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R-K 4th Order Mathematical Model of the Hypothalamic-Pituitary-Adrenal Axis Validation with MATLAB Simulation

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Abstract: The Hypothalamic Pituitary Adrenal (HPA) system operates as complex feed forward and feed-back control system whose main purpose is to regulate wide variety of bodily processes, under basal physiological conditions or during stress by regulating the plasma levels of corticosteroids secreted from adrenal glands. The Hypothalamic Pituitary Adrenal (HPA) axis is a biological system connecting three areas in the body by mainly three hormones, Corticotrophin Releasing Hormone (CRH) Adreno Corticotrophin (ACTH) and Cortisol. The HPA Axis was simulated using non-linear equations modeled for important phenomena and the euler and RK-4th order methods were also used. By using the simulink, non-linear equations were also solved and it was concluded that the results are useful for a simulation of resilience in human.

Key words: Hypothalamic, differential equation, corticotrophin releasing hormone, simulation of resilience, adrenal glands, phenomena

INTRODUCTION

A hormone is a messenger molecule released into the bloodstream where it flows with the blood and then binds to a specific target receptor in the body tissue. In Hypothalamic Pituitary Adrenal (HPA) axis, we will consider a mathematical model with hormone concentrations as variables. HPA axis plays an important role under stress conditions by raising the concentration of the HPA axis hormones which leads to energy directed to the organism (Andersen *et al*., 2013; Jelic *et al*., 2005). Corticotrophin Releasing Hormone (CRH) is secreted in hypothalamus and reaches another area in the brain the anterior pituitary. Then CRH stimulates the secretion of Adreno Cortico Tropic Hormone (ACTH) from the pituitary gland, the HPA axis anatomy is shown in Fig. 1 (Hoeyer *et al*., 2014). ACTH moves with the bloodstream and when it reaches the adrenal glands it stimulates secretion of cortisol. The cortisol inhibits the secretion of CRH in the pituitary and it is also performs a negative feedback on the secretion of ACTH in the hypothalamus. The stress response provides the necessary metabolic realignment essential for survival when faced with a challenge (Panagiotakopoulos and Neigh, 2014) their relationship is given in Fig. 2. The hypothalamic-pituitary-adrenalaxis is a complex set of direct influences andfeedback interactions among the hypothalamus, the pituitary gland (a pea-shaped structure located below the hypothalamus) and theadrenal (also called "suprarenal") glands (small, conical organs on top of the kidneys).

The interactions among these organs constitute the HPA axis, a major part of theneuroendocrine system that controls reactions tostress and regulates many body processes, includingdigestion, theimmune system, mood and emotions and energy storage (Kyrylov *et al*., 2005). Any stress lasting longer than a few minute's results in increased levels of cortisol being released from the adrenal cortex. The release of cortisol is controlled by the Peri Ventricular Nucleus (PVN) of the hypothalamus (Jelic *et al*., 2005; Hoeyer *et al*., 2014) where Corticotrophin-Releasing Hormone (CRH) denoted by x_1 is released in response to the stress. CRH then acts on the pituitary gland, causing it to release Adreno Cortico Trophic Hormone (ACTH) denoted by x_2 which in turn causes the adrenal cortex to release cortisol, denoted by x_3 (Savic and Jelic, 2005).

During normal, non-stress situations, a certain level of cortisol is maintained in the bloodstream. There is a circadian rhythm of ACTH and cortisol release with the highest levels occurring around 8-10 am. in the morning and the lowest levels around midnight (Couture *et al*., 2008; Conrad *et al*., 2009). Other hormones released by the hypothalamus also follow a circadian rhythm, although not necessarily peaking at the same time. For example, growth hormone release peaks during sleep and melatonin is released at night.

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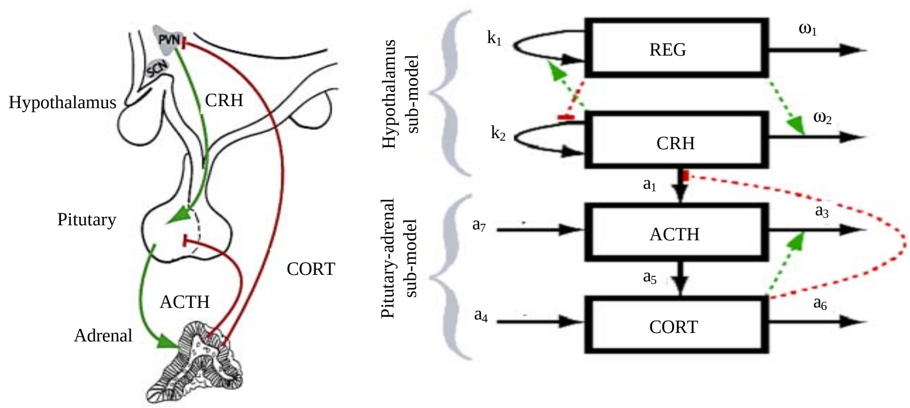

Fig. 1: a) Anatomy of HPA-axis showing the related location of hypothalamus, pituitary and adrenal glands and b) compartmental diagram of the CRH driven model (Hoeyer *et al*., 2014)

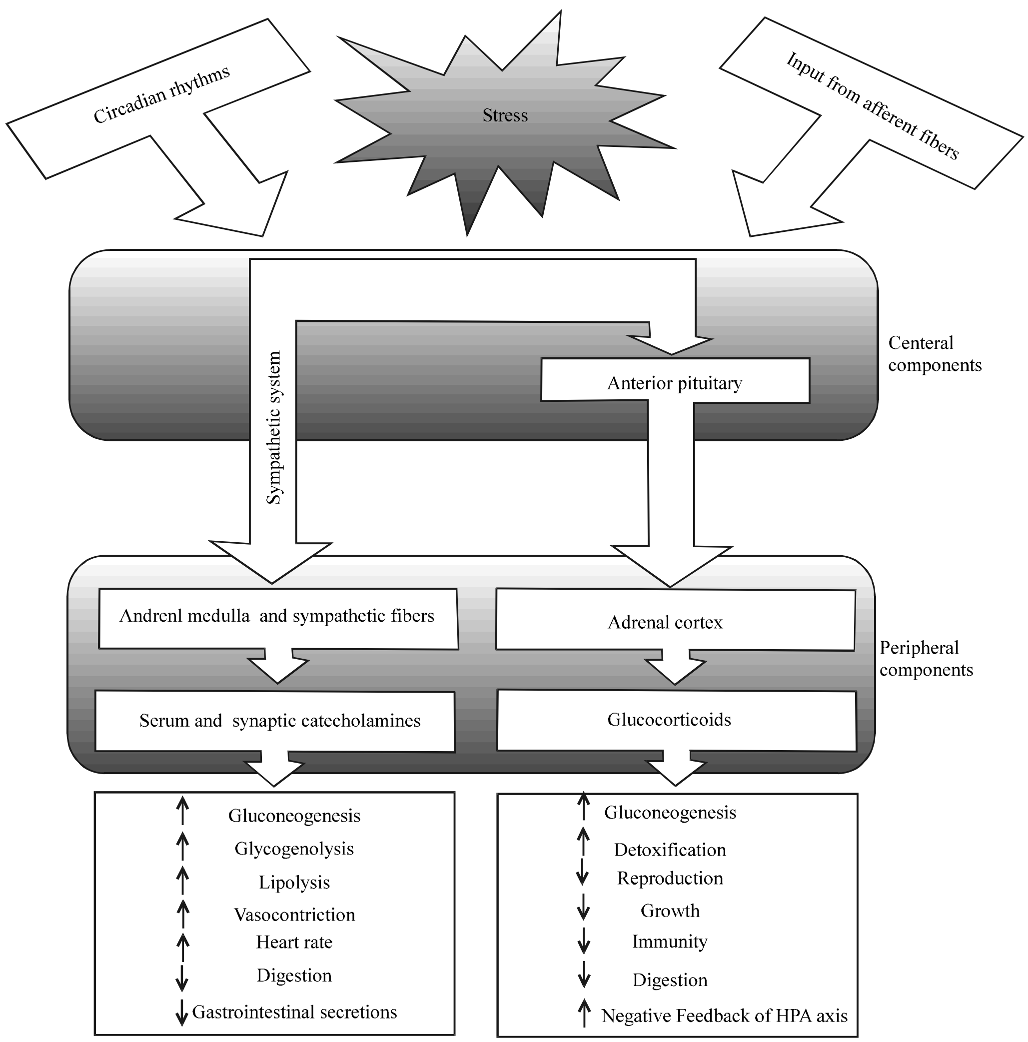

Fig. 2: Overview of the stress response (Panagiotakopoulos and Neigh, 2014)

MATERIALS AND METHODS

Mathematical model: Using the laws of mass action the reaction scheme can be transformed into differential equations. This means mathematical model crucially dependent on reaction scheme. However, there is no reference nor derivation of reaction scheme. Since, four hormones are considered the result is four differential equations.

An assumption about a slow dynamics of CRH compare to the dynamics of ACTH and cortisol leads to reduction of differential equations from four to two. The crucial nonlinearity of two equations comes from a reaction where one ACTH molecule reacts with two cortisol thus becoming three cortisol molecules. The following chemical reactions to the model HPA-axis are assumed to be valid:

$$\xrightarrow{K_0} x_1 \quad (1)$$

$$\xrightarrow{K_m} A \quad (2)$$

$$x_1 \xrightarrow{k_1} x_2 \quad (3)$$

$$x_2 \xrightarrow{k_2} x_3 \quad (4)$$

$$x_2 \xrightarrow{k_3} A \quad (5)$$

$$x_2 + 2x_3 \xrightarrow{K_4} 3x_3 \quad (6)$$

$$A + 2x_3 \xrightarrow{k_5} x_3 \quad (7)$$

$$x_2 \xrightarrow{k_6} P_1 \quad (8)$$

$$x_3 \xrightarrow{k_7} P_2 \quad (9)$$

The reduced model is given in following Eq. 10-12:

$$\frac{d_{x_1}}{dt} = k_0\text{-}w_1x_1 \quad (10)$$

$$\frac{d_{x_2}}{dt} = k_1x_1\text{-}w_2x_2 \quad (11)$$

$$\frac{d_{x_3}}{dt} = k_2x_2\text{-}w_3x_3 \quad (12)$$

Solution method: For one dimensional function the Euler method is given by Eq. 13:

$$\frac{d_y}{dt} = f(y,t) \quad (13)$$

where, y_n+1 = y_n+Δt×f (y_n, t_n). The model equation are given in Eq. 14 - 17:

$$\frac{d_{x_1}}{dt} = k_0\text{-}k_1x_1 \quad (14)$$

$$\frac{dA}{dt} = k_m + k_3x_2\text{-}k_5Ax_3^2 \quad (15)$$

$$\frac{dx_2}{dt} = k_1x_1\text{-}k_2x_2\text{-}k_3x_2\text{-}k_4x_2x_3^2\text{-}k_6x_2 \quad (16)$$

$$\frac{dx_3}{dt} = k_2x_2 + k_4x_2x_3^2 + k_5Ax_3^2\text{-}k_7x_3 \quad (17)$$

The results of this method are given in Fig. 4. To solve the above model equations, the R-K 4th thorder method is used. The complete step of solving the Eq. 14-17 are given below:

$$s_1 = \Delta t\times f(y_0, t_0) \quad (18)$$

$$t_1 = \Delta t\times f(y_0, t_0) \quad (19)$$

$$u_1 = \Delta t\times f(y_0, t_0) \quad (20)$$

$$v_1 = \Delta t\times f(y_0, t_0) \quad (21)$$

$$s_2 = \Delta t\times f(y_0+s_1/2, t_0+\Delta t/2) \quad (22)$$

$$t_2 = \Delta t\times f(y_0+t_1/2, t_0+\Delta t/2) \quad (23)$$

$$u_2 = \Delta t\times f(y_0+u_1/2, t_0+\Delta t/2) \quad (24)$$

$$v_2 = \Delta t\times f(y_0+v_1/2, t_0+\Delta t/2) \quad (25)$$

$$s_3 = \Delta t\times f(y_0+s_2/2, t_0+\Delta t/2) \quad (26)$$

$$t_3 = \Delta t\times f(y_0+t_2/2, t_0+\Delta t/2) \quad (27)$$

$$u_3 = \Delta t\times f(y_0+u_2/2, t_0+\Delta t/2) \quad (28)$$

$$v_3 = \Delta t\times f(y_0+v_2/2, t_0+\Delta t/2) \quad (29)$$

$$s_4 = \Delta t\times f(y_0+s_3, t_0+\Delta t) \quad (30)$$

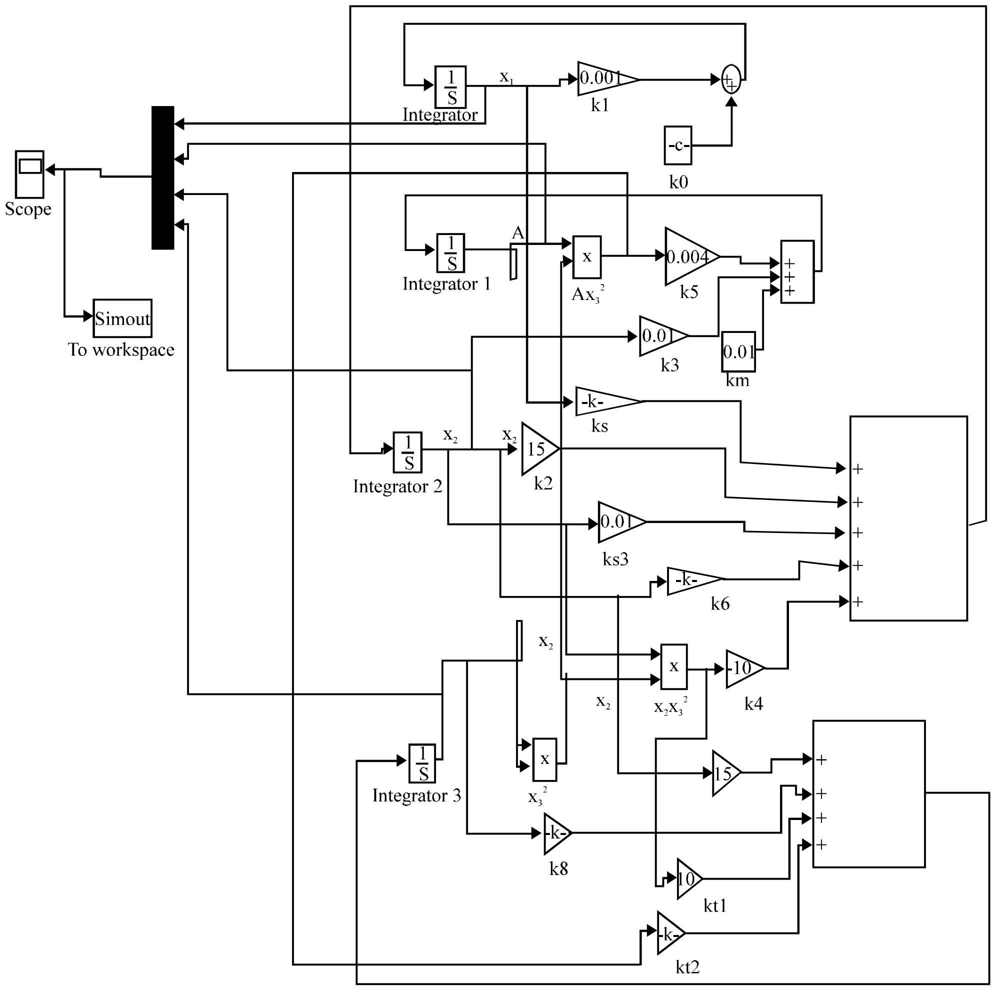

Fig. 3: Simulink Model

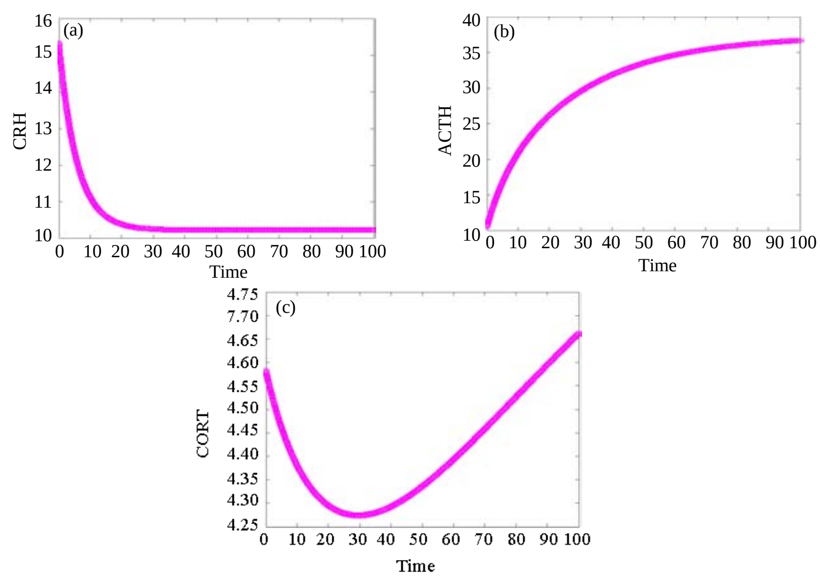

Fig 4: Results of Euler's method: a) CRH; b)ACTH ; c) CORT concentration as a function of time

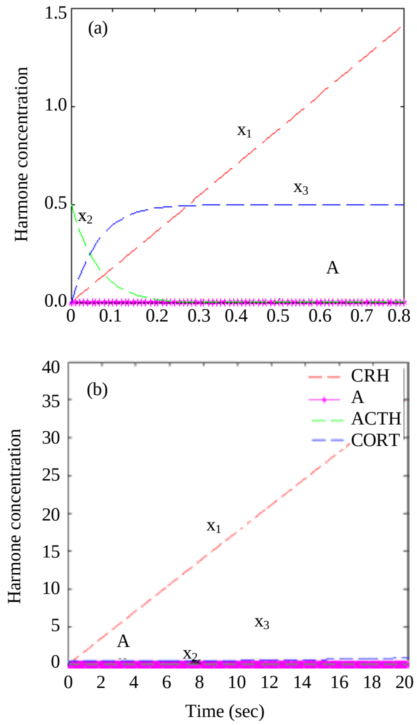

Fig 5: Results of R-K 4th order method

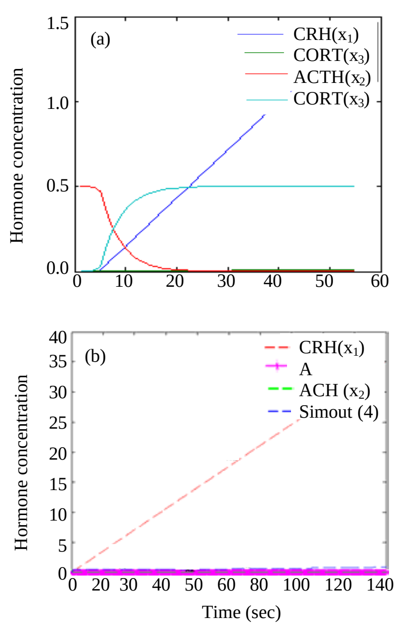

Fig 6: Results of MATLAB simulation

$$t_4 = \Delta t \times f(y_0 + t_3, t_0 + \Delta t) \quad (31)$$

$$u_4 = \Delta t \times f\left(y_0 + u_3, t_0 + \Delta t\right) \quad (32)$$

$$v_4 = \Delta t \times f(y_0 + v_3, t_0 + \Delta t) \quad (33)$$

$$x1_{n+1} = x1_n + \frac{1}{6} \times (s_1 + 2 \times s_2 + 2 \times s_3 + s_4) \quad (34)$$

$$A_{n+1} = A_n + \frac{1}{6} \times (t_1 + 2 \times t_2 + 2 \times t_3 + t_4) \quad (35)$$

$$x2_{n+1} = x2_n + \frac{1}{6} \times (u_1 + 2 \times u_2 + 2 \times u_3 + u_4) \quad (36)$$

$$x3_{n+1} = x3_n + \frac{1}{6} \times (v_1 + 2 \times v_2 + 2 \times v_3 + v_4) \quad (37)$$

The results of this method are given in the Fig. 3-5. Finally, the R-K 4th order method were simulated for appropriate results in MATLAB simulink tool. Because, it also supports linear and nonlinear systems, modeled in continuous time, sample time or a hybrid of the two. The Simulink Model diagram is given in Fig. 3 and the results are shown in Fig. 6.

RESULTS AND DISCUSSION

The simulation results were then plotted in the graph w.r.t CRH and time functions. Figure 4 shows that the CRH is releasing and concentrating with respect to time. The increase in time cause decrease in CRH up to one stage the line become straight line. The CRH concentration plotted as a function of time and the parameters used as the default parameter values. Figure 5 shows CRH data corresponding to the individuals. Time t = 0 corresponds to midnight. Data was sampled every tenth minutes through 24 h. The data of three individuals from the hyper cortisol depressed group, the low cortisol depressed group and a normal person. Time t = 0 corresponds to midnight. Data was sampled every tenth minutes through 24 h.

CONCLUSION

This study presents the mathematical modeling of the HPA-axis and its most difficult part of the modeling was to identify the reactions parameters. These reactions parameters were used to model HPA-axis by defining known linear differential equation. This was an extension of the previous research and solved those nonlinear differential equations by various numerical techniques. Firstly, a linear HPA Model equation was solved by Euler method and the results were found similar to earlier work. Similarly, the complete non-linear model equations were solved by using higher order R-K Methods. The results were in close agreement with the published resesrch. Finally, for the validation of results obtained by R-K Method, MATLAB Simulink tool used to solve nonlinear differential equations. The results were exactly the same as in the case of RK-4th order method.

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