Oscillations in hypothalamic-pituitary-adrenal axis

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Abstract

A structured model of the HPA axis that includes the glucocorticoid receptor (GR) is considered. The model includes nonlinear dynamics of pituitary GR synthesis. The nonlinear effect arises from the fact that GR homodimerizes after cortisol activation and induces its own synthesis in the pituitary. This homodimerization makes possible two stable steady states (low and high) and one unstable state. The model includes also delay on stress. It is shown that concurrence between trajectories of dynamical system, which are produced by the unstable manifold and the value of delay time τ produce slow oscillating asymptotic periodic oscillations of cortisol with a period, which is grater then 2τ. It is shown that such oscillations exist only in an interval $\tau_1 < \tau < \tau_2$, where exact formulas for τ_1 and τ_2 has been obtained. Such oscillation arise when an initial values of stress are lager of some threshold.

Keywords: hypothalamic-pituitary-adrenal axes • asymptotic periodic oscillations • negative feedback • difference – differential delay equations • normal state.

1 Introduction

We consider HPA dynamics which includes stored CRH, circuiting CRH and $ACTH$, cortisol and glucocorticoid receptor that plays a role of 'dispatcher' that drives by distributions of hormones in the system. Our model incorporate a self–upregulation of CRH release, a negative and positive feedback effect on cortisol in CRH synthesis and a delay in $ACTH$ – activated on cortisol synthesis [12]. Remind that hypothalamic – pituarity – adrenal (HPA) axis ia neuroendocrine system that regulates hormones. The regulation is mediated by the inhibition of peptide hormones such as corticotropin – releasing hormone (CRH) and adrenocorticotropic hormone ($ACTH$) by circulating glucocorticoids such as cortisol ($CORT$).

Notice that in this paper, we have not begun with local linear stability theory, because as noted by our experience suggests that, while as sited in [14]: 'Many experimentalists have excellent intuition about rates of change at their fingertips, the abstraction of eigenvalues

presents a road block'. Our model includes three equilibria states for HPA system, one of which is unstable and another two are stable. We developed a dynamical model of HPA axis to describe interactions between key hormones and the glucocorticoid receptor (GR). Notice that well known mediate feedback activity of cortisol. For example, in [8] it has been considered a model when in HPA system arise two attracting limit cycles over which cortisol and that $ACTH$ oscillate with an ultraradian (hourly) rhythms. For our model, there are two oscillating states, one with lower cortisol level is associated with the normal state. Within this model, stress–induced secretion of CRH can trigger transition between normal and diseased states, respectively. Such simple attractor of the dynamical system of hyperbolic that contains two attractive fixed points and one repelling fixed point of codimension 1 (saddle type point) forms slow oscillating asymptotic periodic oscillations of cortisol in the HPA axis.

In the present paper, we follow to [11] and discuss HPA axis model of [12] that capture the basic feedback mechanism and includes an intracellular glucocorticoid receptor GR as one of the four state variables of the dynamical system, where variables $[CRH], [ACTH], [GR]$ and $[COR]$ define concentrations. Here, $[GR]$ is bounded to cortisol. The resulting complex $COR--GR]$ determines general behaviour of solutions of the model. It turns out that $GR := \Phi[COR])$, where Φ is a given nonlinear function (see, [11], Fig.1) which plays the mane role in the quantitative behavior of limit distributions of cortisol in a physiological system.

We define $[GR] := u$ and assume that: (1) $\Phi(I) \subset I$ for each $u \in I$, where I is an open bounded interval. Then from (1) it follows that all solutions of the problem are bounded for all $t > 0$. The phase diagram [11] shows that a state variable $[GR]$ is a cubic type function of the concentration $[COR] := u$ of cortisol. Hence, for a certain stress region, the system exhibits two stable steady states and one unstable steady state.

It will be shown that a corresponding dynamical system in R^3 ($3D$ - dimensional space)can be reduced to the planar system with two delay equations:

$$\dot{x}(t) = y(t) - \rho_1 x(t), \tag{1}$$

$$\dot{y}(t) = -f(x(t-1)) - \rho_2 y(t), \tag{2}$$

where ρ_1 and ρ_2 are given parameters. A function f is determined from a graphics of a function $\Phi : I \to I$, which is determined from phase diagram of 'pitchfork' type that follows from computer experiments in [10].

Thus, HPA mathematical model can be reduced to the study of solutions for system (58,59). Equivalently, the planar system can be reduced to an autonomous second order differential– difference delay equation:

$$\ddot{x} + (\rho_1 + \rho_2)\dot{x}(t) + \rho_1\rho_2 x(t) = -f(x(t-1)), \quad \tau := 1 \tag{3}$$

that explains oscillating behavior for solutions of delay differential difference equations. It is known that the delay system has a nonconstant periodic solutions with a period grater then 2 [9].

Below, using these mathematical results, we found that (for the HPA axis) there are slow oscillating asymptotically periodic solutions, which describe distributions of cortisol. It

will be found a role of delay in the HPA problem. It turns out that oscillating solutions are stable if and only if

$$\tau_1 < \tau < \tau_2, \tag{4}$$

where delay τ_1 and τ_2 are estimated exactly and ones depend on given parameters of the physiological problem. It will be found exact analytical formulas for τ_1 and τ_2, depending on parameters.

2 Postulation of problem

The HPA axis has three components which represent the hypothalamus, pituitary and adrenal. The equation for the hypothalamus is:

$$\frac{dC}{dT} = \frac{K_c + F}{1 - \frac{O}{K_n}} - K_{cd}C, \tag{5}$$

where $-K_{cd}C$ describes a constant degradation rate of CRH. Following [12] we assume that $\frac{\mathcal{O}}{K_n} \ll 1$. Then from (5) we arrive et

$$\frac{dC}{dT} = (K_c + F)\left(1 + \frac{O}{K_n}\right) - K_{cd}C. \tag{6}$$

(Here, all undetermined constants can be found in [12]). Next, from (6) it follows that if $C = \frac{K_c+F}{K_{cd}}$, then we can put $\frac{dC}{dT} \equiv 0$ with accuracy $O(\epsilon)$, where $\epsilon = \frac{\mathcal{O}}{K_n}$.

We write for the hypothalamus [12]

$$\dot{c} = \frac{1 + f}{1 + \frac{o}{k_1}} - k_{cd}c, \tag{7}$$

for the pituitary

$$\dot{a} = \frac{c}{1 + \frac{or}{k_2}} - k_{ad}a, \tag{8}$$

Equation (8) models the degradation rate of $ACTH$ and $ACTH$ production terms with a cortisol inhibition factor,

$$\dot{r} = \frac{(or)^2}{k + (or)^2} + k_{cr} - k_{rd}r \tag{9}$$

For the adrenal we have

$$\dot{o} = -o + a(t - \tau) \tag{10}$$

with delay response τ.

If in (8) we put $c := a$ (for unification with [5]) and consider only equilibrium $\dot{c} = 0$, then we obtain the well-known model [5]

$$\dot{a}(t) = \frac{A}{1 + p_2 o(t) r(t)} - p_3 a(t), \tag{11}$$

$$\dot{r}(t) = -\frac{p_4}{p_4 + (o(t)r(t))^2} + 1 + p_5 - p_6 r(t), \tag{12}$$

$$\dot{o}(t) = -o(t) + a(t-\tau). \tag{13}$$

as a particular case of the model [12] to the model [5]. Thus, we have a projection of trajectories of the dynamical system from R^4 into R^3. The assumption $\dot{c} = 0$ determines only c – null-cline that describes a curve

$$\frac{1+f}{1+\frac{o}{k_1}} - k_{cd}c = 0 \tag{14}$$

The projection on R^3 require that must be at least $\frac{o}{k_1} \ll 1$. We neglect this small term in the first approximation.

Remind [12] that stress to the HPA axis (f) stimulates the hypothalamus to secrete $CRH(c)$. Further, $CRH(c)$ signals the induction of $ACTH$ synthesis (a) in the pituitary. Thus, our assumption means that a velocity of stimulation of $ACTH$ signals is constant, i.e. $c = \frac{1+f}{k_{cd}}$. Mathematically, it means that the function $\mu = or$ can be considered as a parameter (et lest asymptotically). Effect of changing of parameters on c – null-cline has been considered by Kim et. al. [8].

3 Determination of fixed points for the HPA problem

It is known that these equations have three positive steady states (there is also negative state which is not used). These steady states arise beacons of homodimerization of the GR with cortisol. From ([12], Fig.1) it follows that $o = f_1(p_6)$ and $r = f_2(p_6)$, where another parametres are fixed. Here, f_1 and f_2 are multivalued functions.

$$\frac{dC}{dT} = (K_c + F)\left(1 + \frac{\mathcal{O}}{K_n}\right) - K_{cd}C. \tag{15}$$

Next, from (6) it follows that if $C = \frac{K_c+F}{K_{cd}}$, then we can put $\frac{dC}{dT} = 0$ with accuracy $\mathcal{O}(\epsilon)$, where $\epsilon = \frac{\mathcal{O}}{K_n}$.

As a result, we can consider the following approximation [5]:

$$\dot{a}(t) = \frac{A}{1 + p_2 o(t) r(t)} - p_3 a(t), \tag{16}$$

$$\dot{r}(t) = -\frac{p_4}{p_4 + (o(t)r(t))^2} + 1 + p_5 - p_6 r(t), \tag{17}$$

$$\dot{o}(t) = -o(t) + a(t-\tau). \tag{18}$$

The main role hear plays equation (17), which describes the production of GR in the pituitary. The term $-\frac{p_4}{p_4+(o(t)r(t))^2} + 1$ is in Michaelis-Menten form (see, [12] beacons we assumed that the bound glucocorticoid receptor (or) in the dimensionless form dimerizes with fast kinetics, so that the amount of dimer is in constant quasi-equilibrium and ones depends on the excess of or. The model also assumes that cortisol (o) and the glucocorticoid receptor

(r) bind to each other with very fast kinetics, which is compared to the rate of change of the 4 state variables (A, C, O, and R), so that OR stays in quasi-equilibrium as well. These are reasonable assumptions, given that high affinity receptor-ligand kinetics are often much faster than enzyme kinetics, as is assumed in the Michaelis-Menten equation (see, [12]. Equation (17) models a linear production term $K_c r$ and a degradation term $-K_{rd}R$ for pituitary GR production. Below, in the dimensional form for the model, these coefficients are defined as 1 and p_6, respectively.

4 Remark 1

Notice that (c) represents the level of circuiting CRH, (a) defines the level of circuiting $ACTH$, (r) describes the level of glucocorticoid receptor in the pituitary, and (o) is the level of circuiting cortisol. In equations for (a) and (r), the cortisol - receptor complex (or) is assumed to form and dissociate under fast dynamics [8]. Below mathematically it will be proved that it is indeed true beacons there are so-called slow oscillating distributions of cortisol [8]. It has been shown that this level can be approximated as 'steady state' by the production (or).

Indeed, let us define $\mu = or$. Then the origin problem in R^3 can be unfolds as the system in R^3, so that

$$\dot{a} = \frac{A}{1 + p_2\mu} - p_3 a, \tag{19}$$

$$\dot{r} = -\frac{p_4}{p_4 + \mu^2} + 1 + p_5 - p_6 r, \tag{20}$$

$$\dot{o} = -o + a, \tag{21}$$

$$\dot{\mu} = \dot{o}r + \dot{r}o, \tag{22}$$

where, in (21), $a := a(t)$ or $a := a(t - \tau)$.

From these equations it follows that fixed points lie on the curves

$$a = \frac{1}{p_3}\left(\frac{A}{1 + p_2\mu}\right), \tag{23}$$

$$r = \frac{1}{p_6}\left(-\frac{p_4}{p_4 + \mu^2} + 1 + p_5\right). \tag{24}$$

Since fixed points lie on diagonal $o = a$, multiplying these relations and substituting $o = a$, and putting at a fixed point $\dot{\mu} = 0$, we obtain that μ is a solution of 4 – order algebraic equation. Indeed,

$$or = \mu = \frac{1}{p_6 p_3}\left(\frac{A}{1 + p_2\mu}\right)\left(-\frac{p_4}{p_4 + \mu^2} + 1 + p_5\right). \tag{25}$$

Let $\nu = \frac{A}{p_6 p_3}$. Then from (25) we arrive at

$$p_4\mu^4 + \mu^3 + (p_2 p_4 - (1 + p_5))\mu^2 + p_4\mu - \nu p_5 p_4 = 0. \tag{26}$$

From Descartes' rule it follows that this equation has 3 or 1 positive roots and 1 negative root which can not be considered. Descartes' rule means that the number of positive roots of the polynomial is either equal to the number of sign differences between coefficients, or is less than it by an even number. From this property it follows that if we assume that

$$p_2 p_4 < 1 + p_5, \tag{27}$$

then (26) has 3 positive roots μ_1, μ_2, μ_3. Then from (23),(29) we can find three fixed point of the problem.

Thus, there are on the hyperplane $\dot{\mu} = 0$ in R^4 – space that is included in R^4 – space, where μ can be considered as a parameter. Since the basis in R^4 is not a family of independent vectors, we can use this observation to find conditions when trajectories of the dynamical system in R^4 are attractive by trajectories in R^3. If this is true, then the function $\mu(t)$ in R^4 is a constant function in R^3. A condition when it is possible can be easy found. Indeed, let $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ be eighenvalues of the problem. It means that

$$\dot{a} = \lambda_1 a, \quad \dot{r} = \lambda_2 r, \quad \dot{o} = \lambda_3 o, \quad \dot{\mu} = \lambda_4 \mu o. \tag{28}$$

From these equations it follows that

$$\dot{\mu} = \lambda_4 \mu = \dot{or} = (\lambda_2 + \lambda_3)\lambda. \tag{29}$$

From (**??**kjjjjh')) it follows that if $\lambda_2 + \lambda_3 < 0$, then $\dot{\mu} \to 0$ as $t \to +\infty$. It means that μ can be considered as a parametre in asymptotic sence.

5 Geometric method of determination of fixed points of the problem

Now we assume that there is a component $o = o^*$ of a fixed point in R^3. Then from equation (20) for cortisol we see that $\dot{r} \equiv 0$ if $G(r, o) \equiv 0$, where find from (17) the (o, r) - nullcline structure that is determined as a curve $r := r(o)$ such that $G(r(o), o) \equiv 0$ for each admissible o from some interval (corresponding numerical simulation is in ([8], Fig.4)). To make it, we assume that there is a component of fixed

$$G(r, o) := -p_6 o^2 r^3 + (1 + p_5) o^2 r^2 - p_4 p_6 r + p_4 p_5 = 0, \tag{30}$$

where o can be considered as a parameter. Thus, there is (multi-valued) curve $r := r(o)$ such that $G(r(o), o) \equiv 0$ for each positive fixed o. This curve has been found by numerical simulation in ([8], Fig.4)). The curve has S – form as graphic of a cubic polynomial.

6 Applications of the singularity theory for the HPA problem

If we find from (30) the curve $S = r(o)$, then on this curve $\dot{r} = 0$ that follows from the second equation of the HPA problem for the function $r(t)$. Results of computer experiments can

be found in [8]. On this curve, which has S – form (that leads to bistability), the function $r(t)$ is constant.

The behaviour of the RG receptor can be analyzed by the singulary theory [**?**]. The graphic $r := r(o)$ is multi-valued, and ones form S – form curve as shown, for example, in ([10], Fig. 3). From [13] it follows that there is irreversibility if

$$G = G_r = G_{rr} = 0, \quad G_{rrr} \neq 0. \tag{31}$$

From equation $G(r, o) = 0$ it follows that there are one or three fixed points for each fixed positive a. From equation $G_{rr} = 0$, i.e.,

$$-3p_6o^2r + (1 + p_5)o^2 = 0, \quad o \neq 0 \tag{32}$$

it follows that we have here the vertical inflection point value $r = \frac{1+p_5}{3p_6}$, which is independent on o as a parameter. Ignition and extinction points in the $(r - o)$ locus (see, [10]) are determined by the solutions $G = G_r = 0$ with $G_{rr} \neq 0$.

They satisfy to the quadratic equation

$$-(1 + p_5)o^2r^2 + 2p_4p_5r - 3p_4p_5 = 0 \tag{33}$$

that leads to the values

$$r_{1,2} = \frac{-p_4p_5 \pm \sqrt{(p_4p_5)^2 - 3(1 + p_5)p_4p_5}}{-(1 + p_5)}. \tag{34}$$

In the cae of bistability, these points separate three fixed states (one unstable saddle point is between two stable states). From here we see that the inequality

$$(p_4p_5)^2 \geq 3(1 + p_5)p_4p_5 \tag{35}$$

must be satisfied (it is necessary condition) for the bistability to exist.

Notice that according to Descartes' rule of signs the number of the positive roots of a polynomial is equal to the number of sign changes in the coefficients or less than the sign changes by a multiple of 2. Hence polynomial (30) has one or three positive roots. These roots lie on the curve $r(o)$. Intersection of this curve with the line $o = a$ (which follows from (18)) we obtain that $\mu = ar(a)$. Here, $\mu = (\mu_1, \mu_2, \mu_3)$. Using (52,) we find fixed points of the problem, which are $p_k = (a_*^k, a_*^k, r_*^k = r(a_*^k)), \quad k = 1, 2, 3.$

Notice also that according interpretation in ([12], Fig. 3) it has been obtained the variations of steady state for GR and cortisol r, respectively, with a as the parameter. There are three intervals I_1, I_3 and I_2. If $a \in I_1 \bigcup I_3$, then there are two attractive fixed points. If $a \in I_2$, we obtain a repelling fixed point.

7 $2D$ nonlinear dynamics

Let us consider the system of equations

$$\dot{o}(t) = -o(t) + a(t - \tau), \tag{36}$$

$$\dot{a}(t) = -f[o(t)] - p_3 a(t). \tag{37}$$

Then

$$\dot{a}(t-\tau) = -f[o(t-\tau)] - p_3 a(t-\tau). \tag{38}$$

Define $a(t-\tau) = y(t)$. Then from (60) it follows that

$$\dot{y}(t-\tau) = -f[o(t-\tau)] - p_3 y(t), \tag{39}$$

In (58) we define (for unification with [9]) $o(t) = x(t)$. Then (58), (61) can be written as

$$\dot{x}(t) = y(t) - x(t), \tag{40}$$

$$\dot{y}(t-\tau) = -f[o(t-\tau)] - p_3 y(t). \tag{41}$$

$$\dot{y}(t) = y(t) - x(t), \tag{42}$$

Consequently, the first equation can be written as

$$\dot{y}(t) = \frac{A}{1 + p_2 o(t) r(o(t))} - p_3 y(t). \tag{43}$$

Notice that on each plane $\dot{y}(t) \equiv 0$ the following functional relation $r(t) \equiv \Phi(o(t))$ is satisfied, where Φ is known irreversible function. Remind that a function Φ represents the glucocorticoid receptor (GR) that is included in the HPA axis (see, [12], Fig.3(a)) that includes the glucocorticoid. The nonlinear effect arises when GR homodimerizes (after cortisol activation) and induces its own synthesis in the pituitary. The form of graphics $\Phi(o)$ plays the main role in the qualitative study of solutions. The graphic has S form that allows to find three fixed points. Two of these fixed points are attracting, but one of the points o_* must be repelling in R^1..

Indeed, below it will be shown that if o_* is attracting, then there in reality four fixed point (see prev stable solutions. So that there are no of oscillating solutions. If a unique fixed point o_* is repelling then this point plays role of separator. Behaviour of a solution depends on an amplitude of initial data which is given on interval $[-\tau, 0)$. Let $h(t)$ be an initial function on $[-\tau, 0)$. Then if $0 < h(t) < o_*$, a solution tends to a constant solution $o(t) \to o_1 < o_3$ as $t \to +\infty$. If $h(t) > o_*$ on interval $-\tau, 0)$ then $o(t) \to o_1 < o_3$ as $t \to +\infty$. As a result, existence both of delay and repelling fixed point leads to the possibility of oscillating solutions of the problem if the initial data on $-\tau, 0)$ are large enough.

8 Planar case on RG null–isocline

Now, we return to the mathematical aspects of the problem. As shown above, there is i.e., to the equation (43). Define

$$-f(o) := \frac{A}{1 + p_2 o r(o)}, \tag{44}$$

where $r(o)$ is defined by RG form of the RG curve. Then equation (43) can be rewrite as

$$\dot{y}(t) = -f(o) - p_3 y(t). \tag{45}$$

Next, an important observation is that both equations (43) and (60) are equivalent to the system of equations

$$\dot{x}(t) = y(t) - \rho_1 x(t), \tag{46}$$

$$\dot{y}(t) = -f(x(t-\tau) - \rho_2 y(t), \tag{47}$$

where for (46) we put $\rho_1 = 1$, $\rho_2 = p_3$, $\tau = 1$. Then from [9] it follows that system (46), (50) has a monotonic periodic solution with a period grater then 2 and, respectively, 2τ – for the origin physiological problem.

Here, the following conditions must be satisfied: (i) a and b are positive constant, 0(ii) u f(u) > 0 for all $u \neq 0$, (iii) there is a positive constant χ such that $f(u) \geq -\chi$ for all u,

$$\dot{f}(0) > \frac{(\rho_1 + \rho_2)\gamma}{\sin\gamma}, \tag{48}$$

where γ satisfies $0 < \gamma < \pi$, and

$$\coth\gamma = \frac{1}{\gamma}(\gamma - \rho_1\rho_2)(\rho_1 + \rho_2). \tag{49}$$

Remind that, for the physiological problem, $\rho_1 = 1$ and $\rho_2 = p_3$. Hence, the condition (i) is satisfied. Next, the inequality (60) becomes

$$\dot{f}(0) > \frac{(1 + p_3)\gamma}{\sin\gamma}. \tag{50}$$

Notice that in [9] there is only a unique fixed point 0. In our situation, there are three fixed points (o_1, o_2, o_3), where o_1 and o_3 must be attractive fixed points, and $o_2 = o_*$ be a repelling fixed point. So that inequality (62) becomes

$$\dot{f}(o_*) > \frac{(\rho_1 + \rho_2)\gamma}{\sin\gamma}. \tag{51}$$

Further, the point o_* must be repelling. For example, in the limit $\gamma \to 0$ we obtain $\dot{f}(o_*) > 1 + p_3$ and, hence, the condition of the local unstability is satisfied. Since, $p_3 \geq 0$, this fixed point must be repelling at least for small δ. In conclusion, the condition (iii) is the condition of local instability as it will be shown below.

9 Analyses

Define $\alpha = \rho_1 + \rho_2$,$\beta = \rho_1\rho_2$, $\nu = \dot{f}(0)$. Then the characteristic equation is

$$\lambda^2 + \alpha\lambda + \beta + \nu e^{-\lambda} = 0, \tag{52}$$

where we assume that $\tau = 1$. If $\tau \neq 1$ then the problem is reduced to the characteristic equation:

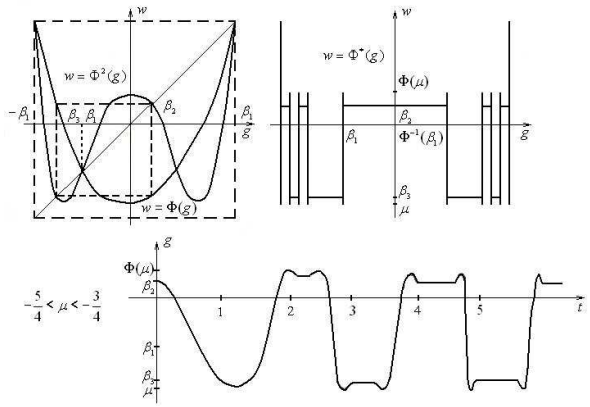

Figure 1: Slow oscillating distributions of cortisol

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$$z^2 + \alpha\tau z + \beta\tau^2 + \nu\tau^2 e^{-z} = 0, \tag{53}$$

where $z = \lambda\tau$, $\nu \to \nu\tau^2$, $\alpha \to \alpha\tau$, and $\beta \to \beta\tau^2$, and we assume that $\tau \neq 0$.

Further, we use results from ([9], Lemma 1). If α, β, ν be positive, and if $\alpha^2 \geq 2\beta$, then the following three conditions are equivalent: (1) Equation (52) has at least one solution. (2) The characteristic equation has precisely one solution λ with $\Re\,\lambda > 0$ and $0 < \Im\,\lambda < \pi$. (3) The following inequality is true

$$\nu > \frac{\alpha\nu_1}{\sin\nu_1}, \tag{54}$$

where $0 < \nu_1 < \pi$ and

$$\coth\nu_1 = \frac{1}{\alpha}\left(\nu_1 - \frac{\beta}{\nu_1}\right). \tag{55}$$

Notice that there are many details about behaviour of trajectories of the dynamical system. We formulate this behaviour as distributions of concentrations of hormones a and o on the $(o-a)$ – plane, where o is the distribution of cortisol. For example, there is an estimation

$$\dot{f}(0) > \frac{\rho_1\rho_2}{e^{\min(\rho_1,\rho_2)} - 1}, \tag{56}$$

where $0 \to o_*$ and $\rho_1 = 1, \rho_2 = p_3$, so that

$$\dot{f}(o_*) > \frac{p_3}{e^{\min(1,p_3)} - 1}. \tag{57}$$

Then a component $o(t)$ has properties as follows: (1) Zeroes for a graphic $o(t)$ form an infinite series $t_k, k = 1, 2, ...$, with $o(t_k) = 0$, $t_{k+1} - t_k > 1$ and $\dot{o}(t_{2k-1}) < 0$, $\dot{o}(t_{2k}) > 0$, and $\dot{o}(t_{2k-1}) < 0$, $\dot{o}(t_{2k}) > 0$, and $a(t_{2k-1}) < 0$, $a(t_{2k}) > 0$, and $a(t_{2k-1} + 1) < 0$, $a(t_{2k} + 1) > 0$; (2) A function $e^{\alpha t}o(t)$ is monotonic increasing on an interval $(t_{2k}, t_{2k} + 1)$ and monotonic decreasing on $(t_{2k-1}, t_{2k-1} + 1)$, where $\alpha = 1 + p_3$ (see, Fig. 1).

10 A necessary and sufficient condition for existence of slow periodic solutions

If $\tau \neq 1$, then we obtain the characteristic equation

$$z^2 + \alpha\tau z + \beta\tau^2 + \nu\tau^2 e^{-z} = 0, \tag{58}$$

where $z = \lambda\tau$. Define $\hat{\alpha} = \alpha\tau$, $\hat{\beta} = \beta\tau^2$ and $\hat{\nu} = \nu\tau^2$. Next, we must verify the assumption $\hat{\alpha}^2 > 2\hat{\beta}^2$ from ([9], Lemma 1). Evidently that this assumption is satisfied foe each $\tau \neq 0$.

Further, we assume that

$$\pi^2 + \frac{\hat{\alpha}^2}{4} - \hat{\beta}^2 > 0. \tag{59}$$

From (59) it follows the necessary condition on delay

$$\tau < \frac{2\pi}{\sqrt{4\beta - \alpha^2}}. \tag{60}$$

From (60) we obtain that must be $2\beta < \alpha^2 < 4\beta$ that leads to the natural condition $p_3 > 1$.

The condition (59) allows to apply Lemma 1 from [9]. It means that characteristic equation (58) has precisely one solution z with $\Re z > 0$ and $0 < \Im z < \pi$. Here, $\hat{\nu}$ must be such that

$$\hat{\nu} > \frac{\hat{\alpha}\hat{\nu}_1}{\sin\hat{\nu}_1}, \tag{61}$$

where $0 < \hat{\nu}_1 < \pi$, and

$$\coth\hat{\nu}_1 = \frac{1}{\alpha}\left(\hat{\nu}_1 - \frac{\beta}{\hat{\nu}_1}\right) \tag{62}$$

(see, [9], conditions (2),(3) from Lemma 1). From (62) it follows that

$$\nu\tau^2 > \frac{\alpha\nu_1\tau^3}{\sin\nu_1\tau^2}. \tag{63}$$

In the limit $\tau \to 0$, from (63) it follows that

$$\tau > \frac{\alpha}{\nu} + O(\tau^2). \tag{64}$$

Remind that $\nu = \dot{f}(o_*)$, where o_* is repelling fixed point of f. Together with (62) it gives

$$\frac{1 + p_3}{\dot{f}(o_*)} < \tau < \frac{2\pi}{\sqrt{4\beta - \alpha^2}}. \tag{65}$$

Inequality (65) gives necessary and sufficient conditions for existence of slow periodic solutions for the HPA problem in $2D$ approximation.

11 Conclusion

In this paper, it has been considered physiological and mathematical mechanisms of formation of ultraradian oscillations in the HPA axis. It is shown that here the main role plays the nonlinear connection between cortisol COR and the glucocorticoid receptor GR that forms a homodimer [?, 3]. A coception of transcriptional regulation is that the GR feedback control works rather slowly compare to other cellular processes.

The corresponding differential–difference equations with delay argument have slow oscillating periodic solutions. The delay has been included because, for example, mammalian cells one can expect at least a delay of the down regulation in the range of 15 minute up to 2 hours (see,[14, 11]. It is proved that at least mathematically) this hypothesis has been confirmed as slow oscillating 2τ (or larger) periodic distributions of cortisol (Fig.1). Here we follows to a mechanistic ODE system model of the glucocorticoid feedback mechanisms within the anterior pituitary gland cell, adding to this model the delay τ.

It is shown that important factor is the consequence between extracellular events such as changes in the CRH and cortisol induced inhibitory effect on anterior pituitary gland cells, which already occur after a few seconds [4, 1]. As a result, the slow oscillating periodic solutions of the mathematical mode explains qualitatively a phenomenon that can not be explained means of the genomic feedback mechanism [11]. An exact interval $\tau_1 < \tau < \tau_2$ for existence of slow oscillating periodic distributions for cortisol it has been found.

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