Modeling the Hypothalamus-Pituitary-Adrenal system: homeostasis by interacting positive and negative feedback

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Abstract

The hypothalamus-pituitary-adrenal (HPA) system is closely related to stress and the restoration of homeostasis. This system is stimulated in the second half of the night, decreases its activity in the daytime, and reaches the homeostatic level during the late evening. In this paper we derive and discuss a novel model for the HPA system. It is based on three simple rules which constitute a principle of homeostasis and include only substantial physiological elements. In contrast to other models, its main components include, apart from the conventional negative feedback ingredient, a positive feedback loop. To validate the model, we present a parameter estimation procedure which enables one to adapt the model to clinical observations. Using this methodology, we are able to show, that the novel model is capable of simulating clinical trials. Furthermore the stationary of the system is investigated. We show that, under mild conditions, the systems has always a well-defined set-point which reflects the clinical situation to be modeled. Finally, the computed parameter may be interpreted from a physiological point of view and thereby gaining connoting insights in diseases like depression, obesity, or diabetes.

Key words: physiological modeling; parameter estimation; physiological system; stress system; hypothalamus-pituitary-adrenal system; homeostasis

Physiology

The hypothalamus-pituitary-adrenal (HPA) system is a neuroendocrine system which is closely linked to stress in humans. This system is responsible for a rapid response to stressful stimuli and for the return to homeostasis through complex feedback mechanisms. Cortical brain regions, e.g. hippocampus and amygdala, are connected by glutamatergic pathways to the hypothalamus (1). An activation of the hypothalamic neurons of the paraventricular nucleus by glutamate causes a release of corticotropin releasing hormone (CRH). By this, CRH is secreted into the hypophyseal portal circulation to reach the anterior pituitary, where it subsequently stimulates the release of adrenocorticotropic hormone (ACTH) into the circulation. ACTH stimulates the release of cortisol in the adrenals (see Figure 1). Serum cortisol concentration has to be sufficiently regulated within a physiological range. A hypercortisolism causes depression, diabetes, visceral obesity, or osteoporosis. Therefore, inhibition of cortisol secretion is an essential component of the regulation within this system. The inhibition is partly achieved by cortisol bindings to glucocorticoid receptors in the amygdala, hippocampus, hypothalamus, pituitary, and adrenals. However, it is also important to maintain cortisol concentrations above a critical threshold since cortisol may result in a disturbed memory formation or a life-threatening adrenal crisis (2, 3).

Two types of corticoid receptors have been described based on biochemical and functional characteristics (4). The mineralocorticoid receptor (MR) has a specificity in binding selectively cortisol. In the brain, MR is most

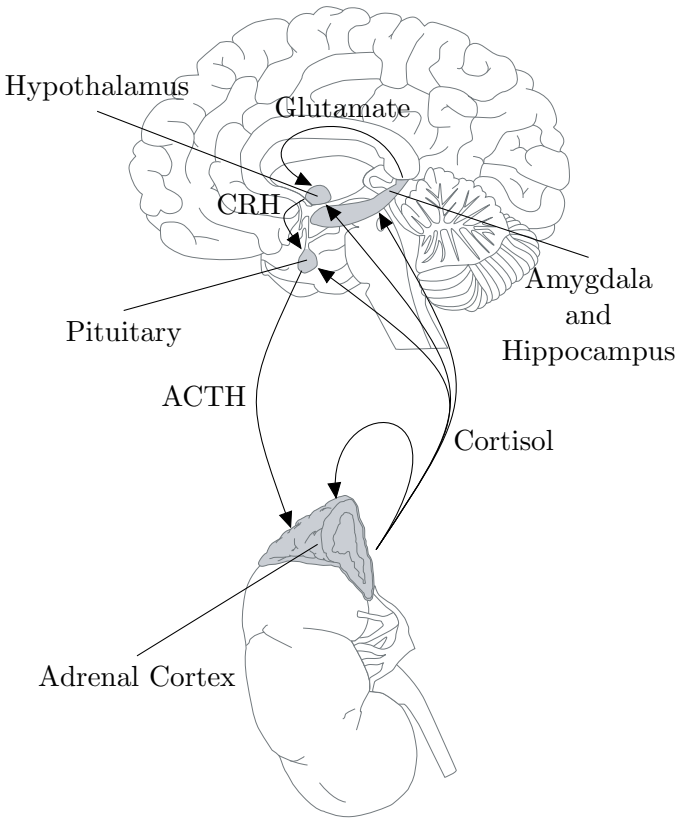

Figure 1: The HPA system: Glutamate (hippocampus and amygdala) stimulates the release of CRH (hypothalamus), which stimulates the ACTH secretion (pituitary), and ACTH in turn stimulates cortisol secretion (adrenal cortex). Cortisol provides a feedback signal at all hierarchical levels via mineralocorticoid (MR) or glucocorticoid receptors (GR).

densely localized in hippocampal and septal neurons. While MR has a high-affinity to cortisol, its efficacy in the periphery and lower brain regions is limited by 11 β hydroxysteroid deshydrogenase 2, which converts intracellularly active cortisol into inactive cortisone. Conversely, the glucocorticoid receptor (GR) is widely distributed and represents the predominant binding site for cortisol in hypothalamus, pituitary, adrenals as well as in organs and tissues in the periphery. However, GR binds cortisol with a lower affinity as compared to MR. These receptor characteristics complement each other and put the MR and GR in a position to modulate HPA responses. MR appears to be sensitive to low and saturates at high cortisol concentrations. On the other hand, GR generates its dynamics at high, while it appears to be non-effective at low cortisol concentrations. It is known from the literature that cortisol binding to GR leads to an inhibitory effect on cortisol secretion (5). However, it is unclear, how cortisol bound MR affects the HPA system.

The HPA system is a dynamical closed loop system, homeostatically regulated, and subject to a daily rhythm. In the second half of the night the HPA system is stimulated during REM sleep phases (6). A maximum of cortisol and ACTH concentrations is attained in the early morning hours. The hormones underlie a constant decay in the daytime. However, cortisol and ACTH concentrations are rising after meals or in a physical or psychological stress situation. During the first half of the night ACTH and cortisol concentrations are reaching a homeostatic level (for illustration see Figure 2).

It remains the question, in which way the HPA system regulated and reaches its homeostatic level. The answer to this fundamental question is

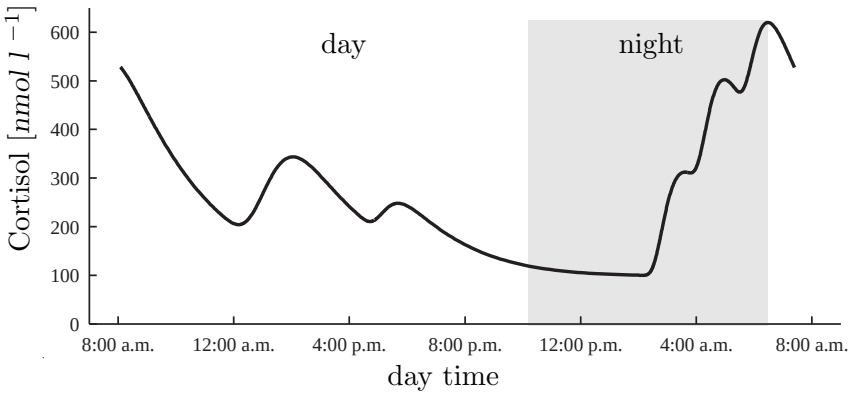

Figure 2: Daily cortisol rhythm: Typical daily plasma cortisol profile in humans.

of foremost interest to the treatment of various diseases. This includes, for example, the defined hypo- or hypercortisolism, such as Addison's and Cushing disease. Also its the close connection to the energy and weight regulation (e.g. obesity, diabetes mellitus and metabolic syndrome) and to psychological illnesses such as depression is a profound motive to investigate the mechanisms of the HPA system regulation (7). From an evolutionary point of view, it is widely accepted that a simple and durable mechanism had to provide a basis for a homeostatic regulated system. This led us to the following principle of homeostasis for the HPA system. Its interactions eventually result in a homeostatic state of cortisol (8).

Principle of homeostasis

Rule 1 *Cortisol binds at low concentrations to the MR and only at high concentrations to the GR.*

Rule 2 *Activated MR and GR operate in an opposing manner.*

Rule 3 *Cortisol raises its own serum concentration via activated MR, while it reduces it via activated GR.*

Note that Rule 3 constitutes a positive feedback of MR on cortisol. In this way, we introduce a novel aspect in the concept of homeostasis.

The remaining part of this paper is organized as follows. Based on the three rules we develop a "homeostatic" mathematical model and prove in a strict sense that this system reaches a stable state over time, that is, in the present context, the system reaches a homeostatic state or set-point. Next we establish a parameter estimation procedure which we bring forward to adapt the new model to clinical data. Finally, we discuss its clinical relevance and conclude.

Model

While quite a number of mathematical models of the glucose metabolism were developed and published (9–11), only a small number of models of the HPA system can be found with rather different aims. The focus of these HPA models varies from the influence of the inner clock to the self-dynamic in this system (12, 13). Despite several dissimilarities certain characteristics of the models are modeled along the same lines. The stimulation of CRH via

ACTH on cortisol is constructed identically in previous HPA models. Additionally, the degradation rates of CRH, ACTH, and cortisol are assumed to be linear. Interestingly, almost all previous HPA models use only pure negative feedback elements (14–16). The absence of positive feedback elements in these models turns out to be a shortcoming since there exist data indicating a positive stimulus in the HPA system (17). We will now present a new model, which includes positive as well as negative feedback elements and which is based on the three rules of homeostasis. Following the first rule of homeostasis (see box), cortisol (Z) binds to the high affine MR (R_1) and to the low affine GR (R_2). Cortisol and MR form a ligand-receptor complex C_1 and cortisol and GR a complex C_2, respectively. Denoting the rates of reaction by k_1, k_{-1}, k_2 and k_{-2} the reaction equation can be written as

$$\mathrm{Z} + \mathrm{R}_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}_1,$$
$$\mathrm{Z} + \mathrm{R}_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{C}_2.$$

Under common assumption of biochemical reaction kinetics and the law of mass action of competitive bindings (see (18)), we arrive at the following dose response relations

$$c_1 = \frac{e_1 z}{z + K_1} \quad \text{and} \quad c_2 = \frac{e_2 z}{z + K_2}.$$

Here, z denotes the concentration of Z in the chemical equilibrium. The coefficients e_1 and e_2 represent the integrated maximal efficacies of all MRs and GRs localized in different brain regions (e.g. hippocampus, amygdala,

hypothalamus, and pituitary) while

$$K_1 := \frac{k_{-1}}{k_1} \quad \text{and} \quad K_2 := \frac{k_{-2}}{k_2},$$

reflecting the binding affinity of MR and GR respectively (compare Figure 3). While the affinity of MR is higher than the affinity of GR, the inequality $K_1 < K_2$ holds. Following the second rule of homeostasis (see box), we add the stimulation via the cortisol-MR complex and the inhibition of the cortisol-GR complex

$$h(z) = \frac{e_1 z}{z + K_1} - \frac{e_2 z}{z + K_2} = c_1(z) - c_2(z). \tag{1}$$

We consider h as a feedback of cortisol in the HPA system (see Figure 3). We pool the integrated influences of glutamate, CRH and ACTH from different brain regions in one molecular cue of the brain/pituitary compartment named Y (with a physiological interpretation as plasma ACTH) and suppose that the concentration y gives a positive stimulus on Z. By denoting the compartment transition of the adrenal cortex to the brain/pituitary compartment by a constant $b_2 \in \mathbb{R}^+$, we obtain the time dependent differential equation

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -b_1 y(t) + \frac{e_1 z(t)}{z(t) + b_2 K_1} - \frac{e_2 z(t)}{z(t) + b_2 K_2} + p(t), \tag{2}$$

where we assume Y to have a linear degradation rate $b_1 \in \mathbb{R}^+$. The function $p : \mathbb{R} \to \mathbb{R}_0^+$ models an external input, e.g. infusion of ACTH. With a linear degradation rate $b_3 \in \mathbb{R}^+$ of Z and a linear stimulation rate $b_4 \in \mathbb{R}^+$ of Y

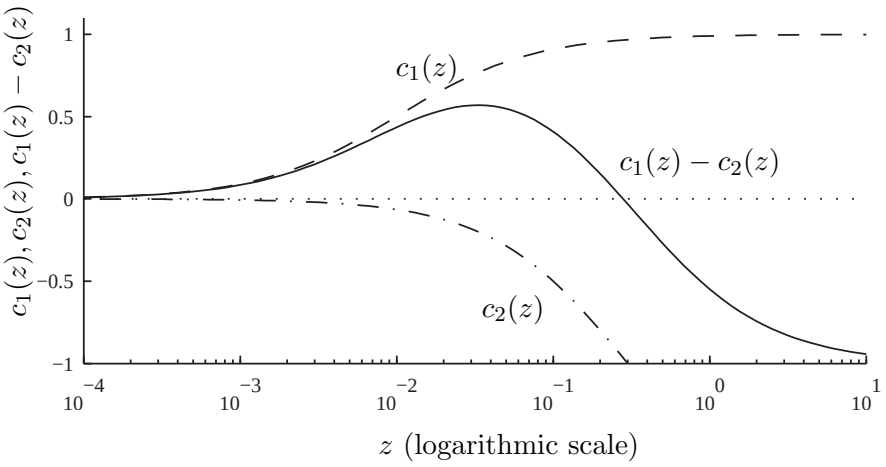

Figure 3: Feedback of the HPA system: Illustration of a competitive antagonism of cortisol and its receptors with $e_1 = 1$, $e_2 = 2$, $K_1 = 0.01$ and $K_2 = 0.3$ for $z \in [10^{-4}, 10]$. The efficacy (activation) of the cortisol-MR complex c_1 (dashed line) and (inhibition) the cortisol-GR complex (dot-dashed line), the feedback $h(z) = c_1(z) - c_2(z)$ arises from an subtraction of the two complexes (solid line).

on Z we arrive at the closed system of two ordinary differential equations (ODE)

$$\begin{aligned} \frac{\mathrm{d}y}{\mathrm{d}t} &= -b_1 y(t) + \frac{e_1 z(t)}{z(t) + b_2 K_1} - \frac{e_2 z(t)}{z(t) + b_2 K_2} + p(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= -b_3 z(t) + b_4 y(t), \end{aligned} \tag{3}$$

with some user prescribed initial conditions $y_0, z_0 \in \mathbb{R}^+$. Figure 4 displays the differential equation (3) schematically in a two compartment model (brain/pituitary and adrenals). By construction, the mathematical model satisfies the three physiological rules of homeostasis (see box). In addition, each parameter in our model has a clear physiological interpretation. The physiological term of homeostasis can mathematically be interpreted as a

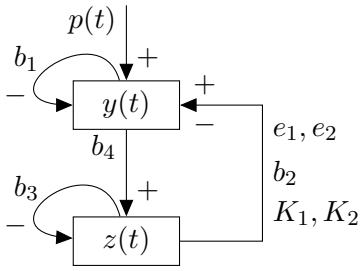

Figure 4: Schematic interpretation of the system of differential equations (3): The alteration of z over time depends on a degradation rate b_3 and a stimulation rate b_4 of y. The alteration of y over time depends on a degradation rate b_1, an external input function p, and a feedback signal h of z (compare equation (1)).

equilibrium point which is asymptotically stable. A point x^∞ is called an equilibrium point for the differential equation $\frac{\mathrm{d}x}{\mathrm{d}t} = f(x(t))$ if $f(x^\infty) = 0$ for all $t \in [t_0, \infty)$. Moreover, x^∞ is called Lyapunov stable if for every neighborhood $U(x^\infty)$ there is a neighborhood $V \subseteq U(x^\infty)$ such that every solution x starting in $x(t_0) \in V$ remains in U for all $t \geq t_0$, otherwise it is called unstable. An equilibrium x^∞ is asymptotically stable if it is Lyapunov stable and, in addition, V can be chosen such that $\|x(t) - x^\infty\| \to 0$ as $t \to \infty$ for all $x(t_0) \in V$ (see (19)). From a physiological as well as mathematical point of view it is interesting to investigate the stability of the derived differential equation (3). The following theorem gives an answer in this direction.

Theorem 1. *If the differential equation (3), with $p \equiv 0$, satisfies the inequality*

$$-\frac{b_1 b_3}{b_4} + \frac{e_1}{b_2 K_1} - \frac{e_2}{b_2 K_2} > 0, \tag{4}$$

then there exists an unique point (y^∞, z^∞), with $y^\infty, z^\infty > 0$, which is

asymptotically stable. Moreover, the point $(0,0)$ *is unstable.*

In other words, provided the inequality (4) is satisfied, the solution of the differential equations settles over time to set-point. How can the inequality (4) be interpreted? In this inequality the addend $\frac{e_1}{b_2 K_1}$ is positive and the two other addends are negative. In comparison, the positive feedback element has to "dominate" the negative feedback element $\frac{e_2}{b_2 K_2}$ and the relation of degradation to forward stimulation $\frac{b_1 b_3}{b_4}$. From a physiological point of view the inequality holds if and only if a positive stimulus on ACTH and cortisol for arbitrarily small concentrations of cortisol is provided.

Proof. The equilibrium points of the differential equation (3) (with $p \equiv 0$) are precisely the zeros of the function

$$g(z) := z \cdot \left(-\frac{b_1 b_3}{b_4} + \frac{e_1}{z + b_2 K_1} - \frac{e_2}{z + b_2 K_2} \right)$$

and the equation $y = \frac{b_3}{b_4} z$. Thus, we either have one equilibrium point $\left(y^{(1)}, z^{(1)}\right) = (0,0)$ or three equilibrium points given by

$$\begin{aligned}
\left(y^{(1)}, z^{(1)}\right) &= (0,0)\,, \\
\left(y^{(2)}, z^{(2)}\right) &= \frac{c_2 + \sqrt{c_2^2 + 4 c_1 c_3}}{2 c_1} \left(\frac{b_3}{b_4}, 1\right), \\
\left(y^{(3)}, z^{(3)}\right) &= \frac{c_2 - \sqrt{c_2^2 + 4 c_1 c_3}}{2 c_1} \left(\frac{b_3}{b_4}, 1\right),
\end{aligned}$$

with the setting

$$\begin{aligned} c_1 &:= \frac{b_1 b_3}{b_4}, \\ c_2 &:= -c_1 b_2 \left(K_1 + K_2\right) + e_1 - e_2, \\ c_3 &:= -c_1 b_2^2 K_1 K_2 + b_2 \left(e_1 K_2 - e_2 K_1\right). \end{aligned}$$

Now, inequality (4) states that g has a positive gradient at zero

$$\frac{\mathrm{d}g}{\mathrm{d}z}(0) = -\frac{b_1 b_3}{b_4} + \frac{e_1}{b_2 K_1} - \frac{e_2}{b_2 K_2} > 0$$

and since $g(0) = 0$, there exists an $\varepsilon > 0$ so that $g(z) > 0$ for all $z \in (0, \varepsilon]$. Since the leading coefficient of g is negative, we deduce that $\lim_{z\to\infty} g(z) = -\infty$. Considering the curvature behavior of g, the differential equation (3) (with $p \equiv 0$) has a unique equilibrium point $\left(y^{(2)}, z^{(2)}\right)$ with $y^{(2)}, z^{(2)} > 0$ and

$$\frac{\mathrm{d}g}{\mathrm{d}z}\left(z^{(2)}\right) = -\frac{b_1 b_3}{b_4} + \frac{e_1 b_2 K_1}{\left(z^{(2)} + b_2 K_1\right)^2} - \frac{e_2 b_2 K_2}{\left(z^{(2)} + b_2 K_2\right)^2} < 0.$$

Hence (3) (with $p \equiv 0$) has precisely one positive equilibrium point $\left(y^{(2)}, z^{(2)}\right)$. Next we verify that $\left(y^{(2)}, z^{(2)}\right)$ is an asymptotic stable point (y^∞, z^∞) of the differential equation (3) (with $p \equiv 0$). Here, it is sufficient to show that the real parts of the eigenvalues of the Jacobian of the right hand side of equation (3) with $p \equiv 0$ are genuinely negative in $\left(y^{(2)}, z^{(2)}\right)$

(see (19)). The eigenvalues (dependent only on z) of the Jacobian

$$J(z) = \begin{pmatrix} -b_1 & \bar{g}(z) \\ b_4 & -b_3 \end{pmatrix} \quad \text{with} \quad \bar{g}(z) := \frac{e_1 b_2 K_1}{(z + b_2 K_1)^2} - \frac{e_2 b_2 K_2}{(z + b_2 K_2)^2}$$

are given by

$$\lambda_{1,2}(z) = -\frac{b_1 + b_3}{2} \pm \frac{\sqrt{(b_1 - b_3)^2 + 4 b_4 \bar{g}(z)}}{2}.$$

For any $z \in \mathbb{R}$ the real part of λ_2 is genuinely negative $\mathfrak{Re}(\lambda_2(z)) < 0$. Thus, it is sufficient to show that $\mathfrak{Re}(\lambda_1(z)) < 0$ for $z = z^{(2)}$. From

$$-\frac{b_1 b_3}{b_4} + \bar{g}\left(z^{(2)}\right) = \frac{\mathrm{d}g}{\mathrm{d}z}\left(z^{(2)}\right) < 0$$

it is easy to deduce that

$$(b_1 - b_3)^2 + 4 b_4 \bar{g}\left(z^{(2)}\right) < (b_1 + b_3)^2$$

is valid. Consequently , $\mathfrak{Re}(\lambda_2(z)) < 0$ and (y^∞, z^∞) is an asymptotically stable point of the differential equation (3) (with $p \equiv 0$). The point $(0, 0)$ is unstable since (4) together with $\bar{g}(0) = \frac{e_1}{b_2 K_1} - \frac{e_2}{b_2 K_2}$ implies $\mathfrak{Re}\left(\lambda_1(0)\right) > 0$. □

Theorem 1 guarantees – under certain conditions that are consistent with the principle of homeostasis – the uniqueness of the asymptotic stable point (y^∞, z^∞). Apart from this important statement, we are able to calculate the asymptotic stable point of the system of differential equations (3) ana-

lytically. Furthermore, it should be mentioned that Theorem 1 holds even in the presence of a smooth external input function p with sufficient decay, e.g., p from equation (6).

Parameter estimation

It should come with no surprise that the solutions $y(t)$ and $z(t)$ greatly vary with respect to the parameters $b_1, b_2, b_3, b_4, e_1, e_2, K_1, K_2$ and with respect to the external input $p(t)$. It is the goal of this section to show that these parameters may be chosen such that the resulting mathematical model closely approximates data stemming from clinical trails. While the constants b_1, b_2, K_1, K_2 in the system of differential equations (3) are known from the literature (8, 20), the parameters b_3, b_4, e_1, e_2 are unknown. The unknown external input $p(t)$ will be treated separately. We combine the unknown parameters e_1, e_2, b_3 and b_4 with some arbitrary initial conditions of the differential equation y_0 and z_0 into a parameter vector $\theta := (e_1, e_2, b_3, b_4, y_0, z_0)$. The variation of y and z is therefore dependent on θ which is $y(\,\cdot\,;\theta)$ and $z(\,\cdot\,;\theta)$. Our goal is to solve the inverse problem: Find a vector $\theta_{\min}$ so that resulting concentrations $y(\,\cdot\,;\theta_{\min})$ and $z(\,\cdot\,;\theta_{\min})$ possess a best fit with respect to given concentrations of ACTH and cortisol given by clinical trials, among all possible vectors θ. Let $\tilde{y}_i$ and $\tilde{z}_j$, with $\tilde{y}_i, \tilde{z}_j \neq 0$, be clinical data of the blood plasma concentration of ACTH and blood serum concentration of cortisol at the times t_i and τ_j with $i = 1, \ldots, k$ and $j = 1, \ldots, \ell$, respectively. We assume that the data values $\tilde{y}_i$ and $\tilde{z}_j$ are associated with measurement errors, which are independent and normally distributed. To

define a proper distance measure $\chi^2 : \mathbb{R}^6 \to \mathbb{R}^+$, we make use of the standard maximum-likelihood-approach (see (21)), that is

$$\chi^2(\theta) := \sum_{i=1}^{k} \left(\frac{y(t_i;\theta) - \tilde{y}_i}{\sigma_i^y} \right)^2 + \sum_{j=1}^{\ell} \left(\frac{z(\tau_j;\theta) - \tilde{z}_j}{\sigma_j^z} \right)^2 . \tag{5}$$

Here, σ_i^y and σ_i^z denote the standard deviations which are assumed to be given (see Figure 7 below).

At each iteration step the differential equation (3) has to be solved in order to evaluate the corresponding distance measure χ^2. The wanted approximations of y and z are computed by means of a numerical ODE solver with respect to approximate initial conditions $y(0,\theta) = y_0$, $z(0,\theta) = z_0$. Due to the nature of the underlying equations, we make use of the MATLAB function `ode23s`, which is based on a modified Rosenbrock formula of order 2 (22). The aim is now to minimize χ^2 with respect to θ

$$\chi^2(\theta_{\min}) = \min_{\theta \in \mathbb{R}^6} \chi^2(\theta).$$

To solve this unconstrained, nonlinear optimization problem, we employ a direct search method (a modified Nelder-Mead algorithm). The selected stop criterion ensures that $\theta_{\min}$ is a local minimum of χ^2. In order to find the global minimum and avoid local minima, we started the process with several randomly chosen initial parameter sets θ_{new} and chose the best set afterwards.

We performed a CRH challenge test for an evaluation of our mathematical model (see (23)). In this clinical trial we injected twenty healthy subjects

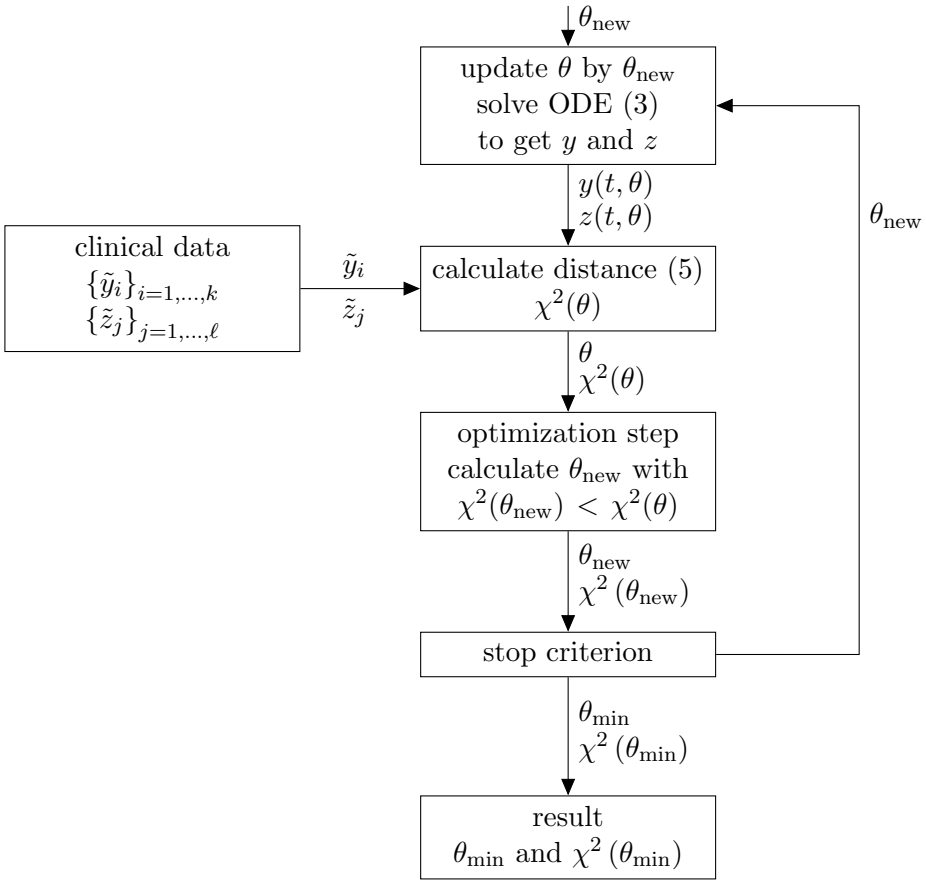

Figure 5: The flow chart is showing the parameter estimation procedure.

a dose of $1\,\mu g$ CRH per kg body weight at the time $t = 0$ (4 p.m.). The blood plasma concentration of ACTH and the blood serum concentration of cortisol were measured during a time period of four hours ($t \in [0, 240]$). We refer to $\tilde{y}_i$ with $i = 1, \ldots, k$ ($k = 17$) as the mean values of the blood plasma concentration of ACTH and to $\tilde{z}_j$ with $j = 1, \ldots, \ell$ ($\ell = 29$) as the mean values of the blood serum concentration of cortisol, while σ_i^y and σ_j^z specify the respective standard deviations, see Figure 7.

Before we perform the process of parameter estimation, the external input p of CRH on ACTH (i.e. y) has to be identified. In the considerations for estimating the external input we only take three assumptions into account. First the separation of external input and feedback and secondly the feedback on ACTH is only caused by cortisol. Thirdly, we assume that the external input p can be represented with some $b_5 \in \mathbb{R}^+$ and $\alpha \in \mathbb{R}^+$ by the exponential function

$$p(t; b_5, \alpha) = b_5 \alpha \mathrm{e}^{-\alpha t}, \tag{6}$$

which is a natural impulse (CRH) response (ACTH) curve (see for instance (11)). Since the effect of CRH on ACTH is unknown, the parameters b_5 and α are to be estimated first. We consider y from the system of differential equations (3) without feedback, i.e. $e_1 = e_2 = 0$. Since b_1 is known from the literature, y can be calculated with some given values of y_0, b_5 and α. The feedback of cortisol has to be responsible for the difference of the so calculated y and some given data $\tilde{y}_i$, namely $\tilde{z}_j$ (separation of external input and feedback and the feedback only caused by cortisol). Therefore, the parameters b_5 and α can be determined in such a way that cortisol concentrations have to correspond to the difference of y and $\tilde{y}_i$ at the best possible rate. The degradation rate b_1 of ACTH is given by $b_1 = \frac{\log(2)}{20}$ $[min^{-1}]$ (24). For the given data (mean values of the mentioned twenty subjects, see Figure 7) we computed $b_5 = 25.12$ $[pmol\ l^{-1}]$ and $\alpha = 0.0243$ $[min^{-1}]$, which corresponds to a degradation rate of approximately 28 minutes.

After these preparations we are able to apply the process of parameter estimation to the differential equation (3) and the data of the CRH challenge

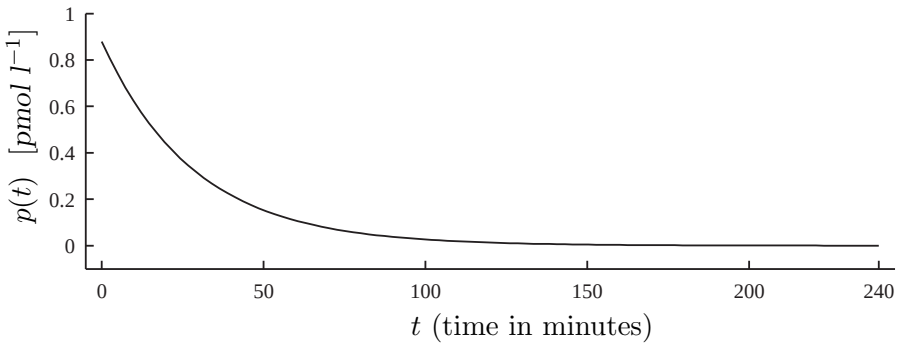

Figure 6: External input function p: The injection of CRH results in the external input on ACTH. By estimating the parameters b_5 and α of the external input function (6) we get $p(t) = 0.61 \cdot \mathrm{e}^{-0.024t}$ with $t \in [0, 240]$.

test. As initial values y_0 and z_0 of the differential equation (3) we picked the data values $y_0 = \tilde{y}_1$, $z_0 = \tilde{z}_1$, and $t_1 = \tau_1 = 0$. The parameters b_2, K_1, and K_2 are well understood and we took $b_2 = 28$, $K_1 = 0.5$ [$nmol\ l^{-1}$], and $K_2 = 5.0$ [$nmol\ l^{-1}$], see (5, 20).

The outlined parameter estimation procedure reveals $\theta_{\min} = (0.1290, 0.1633, 0.0336, 2.2234, 2.5345, 148.0701)$ as the parameter vector with a distance $\chi^2(\theta_{\min}) = 6.3410$. The dimension units are given by [$pmol\ l^{-1}\ min^{-1}$] for e_1, e_2 and [$nmol\ l^{-1}\ min^{-1}$] for b_3, b_4. It should be pointed out that it is not clear whether $\theta_{\min}$ constitutes a global minimum of the distance function χ^2. However, since we start the parameter estimation procedure with arbitrary θ_{new} several times and $\chi^2_{\min}$ is small, it is likely that $\theta_{\min}$ is the global minimum. The assumptions of Theorem 1 are fulfilled for the parameter vector $\theta_{\min}$. The left hand side of the inequality (4) is equal to $7.52 \cdot 10^{-3}$ and therefore greater than zero. The asymptotic stable point is calculated to $(y^\infty, z^\infty) = (1.37, 90.67)$, where y^∞ has the unit of measure-

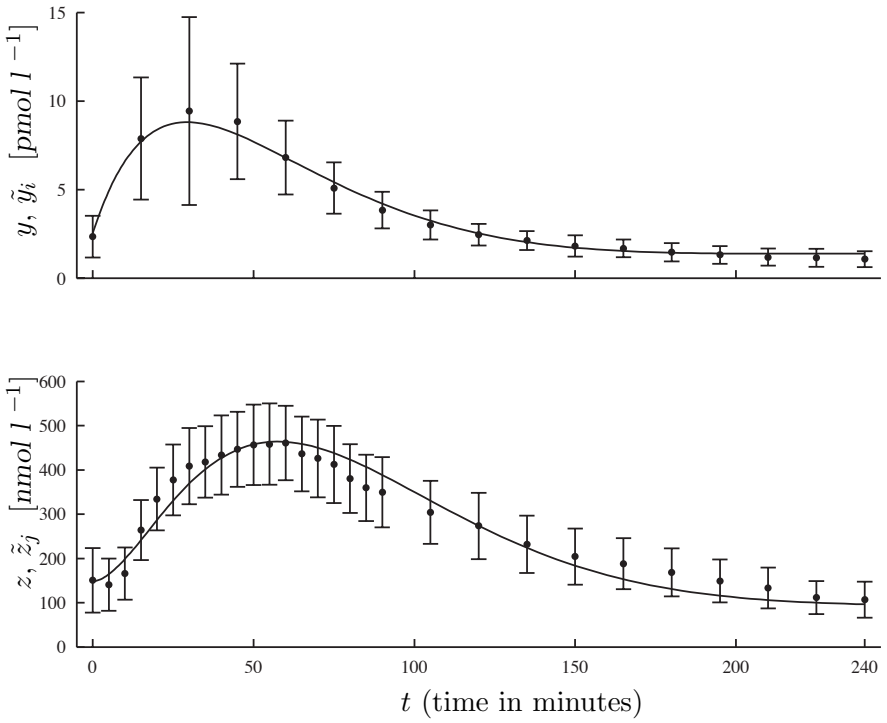

Figure 7: Clinical data (error bars) vs. mathematical model (solid lines): The error bars show the mean values and the standard deviation of ACTH and cortisol concentration of 20 healthy subjects during a CRH challenge test. The upper figure shows the plasma ACTH concentration and the lower figure shows the serum cortisol concentration. The solid lines represent the estimated function $y(\,\cdot\,;\theta_{\min})$ and $z(\,\cdot\,;\theta_{\min})$ with $\theta_{\min} = (0.1290, 0.1633, 0.0336, 2.2234, 2.5345, 148.0701)$. The distance between the data and calculated model is $\chi^2(\theta_{\min}) = 6.3410$.

ment $[pmol\ l^{-1}]$ and z^{∞} has $[nmol\ l^{-1}]$.

Discussion and conclusion

We developed a system of differential equations (3) for plasma ACTH and serum cortisol that fulfills the postulated rules of homeostasis. We proved

that, under mild assumptions, the system reaches a stable state over time. The fact that the system stabilizes in a well-defined state resembles the existence of a set-point for physiological systems that obey the principles of homeostasis. Despite its appealing simplicity, we were able to tune the parameter of the model, such that it fits remarkable well to clinical data.

We deliberately abstained to add further compartments to our mathematical model. Nevertheless, it is imaginable to split the compartments brain/pituitary up into two (e.g. first hippocampus/amygdala/ hypothalamus and second pituitary) or three compartments (e.g. first hippocampus/amygdala, second hypothalamus, and third pituitary) without changing the substantial implications of Theorem 1. Since in clinical trials brain glutamate and CRH signals cannot assessed in living humans and as three or four compartments cause more unknown parameters to estimate, we used the two-dimensional system of differential equations.

One notes that no additional signals (e.g. glutamatergic stimulus from different brain regions) are needed to generate a stable HPA system. With a loss of such stimuli from other systems or outer influences our modeled system does not collapse like purely negative feedback systems (e.g. in (14, 15)) would do. From the physiological point of view the HPA system cannot be regarded as an isolated system. However, on the assumption of the homeostatic rules related systems within the organism may serve as modulators and not as indispensable regulators. The positive feedback via MR is therefore the crucial component to self-stabilize this dynamic system. One should notice that the asymptotic stable point (y^{∞}, z^{∞}) could be used as an indicator for disorders such as depression, obesity, and diabetes.

In (8) we tested a slightly modified system of differential equations referring to various clinical trials. Despite the simple structure of that system of differential equations, the process of parameter estimation performs strongly to various even pathological-clinical trials. Especially in pathological cases our model is in high agreement with clinical data, while purely negative models e.g. (8, 17, 23) result in a poor approximation. Thus, the presented model has a wider scope of validity than purely negative feedback systems. The approach to compute the parameter vector $\theta_{\min}$ enables us to classify the feedback parameters, to calculate the asymptotic stable point (y^{∞}, z^{∞}), and to identify potential pathological states in any subject individually.

Receptors with high and low affinities acting on the same ligand can be found throughout the entire organism (25). It therefore appears plausible that other control systems in the organism are regulated by a similar mechanism. There is physiological evidence that the rules of homeostasis and the structure of our mathematical modeling might be transferred to other homeostatic biological systems (7, 8).

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