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# SINGULARITY THEORY APPROACH APLLIED TO FOUR-DIMENSIONAL MODEL OF THE HYPOTHALAMIC-PITUITARY-ADRENAL SYSTEM ACTIVITY

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## Abstract

The HPA system is a complex neuroendocrine system whose main purpose is to regulate wide variety of bodily processes, under basal physiological conditions and during stress, by regulating the plasma levels of corticosteroids secreted from adrenal glands. In this paper, we apply the singularity theory approach to an initial model of this system, which we have previously published.

## Introduction

The paraventricular nucleus (PVN) is a part of the hypothalamus which controls the secretion of corticotrophin-releasing-hormone (CRH) and arginin-vasopressin (AVP), which cause pituitary release of adrenocorticotropin (ACTH) and consequential adrenal gland stimulation, with release of corticosteroids (glucocorticoids, whose main representative in humans is cortisol (CORT), and corticosterone in rodents, and mineralocorticoids, whose main representative is aldosterone (ALDO)) from appropriate adrenal cortex zones [1]. In our previous paper, the HPA system was described by the following model [2]:

$$\begin{aligned}
&\xrightarrow{k_0} \mathrm{B} \\
&\xrightarrow{k_m} \mathrm{M} \\
&\mathrm{B} \xrightarrow{k_1} \mathrm{A} \\
&\mathrm{A} \xrightarrow{k_2} \mathrm{G} \\
&\mathrm{A} \xrightarrow{k_3} \mathrm{M} \\
&\mathrm{A} + 2\mathrm{G} \xrightarrow{k_4} 3\mathrm{G} \\
&\mathrm{M} + 2\mathrm{G} \xrightarrow{k_5} \mathrm{G} \\
&\mathrm{A} \xrightarrow{k_6} \mathrm{P}_1 \\
&\mathrm{G} \xrightarrow{k_7} \mathrm{P}_2
\end{aligned}$$

$$\begin{aligned}
\frac{db}{d\tau} &= K_0 - b \\
\frac{dm}{d\tau} &= K_m + \alpha\, a - \varphi\, m\, g^2 \\
\frac{da}{d\tau} &= b - (\alpha + \beta + \gamma)\, a - a\, g^2 \\
\frac{dg}{d\tau} &= \beta\, a + a\, g^2 - \varphi\, m\, g^2 - \delta\, g
\end{aligned} \tag{1}$$

Here letters *b*, *m*, *a* and *g* represent dimensionless plasma concentrations of CRH, ACTH, cortisol and aldosterone, respectively. If we find the stationary state equation for dimensionless cortisol concentration

$$F(g_{ss}, K_0; \alpha, \beta, \gamma, \delta, K_m) = (g_{ss}^2 + \alpha + \beta + \gamma)\left(g_{ss} - \frac{K_0 - K_m}{\delta}\right) + \frac{K_0(2\alpha + \gamma)}{\delta} \tag{2}$$

then the condition for appearance/disappearance of a hysteresis loop (bistability) [3] can be written as

$$F(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = F_g(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = F_{gg}(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = 0$$

with $F_{ggg}(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) \neq 0$. (3)

Here, $K_0$ is the bifurcation parameter, and $F_g$, $F_{gg}$ , and $F_{ggg}$ are corresponding partial derivatives of $F$ with respect to $g_{ss}$ (other higher partial derivatives of $F$, with respect to $g_{ss}$ and bifurcation parameter $K_0$, must all be non-zero). In our case

$$F(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = (g_{ss}^2+\alpha+\beta+\gamma)(g_{ss}-\frac{K_0-K_m}{\delta}) + \frac{K_0(2\alpha+\gamma)}{\delta} = 0 \qquad (4)$$

$$F_g(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = g_{ss}^2+\alpha+\beta+\gamma+2g_{ss}(g_{ss}-\frac{K_0-K_m}{\delta}) = 0 \qquad (5)$$

$$F_{gg}(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = 2\,(3\,g_{ss}-\frac{K_0-K_m}{\delta}) = 0 \qquad (6)$$

When all three right hand sides of equations (4)-(6) equal zero simultaneously they fix the values of three quantities. For the selected $\alpha, \beta, \gamma$ and $K_m$ , the values of $g_{ss}$ , $K_0$ and $\delta$ can be determined at the point where the histeresis loop just unfolds (uniquely). Solving the equation (6) we have the vertical inflection point value

$$g_{ss,V} = \frac{K_0-K_m}{3\delta} \qquad (7)$$

Again, as in the case of two-dimensional system, since only positive values of $g_{ss}$ are realistic, we see that $K_0$ value must be larger then $K_m$. In the case of four dimensional system, vertical inflection point value does not depend on parameters $\alpha, \beta$ and $\gamma$. The region of multiple solutions is determined by the equations

$$F(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = F_g(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = 0,$$

with $F_{gg}(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) \neq 0$ (8)

thus, we have the ignition and extinction point (or turning points) in the $g$-$K_0$ locus:

$$g_{ss,1,2} = \frac{K_0-K_m \pm \sqrt{(K_0-K_m)^2-3(\alpha+\beta+\gamma)\delta^2}}{3\delta} \qquad (9)$$

and the following inequality $(K_0-K_m)^2-3(\alpha+\beta+\gamma)\delta^2 > 0$ must be satisfied for bistability of the system to exist, if not, $F_{gg}(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m) = 0$ when $F_g(g_{ss},K_0;\alpha,\beta,\gamma,\delta,K_m)$ vanishes, and two turning points (9) merge into the point of inflection (7).

Taking into account discussion about region of multistability given above, we performed further analysis of considered system numerically. Since the HPA system daily rhythm is dictated by one part of the hypothalamus, called the suprachiasmatic nucleus (SCN) [4], in numerical simulations made, we have described the HPA system daily rhythm by introducing one 24-h periodic function (P), and thus following result was obtained (Figure 1):

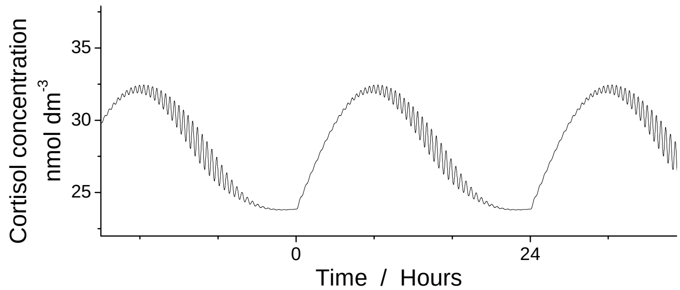


**Fig. 1.** Numerical simulations of the time evolution of cortisol concentrations with daily rhythm described by function P = 0.8095 + 0.061248 × sin (2πt/1440) + 0.11484 × abs (sin (πt/1440)). $G(0) = 2.76 \times 10^{-8}$ mol dm$^{-3}$, $K_0 = 0.0831$, $K_m = 2.7693 \times 10^{-4}$, $\alpha = 1.5776 \times 10^{-4}$, $\beta = 0.0197$, $\gamma = 0.0293$, $\delta = 0.2245$, $\varphi = 0.0560$, $k_P = k_0 \times P$.

## Conclusion

Analytical analysis performed, show that, for certain set of systems parameters, bistability of considered system exists. Numerical simulations give the HPA system daily rhythm in accordance with medical literature. Further improvements of considered model are possible, by taking into account influences of other hormones (such as AVP, progesterone, or testosterone for example), that are able to modulate the HPA system activity.

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