate a system which contains all occurring frequencies. We present, in Fig. 4, two examples in which food availability oscillates three times, in equidistant time windows $\Delta t = 1$, within each time period $T = 20$. The oscillations of the brain energy level are shown in an unrealistic exaggeration; a larger k fixes it to a constant level. In the first example, the left panel of Fig. 4, the food availability is given by $(1.8, 2.2, 2)$ in the three time windows. Then, the maximal food intake $f_{\max}(1.8 + 2.2 + 2) = 30$ slightly exceeds the need S . We observe that even a smaller availability in the first time window leads to a larger intake than in the third one, cf. Fig. 4, left. In the second example (Fig. 4, right panel), the food availability is assumed to be $(1.6, 1.6, 2.5)$ in the three time windows. Although the food availability in the first two time windows is equal, the intake in the first window is rather small. This situation can be interpreted as the mediterranean breakfast.

These simulations are merely examples. Obviously, they lack the rhythm of sleep and alertness and the work/rest cycle. In addition, the interaction of the internal cycling of

Fig. 5 *Left:* Primitive hunter-gatherer society which is not able to significantly store food, modeled by a spoiling rate $q = 0.03$ in (9). *Right:* Advanced society with the ability of storing food. *Upper plots:* available food. *Lower plots:* For the legend, see Fig. 3; note the exaggerated oscillations of brain energy

Fig. 6 Model including details of the body periphery. The brain competes with the body periphery for energy. The inner loop marks the energy allocation of the brain

human need and the social cycling of food availability is a field of research far exceeding the scope and the volume of this article.

The second idea of modeling a hunter-gatherer society requires the description of the random availability of food. This random success is described by a randomly pulsed function $u(t)$, which increases the amount a of available food. For instance, $u(t)$ can be assumed as the derivative of a stochastic Poisson process. Furthermore, we model the development of such a society by its ability to store food, i.e., a small spoiling parameter q means an advanced society. Alternatively to (8), the actual intake is assumed to be the minimum of the appetite or hunger and the available food. We get the system

$$\begin{aligned}
 \dot{a} &= -\min\{a, z\} + u(t) - qa \\
 \dot{x} &= -x + ky + \min\{a, z\}, \\
 \dot{y} &= x - ky - 1, \\
 \dot{z} &= p(f(x, y) - z),
 \end{aligned} \tag{9}$$

where the minimum function should be smoothed for numerical reasons. It is an alternative to the product term $a(t)z$ in (8). Again, in longer periods, the available food should exceed the need to prevent the modeled society from dying out.

Simulation results are presented in Fig. 5 with identical $u(t)$. The primitive society (left) with $q > 0$ suffers from lack of food in less successful times, and the energy level in the body decreases correspondingly. This is supported by the observations in [14]. Again, the brain energy levels are exaggerated in the plots in Fig. 5. An increased parameter k leads to a constant brain energy [15].

The advanced society experiences shorter periods of hunger, but the eigenfrequency of the system (4) is obtained again after the first successive larger intake. A very important mechanism, which does not enter (9), is the increased explorative behaviour in the absence of food. Within that frame, the primitive and the advanced societies would not experience identical success functions $u(t)$. Simulations including behavioural aspects are planned in a forthcoming paper.

6 Conclusion and Outlook

This paper has given a core model of the appetite activation and the cyclic ingestive behaviour on a short time scale. We have followed a deductive approach by starting from the single observation of a cyclic ingestive behaviour and identifying necessary conditions of the regulatory mechanism. The rather simple core model is supported by the physiological mirror of these indispensable elements.

We regard this approach as useful for mathematical modelling in medicine because an inductive model including all known substances and regulatory mechanisms of a certain physiological application like appetite regulation [3–5] would be huge, redundant and full of parameters to be determined by experiments. The deductive approach, however, yields a core model and a small amount of critical parameters.

The result of the deductive approach consists in the selection of models within a model class. This selection has been supported by the discussion of the underlying physiological mechanisms and by the ability of the selected models to explain the experimental observations [14, 15]. Furthermore, the model has been adapted to different exogenic conditions like social and natural cycling.

The core models grow with an increasing number of observations to model. Figure 6 shows a schematic model including details of the body periphery. The upper part shows the energy supply chain from the exterior via the stomach/liver store compartment and the blood to the brain. Furthermore, Fig. 6 contains the allocation loop, which is hierarchically closer to the brain than the appetite loop and which is mediated by the ventromedial hypothalamus. The structure of the allocation loop is similar to that of the appetite loop. Its action on the side-compartment fat directs the blood glucose into the brain. Due to the hierarchical structure recognizable in Fig. 6, the conclusions of the paper still hold if the model is extended by the allocation loop and by the energy consumed in the body.

Further extensions are the consideration of the stress axis, the leptin response of the periphery to the brain, metabolic learning, the rhythm of sleep and alertness, etc. [1]. The deductive approach allows complexity reduction and a systemic understanding by the analysis of hierarchically ordered metabolism models.

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