Patient Specific Modelling in Diagnosing Depression
Combining Mixture and Non-linear Mixed Effect Modelling

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Abstract: Depression is a very common disease. Approximately 10% of people in the Western world experience severe depression during their lifetime and many more experience a mild form of depression. It is commonly believed that depression is caused by malfunctions in the biological system constituted by the hypothalamus-pituitary-adrenal (HPA) axis. We pose a novel model capable of showing both circardian as well as ultradian oscillations of hormone concentrations. We show that these patterns imitate those observed in the corresponding data. We demonstrate that patient-specific modelling shows its ability to make diagnoses more precise and to offer individual treatment plans and drug design. Efficient and reliable methods for parameter estimation are crucial. Presently we are examine how well the shuffled complex evolution algorithm do in estimating parameters. The next step is to investigate which parameters there are responsible for which pathologies by non-linear mixed effect modelling and statistical hypothesis testing. Preliminary results are promising. Finally, we plan to investigate how well the Metropolis-Hastings Algorithm of the Bayesian Markov Chain Monte Carlo method for estimating the parameters is working and we are about to do the same using iteratively refined principal differential analysis or the approximated maximum likelihood estimate.

1 INTRODUCTION

Depression is a mental disease normally diagnosed by psychiatrists. However, it is commonly believed that it is caused by malfunctions in some coupled endocrine glands producing hormones. The biological system made up by these glands and the hormones they produces are denoted the hypothalamus-pituitary-adrenal (HPA) axis. The interactions between these glands are constituted by mainly three hormones. Corticotropin releasing hormone (CRH) is secreted in hypothalamus and released into the portal blood vessel of the hypophyseal stalk, where it is transported to the anterior pituitary and it stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH moves with the bloodstream and when it reaches the adrenal glands it stimulates secretion of cortisol into the blood steam. Furthermore, cortisol feeds back on hypothalamus and pituitary influence the production of CRH and ACTH, respectively.

The HPA axis plays an important role under stressed conditions by raising the concentration of the hormones which leads to energy directed to the organism (Savic and Jelic, 2006). The return to the basal hormone levels after a while is an important feature of the system when it is working properly. Keeping cortisol concentration within a certain range is important for various reasons. A maintained, too high level of cortisol (hypercortisolism) can cause depression, diabetes, visceral obesity or osteoporosis (Conrad et al., 2009). Too low concentration (hypocortisolism) is neither desirable since it can result in a disturbed memory formation or life-threatening adrenal crisis (Conrad et al., 2009) beyond depression. The regulation of the HPA axis is thus important to stay healthy.

The cortisol concentration has a circadian pattern. It is typically low between 8 p.m. and 2 a.m. and rises to peak in the period 6-10 a.m. (Jelic et al., 2005). CRH is secreted in a pattern with a frequency of one to three secretory periods per hour often referred to as ultradian oscillations (Chrousos, 1998). Throughout the literature circadian as well as ultradian oscillations in the hormone concentration of ACTH and cortisol is seen (Griffin and Ojeda, 2004; Carroll et al., 2007). Thus circadian as well as ultradian oscillations are characteristics of the system. It is generally believed that circadian pattern is caused by exogenous factors (daylight, temperature, psychological as well

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as physical stress, etc.) but that ultradian pattern is caused by intrinsic dynamics of the HPA axis.

According to (Chrousos, 1998) the frequency of the ultradian oscillations is rather insensitive to stress whereas the amplitude increases. Examples of data for normal and depressed subjects (diagnosed by psychiatrists) showing circadian and ultradian oscillations are illustrated in figure 1 and figure 2.

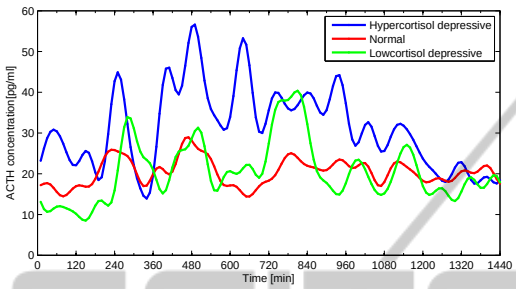

Figure 1: Example of filtered ACTH data of three individuals from the hypercortisol depressed group, the low cortisol depressed group and a normal person. Time t=0 corresponds to midnight. Data was sampled every tenth minutes through 24 hours.

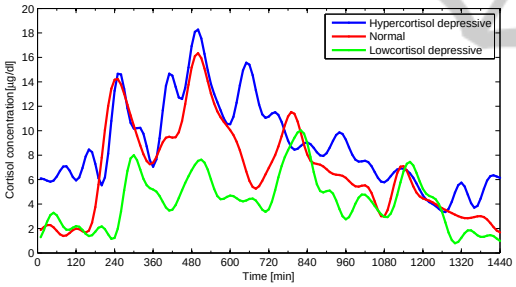

Figure 2: Example of filtered cortisol data corresponding to the individuals represented in figure 1. Time t=0 corresponds to midnight. Data was sampled every tenth minutes through 24 hours.

Understanding the interplay between the various elements of the HPA axis is interesting and important. Since several feedback mechanisms are working simultaneously in the HPA axis cause and effect may be hard to distinguish. A mathematical model may help understand this and can be an important tool for pointing out different ways in which malfunctioning may occur. More specifically, if we are able to estimate parameters based on a correct model of the HPA axis and individual data, i.e. concentrations of the hormones ACTH and cortisol in blood plasma samples, and some of these parameters varies significantly between groups of depressed subjects and normal subjects, then these parameters characterise the state of the disease and at the same time pinpoint the mechanisms which are malfunctioning.

2 MODELS OF THE HPA AXIS

It is commonly known that cortisol inhibits the secretion of CRH through glucocorticoid receptors (GR) situated in the hypothalamus (Wilson and Foster, 1992). In addition cortisol also performs a negative feedback on the secretion of ACTH through GR situated in pituitary (Tortora and Derrickson, 2006). This description is called 'the minimal model of the HPA-axis' and has been thoroughly investigated in (Vinther et al., 2011). In (Vinther et al., 2011) as well as in (Kyrylov et al., 2004; Kyrylov et al., 2005; Jelic et al., 2005; Savic and Jelic, 2005; Savic and Jelic, 2006; Liu et al., 1999; Bingzhenga et al., 1990) the splitting of the circadian and ultradian rhythm is assumed. This is in such a way that the ultradian rhythm is considered an inherent behaviour of the HPA axis whereas the circadian rhythm is thought of as an external input to the axis. The models presented in (Vinther et al., 2011; Kyrylov et al., 2004; Kyrylov et al., 2005; Jelic et al., 2005; Savic and Jelic, 2005; Savic and Jelic, 2006; Liu et al., 1999; Bingzhenga et al., 1990) all consist of a system coupled non-linear ordinary differential equations. Despite different approaches the common aim of these publications is to have unstable and oscillating solution curves. In (Vinther et al., 2011; Savic and Jelic, 2005; Savic and Jelic, 2006) this was done by looking for a Hopf-bifurcation of a stable fixed point, thus guaranteeing oscillating solutions. However previous results documented in (Vinther et al., 2011) was that this 'minimal model of the HPA axis' was not capable of reproducing the characteristics seen in data using reasonable parameter values. This suggests that the ultradian oscillations arise from other mechanisms like bursting which has been investigated successfully by (Veldhuis et al., 1989; Keenan et al., 2001; Keenan and Veldhuis, 2003). It has also been suggested that the ultradian oscillations may arise from the introduction of a time delay (Vinther et al., 2011; Bairagi et al., 2008). However, investigations show that rather large time-delays (i.e. at least 18 minutes) in the feedback mechanisms are needed (Vinther et al., 2011). Furthermore, one might suggest that the ultradian oscillations are not an inherent behaviour of the HPA-axis but imposed from outside. A last possibility is that something is missing in the minimal description of the HPA-axis. In the latter case, we have suggested the inclusion of mechanisms from hippocampus, see (Andersen et al., 2010; Andersen et al., 2013).

2.1 Inclusion of Hippocampal Dynamics

It has been suggested that hippocampus is also play-

ing a role for the dynamics of the HPA axis in such a way that hippocampus stimulates hypothalamus to produce CRH (Jelic et al., 2005; de Kloet et al., 1998; Jacobson and Sapolsky, 1991; Oitzl et al., 1995). Furthermore cortisol should be able to exert a feedback on mineralcorticoid receptors (MR) and GR situated in hippocampus. More specific cortisol should exert a positive feedback through GR in hippocampus and a negative feedback through MR in hippocampus (Jelic et al., 2005; Oitzl et al., 1995).

To our knowledge there is no known hormone secreted from hippocampus to stimulate secretion of CRH from hypothalamus neither does data for concentration of CRH exist for humans. Therefore one is faced with the challenge of how to model the hippocampal dynamics. The amount of cortisol binding to MR compared to the amount binding to GR determines whether the inclusion of hippocampal mechanisms corresponds to a positive or negative feedback. However this may depend on the concentration of cortisol thus given a positive feedback for some concentrations and a negative for others.

The inclusion of a competing positive and negative feedback mechanism widens the possible behaviour of the model compared to a purely negative feedback model. The idea is that the inclusion of hippocampal mechanisms would give an unstable fixed point that could explain the ultradian oscillations seen in data.

The known features the model reflects are feedback from cortisol on the secretion of CRH and ACTH and the combined feedback effect from hippocampus. Since no known hormone is secreted from hippocampus the known features from hippocampus is directly included in the differential equation governing CRH. This approach leads to the model given in equations (1) - (3) and is denoted *the general model*,

$$\frac{dx_1}{dt} = f_1(x_3) - w_1 x_1, \quad (1)$$

$$\frac{dx_2}{dt} = f_2(x_3) x_1 - w_2 x_2, \quad (2)$$

$$\frac{dx_3}{dt} = k_2 x_2 - w_3 x_3 . \quad (3)$$

The overall feedback from cortisol (x_3) in hippocampus and on CRH (x_1) is modelled through the function $f_1(x_3)$. The negative feedback from cortisol on ACTH (x_2) is modelled through the function $f_2(x_3)$. w_1, w_2, w_3 are elimination constants and $w_1, w_2, w_3 > 0$, $f_1, f_2 : \mathbf{R}_+ \cup \{0\} \mapsto \mathbf{R}_+ \cup \{0\}$, $f_1, f_2 \in C^1$, $\sup(f_1) = M_1 \in \mathbf{R}_+$, $\sup(f_2) = M_2 \in \mathbf{R}_+$, $f_1(0) > 0$ and $f_2(0) > 0$. This means f_1 and f_2 are bounded functions mapping non negative real numbers into non negative real numbers. f_1 and f_2 have non negative domains since the cortisol concentration is non negative. The ranges of f_1 and f_2 are non negative since the positive stimulation of the hormones must not turn negative. The criteria that f_1 and f_2 are bounded reflects the saturation of receptors through which the feedbacks are realized. When no cortisol is present the feedbacks must not completely shut down the stimulation of hormone production. This justifies $f_1(0) > 0$ and $f_2(0) > 0$. It is further assumed that the feedback on ACTH is negative meaning $f_2'(x_3) < 0$, $\forall x_3 \in \mathbf{R}_+ \cup \{0\}$. An approach similar to this has been investigated by (Conrad et al., 2009). However, in (Conrad et al., 2009) the ACTH and CRH compartment are pooled together.

The major conclusions (see (Vinther et al., 2011; Andersen et al., 2010; Andersen et al., 2013)) concerns the possibility of oscillating solutions:

- For the general model there exist a trapping region. This means that all solutions are guaranteed not to become negative or tend to infinity.
- The characteristic ultradian oscillations seen in data has been suggested to be an inherent behaviour of the HPA-axis. However the general model is not capable of giving oscillating solutions within physiologically reasonable parameter values. This suggests that origin of the ultradian rhythm should be found in different mechanisms than the ones included in the general model.
- Using the default parameters the system is globally stable. This means that the solution curves will converge to a unique fixed point for all initial conditions. This can be interpreted as healthy people returns to normal cortisol levels after periods of stress.
- A perturbation of the parameters may lead to bifurcations where the system undergo a transition from having a unique stable fixed point to having three fixed points where one is unstable and the two others are stable. All solution curves converge to one of the two stable fixed points depending on the initial conditions. This is accordance with the fact that depressed individuals is either hypercortisolemic depressive or hypocortisolemic depressive.

In the following we will pose a novel model extending the general model capable of showing both circadian as well as ultradian oscillations.

2.2 A Novel Model of the HPA Axis

The fundamental extension from earlier, e.g. equations (1) - (3), is that we allow a positive (super-short) feedback in hypothalamus, i.e. from CRH on its own

production. However, this is not based on pure speculation but on experimental evidence, see (Motta et al., 1970; Louis et al., 1987; Zanisi et al., 1987). In comparison with most specific models in the literature another novelty is the inclusion of non-linear terms in the feedbacks and the feedforwards (i.e. the terms x_3^2 and x_2^2) thus large concentration of ACTH and cortisol affects the production of cortisol and CRH, respectively, more pronounced than linear terms.

Hence we propose the improved novel model,

$$\frac{dx_1}{dt} = C(t)\frac{a_1 + a_2 x_1}{1 + a_3 x_3 + a_4 x_3^2} - w_1 x_1, \quad (4)$$

$$\frac{dx_2}{dt} = \frac{a_5 x_1}{1 + a_6 x_3} - w_2 x_2, \quad (5)$$

$$\frac{dx_3}{dt} = a_7 x_2 + a_8 x_2^2 - w_3 x_3 . \quad (6)$$

Here the circadian rhythm is generated by the endogenous input

$$C(t) = t_m^3 exp(-\frac{t_m}{120}), \quad (7)$$

where t_m denotes time t modulo 24 hours (the time units used is minutes).

3 METHODS

Models should be developed so they incorporate the responsible mechanisms for the modelled phenomena, i.e. they should be mechanisms-based and they should be based on first principles (conservation laws, etc.) whenever possible. Thus mechanisms-based models may be rather detailed models. Somehow in oppose to this demand but in order to identify and estimate patient-specific parameters in an effective and reliable way, the number of parameters has to be kept as low as possible, which means that any unimportant factors and elements should be excluded. Hence a compromise between these conflicting demands often result in models based on elements resembling the underlying mechanisms as well as lumped elements. In any case, all parameters should have physiological interpretations. Following the principle of parsimony a model should be as simple as possible fulfilling the purpose of the modelling task without contradicting existing knowledge. This has been the guidance in deriving the novel model presented in section 2.2.

Patient-specific models are (preferable mechanisms-based) models with physiologically interpretable parameters related to different pathologies and healthy states in which the values of the parameters can be individually estimated. Thus, patient-specific models are models that can be adjusted to specific individuals. Hence, in patient-specific models, pathologies are clarified by the values of certain parameters. The parameters are estimated from measurements in combination with the model, thus giving rise to more precise clinical diagnoses and more reliable suggestions for treatments than are known based on today's practices. In addition, existing classes of diagnosed cases may be refined into subclasses of pathologies corresponding to the actual defect of the physiological system by use of such patient-specific models. Moreover, knowing the actual defect(s) makes the development of target-specific drugs and other treatments possible. Development of this kind can guide the pharmaceutical industry in its search for new and improved drugs. In addition, a huge reduction in the cost of developing new drugs may be expected not only due to a more beneficial process when searching for drug candidates but also because models may be used to substitute some costly animal and human experiments in future pre-clinical and clinical trials, respectively.

The parameters have to be estimated by statistically founded algorithms (for example, the extended Kalman filter, the Nelder-Mead algorithm combined with simplex methods, multidirectional search, particle filter/sequential Monte Carlo methods, genetic algorithms, Bayesian methods etc.) or by functional analysis, i.e. optimal control, functional differential analysis, collocation methods, etc. Not all the parameters will necessarily be identifiable due to limitations concerning available data and/or an over-parameterization of the model. Thus, the estimation process has to be an iterative procedure coupled with sensitivity analyses or generalized sensitivity analyses combined with subset selection strategies, for instance.

Presently we are examine how well the shuffled complex evolution (SCE) algorithm do in estimating parameters and are about to do the same using the Metropolis-Hastings Algorithm of the Bayesian Markov Chain Monte Carlo (MCMC) method and the iteratively refined pricipal differential analysis (iPDA) also denoted approximated maximum likelihood estimate (AMLE).

When well-validated models with patient-specific estimated parameters exist, the identification of potential biomarkers becomes achievable. Potentially parameter estimation by patient-specific models may identify windows for parameter values defining different states for patients, e.g diseased or healthy. This would be a big step forward for healthcare compared with empirical developed biomarkers, since the former also pinpoint the pathological part of the system

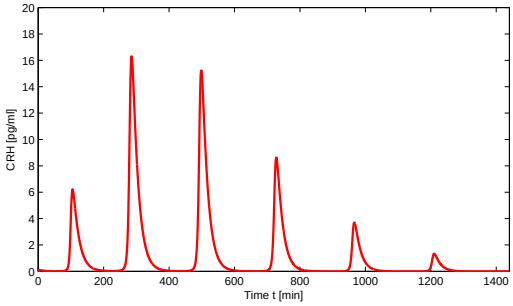

Figure 3: Example of simulated CRH concentration for an individual.

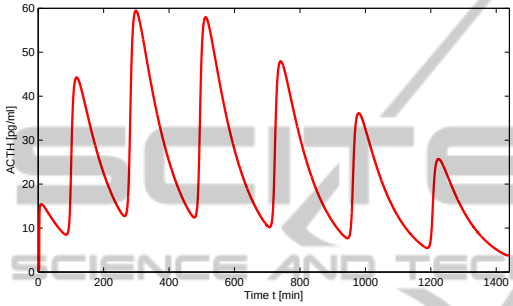

Figure 4: Example of simulated ACTH concentration for an individual.

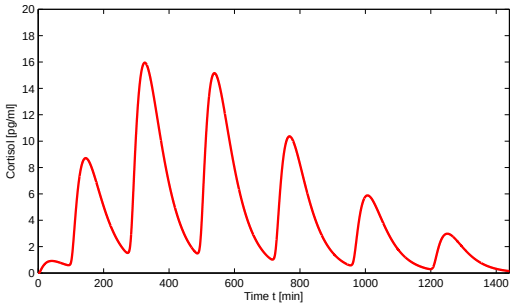

Figure 5: Example of simulated cortisol concentration for an individual.

for diseased patients. When such potential biomarkers are identified, different groups of patients, i.e. pathological subjects versus non-pathological subjects, can be examined. Notice that, some of the parameters between two different groups have to vary. To determine whether there is a real difference between the values of the parameters (i.e. the biomarkers) within two groups or whether suggested biomarkers can identify variant causes (i.e. pathologies) of the illness (diagnosed by symptoms), statistical tests have to be performed. The biomarkers will definitely give rise to a classification of variants of the illness because they have inherent features that are naturally in accordance with data from clinical diagnoses.

4 RESULTS

The values of the 11 parameters of the model presented in section 2.2 are initially guessed to be $a_1 = 4.6$, $a_2 = 7.6$, $a_3 = 2.0$, $a_4 = 0.5$, $w_1 = 0.34$, $a_5 = 0.126$, $a_6 = 3.0$, $w_2 = 0.011$, $a_7 = 0.064$, $a_8 = 0.0165$ and $w_3 = 0.057$. In the near future the parameters will be estimated by a Bayesian MCMCM method as described in section 3 using these parameter values as initial guesses. The outcome is shown on figures 3, 4 and 5

5 CONCLUSIONS

Depression is a very common disease. Approximately 10% of people in the Western world experience severe depression during their lifetime and many more experience a mild form of depression. Endocrine pathologies are believed to be responsible for depression as well as for stress. Patient-specific modelling has shown its ability to make diagnoses more precise and to offer individual treatment plans and drug design. Efficient and reliable methods for parameter estimation are crucial. We have proposed a novel model capable of showing both circardian as well as ultradian oscillations. These patterns imitate those observed in the corresponding data. Presently we are examine how well the shuffled complex evolution (SCE) algorithm do in estimating parameters. The SCE algorithm is a stepwise global method where a number of complexes in each step make use of the simplex algorithm and transition between steps evolve according to a random procedure. The next step is to investigate which parameters there are responsible for which pathologies by non-linear mixed effect (NLME) modelling and statistical hypothesis testing (ANOVA). Preliminary results are promising. Finally, we plan to investigate how well the Metropolis-Hastings Algorithm of the Bayesian Markov Chain Monte Carlo (MCMC) method for estimating the parameters is working and we are about to do the same using iteratively refined principal differential analysis (iPDA) or the approximated maximum likelihood estimate (AMLE).

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