

Design of Intermittent Control for Cortisol Secretion under Time-Varying Demand and Holding Cost Constraints

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Abstract—Objective: We take the release of stress hormone cortisol as a part of an *intermittent* control feedback system in contrast to the existing continuous models. By modeling cortisol secretion as an impulsive system, we design an impulsive controller as opposed to a continuous controller for adjusting cortisol levels while maintaining the blood cortisol levels within bounds that satisfy circadian demand and cost constraints.

Methods: We develop an analytical approach along with an algorithm for identifying both the timing and amplitude of the control. **Results:** The model and the algorithm are tested by two examples to illustrate that the proposed approach achieves impulsive control and that the obtained blood cortisol levels render the circadian rhythm and the ultradian rhythm consistent with the known physiology of cortisol secretion. **Conclusions:** The approach successfully achieves the desired circadian impulsive control which has great potential to be used in personalizing the medications in order to control the cortisol levels optimally.

Significance: This type of bio-inspired intermittent controllers can be employed for designing non-continuous controllers in treating Addisonian disease, which is caused by the adrenal deficiency.

Index Terms—Mathematical modeling, algorithm, pulsatile control, endocrine control, circadian rhythm.

I. INTRODUCTION

HORMONES are signaling substances that regulate many vital bodily functions, such as growth, stress, and metabolism. In the endocrine system, the hypothalamus and the pituitary gland communicate with remote target glands such as testes, thyroid and adrenal glands through a combination of continuous and intermittent (pulsatile) signal exchanges [34]. Continuous signaling permits hormone concentrations to vary slowly, while pulsatile signaling allows them to have instantaneous adjustment [34]. In fact, pulsatility is a physiological mechanism through which hormone concentrations can increase rapidly and send distinct signaling

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information to target cells [32]. Compared with continuous signaling, pulsatile signaling is more energy efficient, allows more rapid changes in hormone concentrations, and offers the control flexibility of not only amplitude but also frequency modulation [38]. It is widely known that several hormones such as gonadal steroid, growth, insulin and cortisol are released in a pulsatile manner [3, 15, 22, 27, 28, 30, 32, 33, 37]. However, pulsatile signaling is much less understood since it is significantly different from continuous signaling [25]. Therefore, there is a great need to understand the physiology underlying the pulsatile hormone release [9].

The hypothalamic–pituitary–adrenal (HPA) axis is one of the most important endocrine systems, which controls intermittent release of cortisol. Cortisol is a steroid hormone that is mainly responsible for regulating metabolism and the body’s reaction to stress and inflammation [1]. It is known that the mechanisms of the HPA axis are governed not only by a circadian rhythm, but also by an ultradian pattern of pulsatile release of cortisol [1, 7, 9, 34, 37, 38]. The pulsatile release of cortisol from the adrenal glands is triggered and controlled by a hierarchical system involving corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotrophic hormone (ACTH) from the anterior pituitary, and cortisol from the adrenal glands [1, 7, 26, 29]. CRH induces the release of ACTH, followed by the stimulation of ACTH on the release of cortisol. The hormone cortisol, which is cleared by the liver, in turn exerts negative feedback effect on the release of CRH and ACTH [1, 16, 26, 29], see Fig. 1.

Dysregulation of cortisol pulsatility is related to a number of psychiatric and metabolic diseases [40, 41]. Due to ethical reasons, direct measurement of endocrine glands (e.g., CRH) cannot be made for healthy humans [34]. One may have to rely on reasonable theoretical models to understand the sophisticated control mechanisms, which involves (i) determining the number, timing and amplitude of cortisol pulses, so-called “secretory events”, to better understand the physiology, effects of drugs and other interventions [6, 8]; (ii) designing intermittent controllers to optimally control cortisol levels (i.e., minimizing the number of secretory events as well as maintaining the blood cortisol levels within bounds that satisfy circadian demand and cost constraints) linked to cortisol pulsatility [6, 9]. The latter might be useful in treating, e.g., Addisonian disease which is caused by the adrenal deficiency.

Since the hypothalamus, the pituitary gland, and the adrenal glands are interacting in the HPA axis, in order to investigate

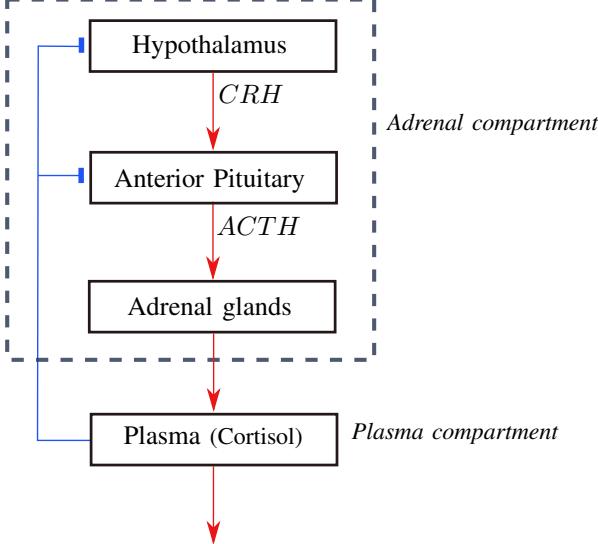


Fig. 1: Compartment representation of plasma cortisol levels where stimulatory and inhibitory interactions are depicted, respectively, by \rightarrow and \dashv . The adrenal compartment includes all elements of the HPA axis within the dotted box, while the plasma compartment is where the diurnal cortisol rhythm is observed.

pathological conditions related to cortisol and design optimal treatment strategies, one may build a mathematical model based on the physiology underlying the HPA axis, and then develop signal processing and control algorithms for diagnostic and treatment purposes. In addition to considering all of the hormonal stimulations and inhibitions involved in the HPA axis, a complete mathematical model of the diurnal cortisol variation should also include the effects of the exogenous factors such as stress, meals, and sleep state [1, 20, 24]. Note that simultaneous measurements of all these variables is impossible for humans [1]. For this reason, in order to understand essential control mechanisms of the HPA axis, we consider a “minimal” model based on the known physiology of the HPA axis, which captures those known essential characteristics of the observed diurnal patterns [1, 7]. Biochemical and physiological evidence from human investigations reveals that a minimum of two compartments must be considered to represent the cortisol diurnal pattern [1]. Following [1, 7], in this work we consider two compartments as follows: (i) the adrenal compartment including all elements of the HPA axis (see the dotted box in Fig. 1), and (ii) the plasma compartment where the diurnal cortisol rhythm is observed.

According to [1], the following three factors govern the diurnal variation in plasma cortisol levels: (i) ultradian timing of the cortisol secretory events, (ii) circadian control of cortisol secretory amplitudes, and (iii) the kinetics of the cortisol synthesis in the adrenal glands and infusion into, and the clearance from the plasma from the liver.

Mathematically recovering the number, timing and amplitude of hormone pulses can lead to an ill-posed problem mainly due to existence of multiple solutions [6, 7]. Nevertheless, by using the characteristic of the sparsity of hormone

pulses and taking into account more constraints, several methods have been presented to estimate such quantities [7, 8, 13, 14, 34, 35, 36]. In some recent work [9, 6], an optimization approach based on a two dimensional deterministic model has been proposed to design impulsive inputs (i.e. determine the timing, amplitude, and number of secretory events) to achieve pulsatile dynamics in presence of circadian amplitude constraints on the cortisol levels. As this optimization problem is solved by the ℓ_1 -norm minimization algorithm presented in [2, 10], it can lead to finding suboptimal solutions, i.e., cortisol levels do not satisfy the conditions that have to be satisfied.

The contribution of this paper is twofold. First, we present a linear two dimensional impulsive system to describe the pulsatile cortisol release. In sharp comparison to previous works [6, 7, 8, 9, 13, 14, 35, 36] which take into account the characteristic of the sparsity of hormone pulses, in this paper we postulate that there exists an “impulsive” controller in the anterior pituitary which allows the state of the system to have instantaneous changes, and controls the cortisol secretion and the ultradian rhythm of the pulses. Second, we propose an *analytical approach* to the design of an intermittent controller (i.e. calculating the number, timing, and amplitude of impulsive control input) in presence of circadian demand and holding cost constraints on the blood cortisol level, which are assumed to be two-harmonic time-varying circadian functions with periods of 12 and 24 h [9] respectively. Different from previous works [6, 7, 9] which gave an approximation of the secretory events, our proposed method *precisely* calculates the secretory events. The illustrated examples in Section III clearly show the efficiency and accuracy of our method. One direct application of our intermittent control design is determining the timing and dosage of hydrocortisone (i.e. synthetic cortisol) injections in Addisonian patients given desired circadian demand and holding cost constraints on the blood cortisol levels and the patients’ metabolic rate.

II. METHODS

A. Problem formulation

In this subsection, we propose an impulsive differential equation model of diurnal cortisol patterns using the stochastic differential equation model presented in [1], which is based on the first-order kinetics for cortisol synthesis in the adrenal glands, cortisol infusion to the blood, and cortisol clearance by the liver [1, 7, 9, 5]. In the stochastic model proposed in [1], the “pulsatile” input in the adrenal glands is supposed to be doubly stochastic with amplitudes in Gaussian and inter-arrival times in gamma distributions respectively. However, in the model presented here, the input is considered to be an “abstraction” of hormone pulses which results in cortisol secretion. We make the following physiologically plausible assumptions for the proposed model:

Assumption 1. (i) *Cortisol levels can be described by the first-order kinetics for cortisol synthesis in the adrenal glands, cortisol infusion to the blood, and cortisol clearance by the liver [1, 9].*

(ii) *There is a time-varying circadian holding function $H(t)$ on the cortisol level which is the highest cortisol level that*

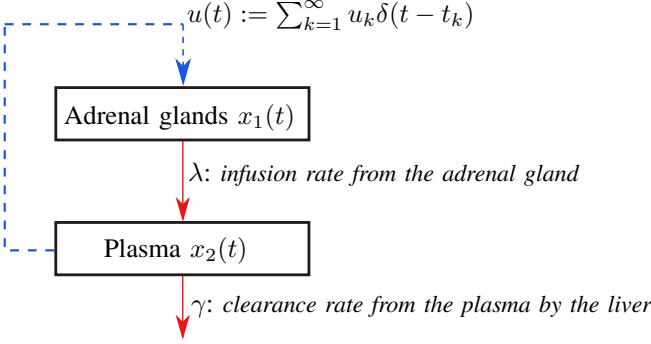


Fig. 2: Representation of the two dimensional differential equations (1) and (2). The variable $x_1(t)$ denotes the cortisol concentration in the adrenal glands, and the variable $x_2(t)$ denotes the serum cortisol concentration. The parameter λ is the infusion rate from the adrenal glands to the plasma, while γ is the clearance rate from the plasma by the liver. The input $u(t)$ is an abstraction of hormone pulses where the quantities u_k and t_k ($k = 1, 2, \dots$) are determined based on the state variables of the system as well as the lower and upper bounds $D(t)$ and $H(t)$ on $x_2(t)$; see Remark 3.

the body should produce in order to have a normal cortisol profile [9]

(iii) There is a time-varying cortisol demand $D(t)$ that should be satisfied throughout the day, which is a function of the circadian rhythm [9].

(iv) The input $u(t)$ is non-negative since it is a hormone secretory event (see Fig. 2).

In view of Assumption 1, we propose the following model to control the secretion of cortisol:

$$\frac{dx_1(t)}{dt} = -\lambda x_1(t) + u(t), \quad (1)$$

$$\frac{dx_2(t)}{dt} = \lambda x_1(t) - \gamma x_2(t), \quad (2)$$

where the controller $u(t)$ is denoted by

$$u(t) := \sum_{k=1}^{\infty} u_k \delta(t - t_k), \quad (3)$$

and the quantities u_k and t_k ($k = 1, 2, \dots$) need to be computed such that

$$D(t) \leq x_2(t) \leq H(t), \quad \forall t \geq 0. \quad (4)$$

Equations (1) and (2) describe the adrenal and the plasma compartments, respectively (see Figs. 1 and 2). The variables $x_1(t)$ and $x_2(t)$ respectively describe the concentration of cortisol in the adrenal glands and the serum cortisol concentration at time t . Following [1, 7], we denote $\lambda > 0$ as the infusion constant governing the rate at which cortisol enters the blood from the adrenal gland, and $\gamma > 0$ as the clearance parameter describing the rate at which cortisol is cleared from the blood by the liver. In (3), $u(t)$ is an abstraction of the hormone pulses leading to cortisol secretion, where $\delta(t)$ denotes the Dirac delta-function, and u_k represents the amount of the

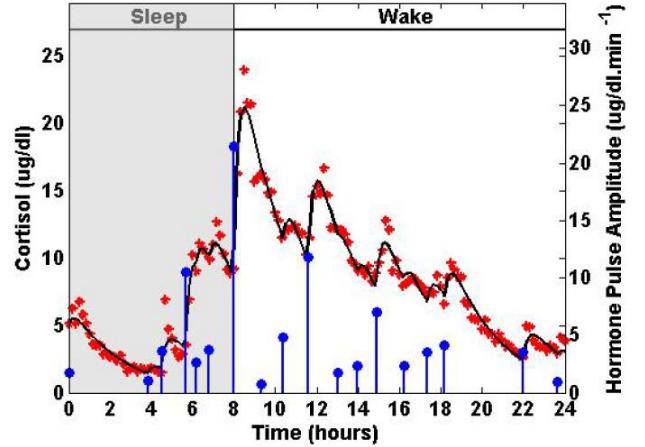


Fig. 3: Estimated Deconvolution of the Experimental Twenty-Four-Hour Cortisol Levels Using Model (1)-(2). This figure shows the measured 24-hour cortisol time series (red stars), the estimated cortisol level (black curve), the estimated pulse timings and amplitudes (blue vertical lines with dots). This figure is adapted from [7, Fig. 1].

hormone's input which is implemented into the adrenal glands at time t_k . Once the quantities t_k and u_k ($k = 1, 2, \dots$) are known, the input $u(t)$ is determined. Note that u_k is zero if a hormone pulse is not fired at time t_k . In view of the known physiology of *de novo* cortisol synthesis, which indicates that no cortisol is stored in the adrenal glands, we assume that the initial condition of the cortisol level in the adrenal glands, denoted by x_1^0 , is zero [1, 13], i.e. $x_1^0 = 0$.

Remark 1. Since $D(t)$ and $H(t)$ are, respectively, the lower and upper bounds on the cortisol level, we are only interested in secretion times t_k and inputs u_k such that $x_2(t)$ remains within these bounds (see Fig. 4).

Remark 2. In our analysis, we let the initial condition $x_2(t_0)$, denoted by x_2^0 , be any number within the upper and lower bounds, i.e., $D(t_0) < x_2^0 \leq H(t_0)$.

Remark 3. In equation (3), the quantities u_k and t_k ($k = 1, 2, \dots$) are computed such that $x_2(t)$ satisfies the constraints (4). In this paper, we develop a method through which we precisely calculate u_k and t_k step-wise forward in time. These quantities are computed based on $x_2(t_{k-1})$, $D(t)$ and $H(t)$ where $t \geq t_{k-1}$. So u_k and t_k can be viewed as functions of $x_2(t_{k-1})$, $D(t)$ and $H(t)$; see Algorithm 1 below. Therefore, one can interpret that we have provided a feedback control law. Note that for the closed-loop system, its trajectory is computed for given $x_1(t_0)$, $x_2(t_0)$, $D(t)$ and $H(t)$. This is the reason in Algorithm 1 that the quantities u_k and t_k are computed only by using $x_1(t_0)$, $x_2(t_0)$, $D(t)$ and $H(t)$.

Remark 4. Assuming that (i) the input $u(t)$ is a sum of impulses, (ii) the number of pulses is between 15 and 22 over 24 hours, and (iii) the jumps can happen in integer minutes, the model (1)-(2) has been validated by collecting blood samples

from 10 healthy women every 10 minutes for 24 hours [17]. Figure 3 shows the measured 24-hour cortisol time series (red stars), the estimated cortisol level (black curve), the estimated pulse timings and amplitudes (blue vertical lines with dots) for participant 1. For the other participants, the interested reader is referred to [7, Fig. 1].

In view of equations (1) - (4), our goal hereafter is to compute

- (a) the secretory time t_k at which $x_2(t_k) = D(t_k)$, and
- (b) the input u_k at the secretory time t_k such that $x_2(t)$ reaches the upper bound $H(t)$ from $D(t_k)$ while not cross it,

for $k > 0$ (see Fig. 4). The objective (a) gives time t_k at which $x_2(t)$ reaches the lower bound $D(t)$ from the upper bound $H(t)$. This time needs to be calculated in order to know when the next secretory event should occur. The objective (b) gives the amount of the input u_k so that after some time, $x_2(t)$ reaches the upper bound $H(t)$ from the lower bound $D(t)$. More precisely, when the input u_k is implemented into system at time t_k , there exists $\tilde{t}_k > t_k$ ($k > 0$) such that $x_2(\tilde{t}_k) = H(\tilde{t}_k)$, see Fig. 4.

Equations (1)-(3) can be represented equivalently as follows:

$$\begin{aligned} \frac{dx(t)}{dt} &= Ax(t), & t \neq t_k, \\ x(t_k^+) &= x(t_k^-) + Bu_k, & t = t_k, \end{aligned} \quad (5)$$

where $t_{k+1} > t_k$ ($\forall k \geq 0$), and

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix}, \quad A = \begin{bmatrix} -\lambda & 0 \\ \lambda & -\gamma \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}.$$

The notations $x(t_k^-)$ and $x(t_k^+)$ in (5) denote, respectively, the left- and right-hand sided limits of $x(t)$ at time t_k .

Mathematically, equations (5) are treated as follows. At time t_k , a pulse is fired, corresponding to the concentration of cortisol in the adrenal gland, which is described by the jump of its concentration, i.e. $x_1(t_k^+) = x_1(t_k^-) + u_k$, while it does not affect the serum cortisol concentration, i.e. $x_2(t_k^+) = x_2(t_k^-)$. In this paper, $x_1(t)$ is considered to be left-continuous, i.e., $x_1(t_k^-) = x_1(t_k)$.

B. The algorithm

In this subsection, we present a method through which we are able to calculate t_k and u_k *analytically*. To this end, let us use \tilde{t}_{k-1} ($k > 1$) to denote the time at which $x_2(t)$ reaches the upper bound, see Fig. 4. For the case $k = 1$, we set $\tilde{t}_0 := t_0$. Note that the inputs in our algorithm, i.e. the initial time and initial states, are explicitly given (see Algorithm 1). Our approach for the computation of t_k and u_k is presented in the following parts (a) and (b), respectively.

(a) *Calculation of t_k* : At time \tilde{t}_{k-1} we have $x_2(\tilde{t}_{k-1}) = H(\tilde{t}_{k-1})$. The goal is to calculate t_k such that $x_2(t_k) = D(t_k)$ where $t_k > \tilde{t}_{k-1}$ ($k > 0$), see Fig. 4. From (5) we know that between two consecutive pulses, equations (1)-(3) are described by the linear system

$$\frac{dx(t)}{dt} = Ax(t), \quad t_{k-1} < t < t_k,$$

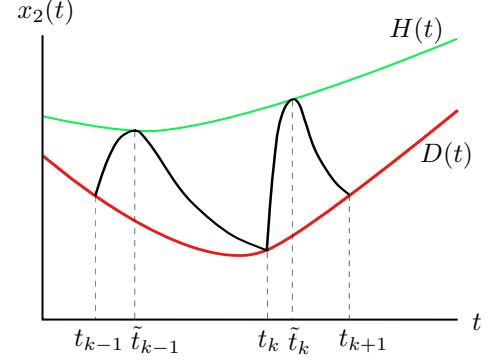


Fig. 4: Schematic representation of the trajectory $x_2(t)$ for the time interval (t_{k-1}, t_{k+1}) .

whose solution is given by

$$x(t) = e^{A(t-t_{k-1})} x(t_{k-1}^+), \quad t_{k-1} < t < t_k. \quad (6)$$

Due to the fact that $\tilde{t}_{k-1} > t_{k-1}$ ($k > 1$), using (6) with the initial time \tilde{t}_{k-1} , the trajectory $x_2(t)$ when $t \in [\tilde{t}_{k-1}, t_k]$ is given by

$$x_2^L(t) := \frac{\lambda}{\lambda - \gamma} \left(e^{-\gamma(t-\tilde{t}_{k-1})} - e^{-\lambda(t-\tilde{t}_{k-1})} \right) x_1(\tilde{t}_{k-1}) + e^{-\gamma(t-\tilde{t}_{k-1})} x_2(\tilde{t}_{k-1}), \quad (7)$$

where $x_1(\tilde{t}_{k-1})$ and $x_2(\tilde{t}_{k-1})$ are computed by (6). Since our goal is to calculate t_k such that $x_2^L(t_k) = D(t_k)$, solving

$$x_2^L(t_k) - D(t_k) = 0, \quad (8)$$

with respect to t gives t_k .

Remark 5. Due to the fact that matrix A is Hurwitz, there exists at least one solution to (8) when $t > \tilde{t}_{k-1}$.

Remark 6. In order to guarantee that $x_2^L(t)$ does not cross the lower bound $D(t)$, we only consider the minimum root of (8) which is greater than \tilde{t}_{k-1} .

In view of Remarks 5 and 6, the secretory time t_k exists and is calculated by

$$t_k = \min\{t^* \mid x_2^L(t^*) - D(t^*) = 0, t^* > \tilde{t}_{k-1}\}. \quad (9)$$

Once t_k is computed in (9), we can plot the dynamics on the interval $[\tilde{t}_{k-1}, t_k]$ by (6).

(b) *Calculation of u_k* : At time t_k , the trajectory $x_2(t)$ is at the lower bound, i.e., $x_2(t_k) = D(t_k)$, see Fig. 4. Our goal is to calculate u_k such that $x_2(t)$ reaches exactly the upper bound $H(t)$ at time $\tilde{t}_k > t_k$ ($k > 0$), while does not crossing it, see Fig. 4.

From (5), the trajectory $x_2(t)$ when $t \in [t_k, \tilde{t}_k]$ is given by

$$\begin{aligned} x_2^J(t; u_k) &:= \frac{\lambda}{\lambda - \gamma} \left(e^{-\gamma(t-t_k)} - e^{-\lambda(t-t_k)} \right) (x_1(t_k) + u_k) \\ &\quad + e^{-\gamma(t-t_k)} x_2(t_k). \end{aligned} \quad (10)$$

By implementing the input u_k at time t_k , the trajectory $x_2^J(t; u_k)$ has to reach the upper bound $H(t)$ at time \tilde{t}_k (i.e.,

$x_2^J(\tilde{t}_k; u_k) = H(\tilde{t}_k)$, while not crossing it, which implies that $x_2^J(t; u_k)$ has to be tangent to $H(t)$ at \tilde{t}_k . So solving the system of equations

$$\begin{cases} x_2^J(t; u_k) - H(t) = 0, \\ \frac{d}{dt} (x_2^J(t; u_k) - H(t)) = 0, \end{cases} \quad t > t_k, \quad (11)$$

with respect to t and u_k gives the time \tilde{t}_k and the input u_k .

Remark 7. For both $\lambda > \gamma$ and $\lambda < \gamma$, $x_2^J(t; u_k)$ is always strictly increasing with respect to u_k . Therefore, the existence of at least one pair (\tilde{t}_k, u_k) for (11) is ensured.

Remark 8. System of equations (11) may have more than one pair of solutions. We hypothesize that the controller $u(t)$ in the anterior pituitary minimizes the number of secretory events [9]. Moreover, we are interested in inputs u_k such that the trajectory $x_2(t)$ does not cross the upper bound $H(t)$ (see Remark 1). Therefore, in the case when (11) has multiple pairs of solutions, we select the pair (\tilde{t}_k, u_k) among which \tilde{t}_k is the greatest whose corresponding input u_k keeps the trajectory $x_2(t)$ within the bounds.

Once (\tilde{t}_k, u_k) are computed by (11), one can obtain the dynamics on the interval $[t_k, \tilde{t}_k]$ by the following equations:

$$\begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} = e^{A(t-t_k)} \begin{bmatrix} x_1(t_k) + u_k \\ x_2(t_k) \end{bmatrix}, \quad t_k \leq t \leq \tilde{t}_k. \quad (12)$$

Now we are ready to present our algorithm to calculate the number N , timing t_k and amplitude u_k ($k > 0$) on the time interval $[t_0, t_f]$, where t_f is our desired final time.

Algorithm 1: Calculating the number, timing and amplitude of the secretory events.

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Input :  $\lambda, \gamma, t_0, t_f, x_2^0, D(t), H(t)$ 
 $x_1(t_0) := 0$ 
 $x_2(t_0) := x_2^0$ 
 $\tilde{t}_0 := t_0$ 
 $k := 1$ 
 $N := 0$ 
repeat
  Calculate  $t_k$  from (9)
  Calculate  $x(t_k)$  from (6)
  Calculate  $(\tilde{t}_k, u_k)$  from (11) in view of Remark 8
  Calculate  $x(\tilde{t}_k)$  from (12)
   $N := k$ 
   $k := k + 1$ 
until  $\tilde{t}_k < t_f$ ;
Output:  $N, t_k, u_k, \tilde{t}_k$ 

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Assume that we have run Algorithm 1 for N iterations to compute t_k , u_k and \tilde{t}_k ($k = 1, 2, \dots, N$) on the time interval $[t_0, t_f]$. By having such information, we can obtain $x_1(t)$ and $x_2(t)$ on $[t_0, t_f]$ from the following equation

$$x(t) = e^{A(t-t_k)} (x(t_k) + B u_k), \quad t \in (t_k, t_{k+1}], \quad (13)$$

for $k = 1, 2, \dots, N$.

TABLE I: Model Parameters for Examples 1 and 2 [9]

Example	λ (min $^{-1}$)	γ (min $^{-1}$)
1	0.0585	0.0122
2	0.1248	0.0061

TABLE II: Lower Bounds on the Cortisol Level for Examples 1 and 2 [9]

Example	$D(t)$ (ug dl $^{-1}$)
1	$3.2478 - 0.7813 \sin(\frac{2\pi t}{1440}) - 2.8144 \cos(\frac{2\pi t}{1440}) - 0.2927 \sin(\frac{2\pi t}{720}) + 1.3063 \cos(\frac{2\pi t}{720})$
2	$5.5065 + 1.5544 \sin(\frac{2\pi t}{1440}) - 4.3112 \cos(\frac{2\pi t}{1440}) - 1.6355 \sin(\frac{2\pi t}{720}) - 0.9565 \cos(\frac{2\pi t}{720})$

III. RESULTS

In this section, we apply our modeling framework to two examples to show that the proposed impulsive controller generates secretory events, resembling both healthy and diseased individuals. For the first example, which corresponds to a healthy subject, the obtained secretory times and the cortisol level are in agreement with physiologically plausible profiles in healthy human data. For the second example, although the number of pulses is not within a physiologically plausible range reported for healthy subjects [1, 33], the cortisol level is still within the desired bounds. This example may refer to a case of cortisol deficiency.

For our examples, we use the parameters λ and γ , given in Table I, which respectively represent the infusion rate of cortisol from the adrenal glands, and the clearance rate of cortisol by the liver. In addition, we use the lower and upper bounds given, respectively, in Tables II and III. All information of Tables I-III are obtained from [9].

A. Example 1

Using Algorithm 1 with the parameters given in Table I, and the lower and upper bounds given respectively in Tables II and III for Example 1, we have calculated the timing and the amplitude of secretory events, and hence using (13) we have plotted the intermittent input/control in panel (a), $x_1(t)$ in panel (b), $x_2(t)$ in panel (c), and the noisy observed $x_2(t)$ in panel (d) of Fig. 5. In this example, the initial conditions are $(x_1(0), x_2(0)) = (0, H(0))$, i.e., $x_2(t)$ starts from the upper bound $H(t)$. This figure shows that the state $x_2(t)$ starts at the upper bound and then decreases until it reaches the lower bound at which point the obtained input implements a jump into the system and hence $x_2(t)$ reaches exactly the upper bound, and this process is repeated until $x_2(t)$ reaches the desired final time.

As illustrated in panel (a), there are 16 pulses over the 24-hour period which is within the physiologically plausible range of 15-22 pulses [1, 33]. Furthermore, our observation from panel (a) is that the amplitudes are lower and less frequent during the night than the day. Panel (b) clearly shows pulsatility of the state x_1 along with its jumps.

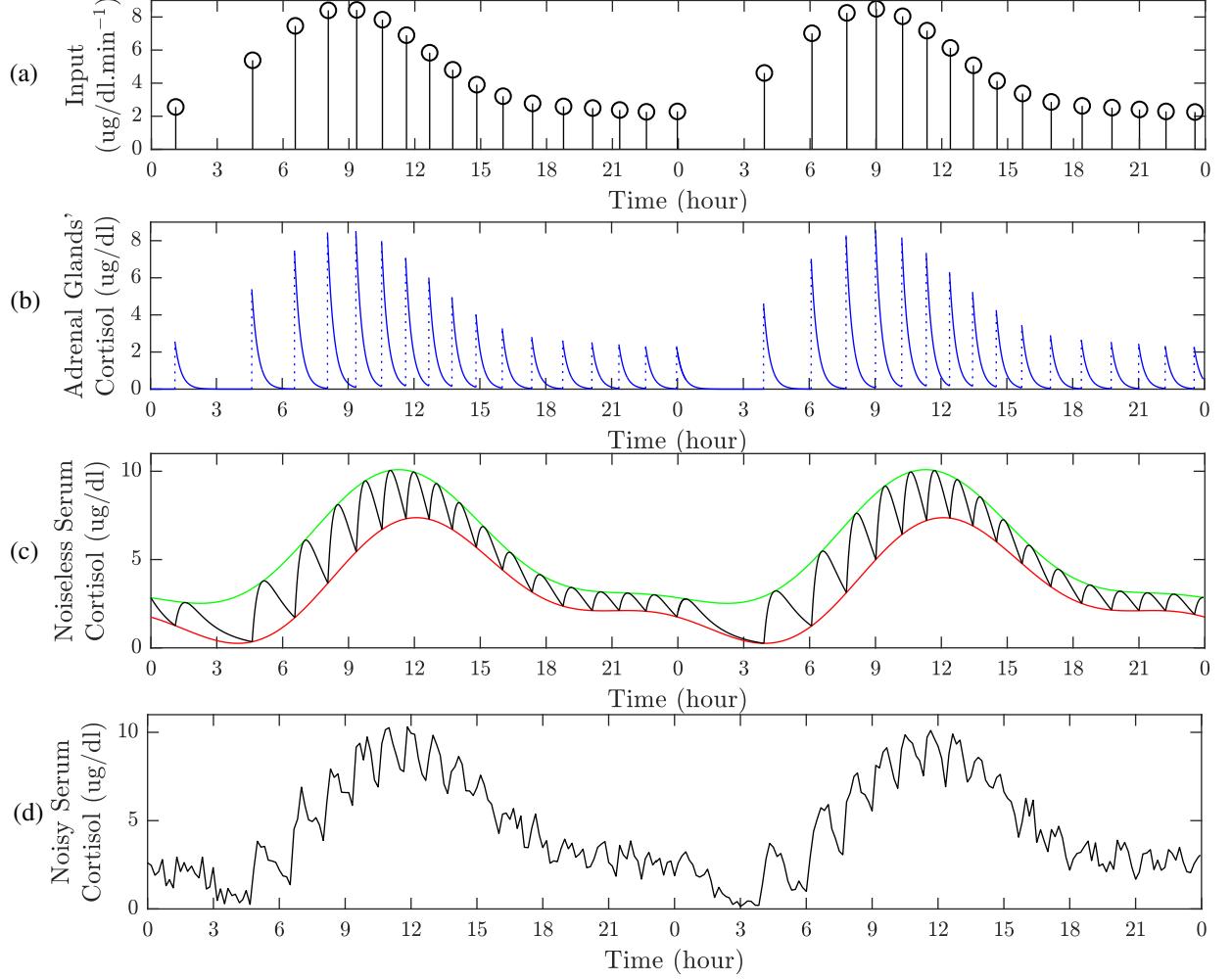


Fig. 5: Obtained cortisol level and control inputs for Example 1. We have used the parameters, and the lower and upper bounds, respectively, given in Tables I-III for Example 1. The initial conditions are $(x_1(0), x_2(0)) = (0, H(0))$, and all panels (a)-(d) are plotted over 48 h. Panel (a) displays 16 impulses over 24 h which control cortisol to remain within upper and lower bounds. In panel (b), solid curves display the state $x_1(t)$, while the dashed lines show the jumps in this state. Panel (c) shows the optimal cortisol profile (black curve), restricted by the lower bound (red curve) and the upper bound (green curve). Panel (d) illustrates the optimal cortisol profile obtained by recording the cortisol level every 10 min, and adding a zero Gaussian measurement error with a standard deviation of $\sigma = 0.45$ to each simulated data point.

TABLE III: Upper Bounds on the Cortisol Level for Examples 1 and 2 [9]

Example	$H(t)$ (ug/dl)
1	$5.3782 + 0.3939 \sin(\frac{2\pi t}{1440}) - 3.5550 \cos(\frac{2\pi t}{1440}) - 0.5492 \sin(\frac{2\pi t}{720}) + 1.0148 \cos(\frac{2\pi t}{720})$
2	$8.6051 + 3.0306 \sin(\frac{2\pi t}{1440}) - 5.0931 \cos(\frac{2\pi t}{1440}) - 1.8151 \sin(\frac{2\pi t}{720}) - 1.6570 \cos(\frac{2\pi t}{720})$

It is widely known that in healthy humans, the cortisol level has regular periodic time-varying patterns which consists of pulsatile release of secretory events with different timings and amplitudes in a regular circadian rhythm. As it is observed in panel (c), the cortisol level is pretty low during the night,

while it increases around 5 AM and reaches its higher amplitude around 12 PM. Afterwards, it decreases slowly until the midnight. This example indicates that the mathematical model (1)-(4) can describe the pulsatile cortisol secretion that have physiologically plausible profiles similar to those observed in healthy human data.

Similar to measurement noise and sampling interval of cortisol data in human subjects [7], we have recorded the cortisol level every 10 minutes, added a zero mean Gaussian measurement error with a standard deviation of $\sigma = 0.45$ to each simulated data point, and hence plotted panel (d) in Fig. 5 which resembles cortisol human data illustrated in [7].

B. Example 2

For this example, the upper and lower bounds as well as the system parameters γ and λ are different from the corresponding ones in example 1 (see Tables I-III). Using

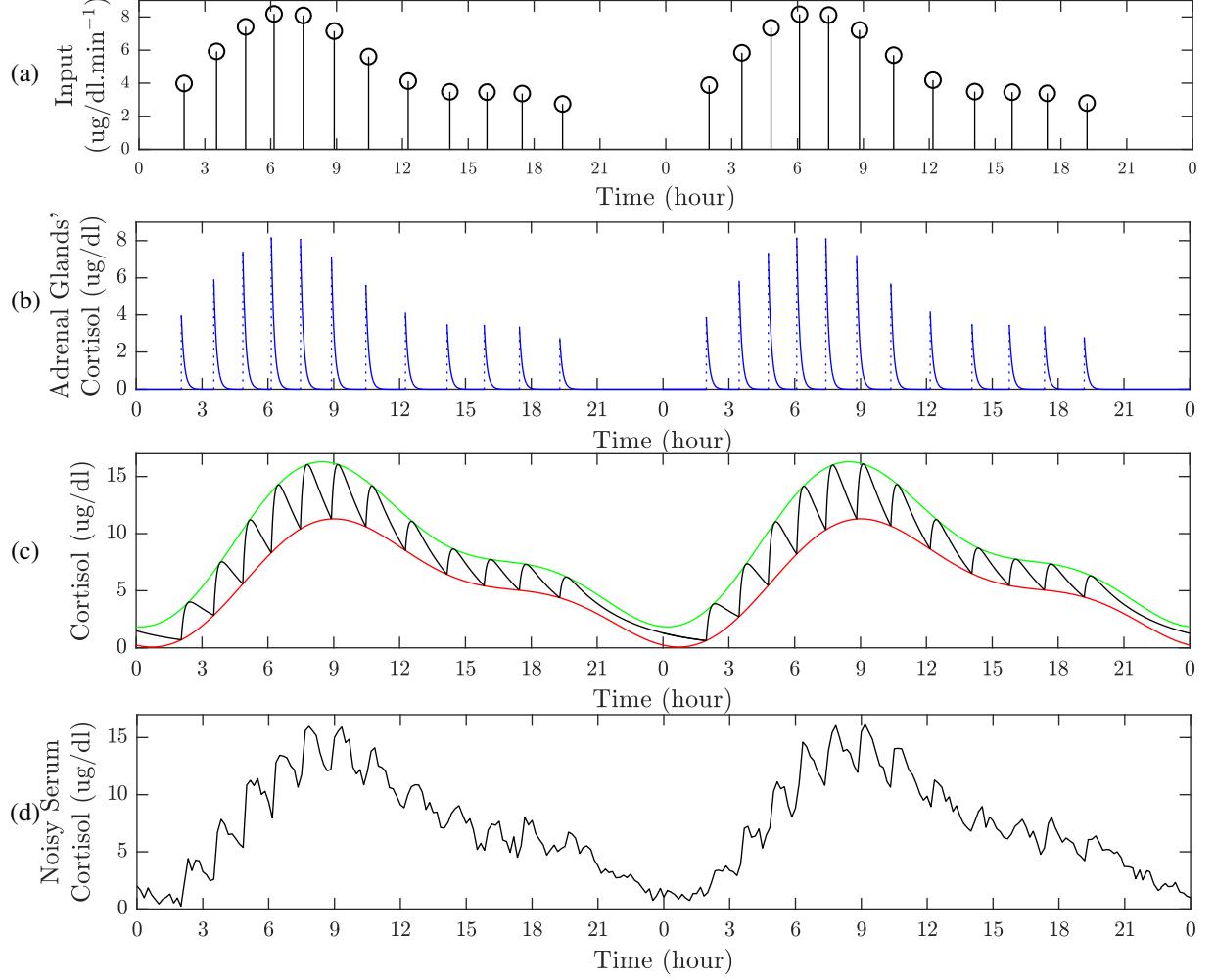


Fig. 6: Obtained cortisol level and control inputs for Example 2. We have used the parameters, and the lower and upper bounds, respectively, given in Tables I-III for Example 2. The initial conditions are $(x_1(0), x_2(0)) = (0, 1.5)$, and all panels (a)-(d) are plotted over 48 h. Panel (a) displays 12 impulses over 24 h which control cortisol to remain within upper and lower bounds. In panel (b), solid curves display the state $x_1(t)$, while the dashed lines show the jumps in this state. Panel (c) shows the optimal cortisol profile (black curve), restricted by the lower bound (red curve) and the upper bound (green curve). Panel (d) illustrates the optimal cortisol profile obtained by recording the cortisol level every 10 min, and adding a zero Gaussian measurement error with a standard deviation of $\sigma = 0.45$ to each simulated data point.

Algorithm 1 and equation (13) with the initial conditions $(x_1(0), x_2(0)) = (0, 1.5)$ we have plotted panels (a), (b), (c), and (d) in Fig. 6 for 48 h.

Panel (a) shows that 12 pulses are fired over 24 h. Panel (b) illustrates pulsatility of $x_1(t)$ along with its jumps. Panel (c) shows that the cortisol level is low at midnight. Then it increases gradually until it reaches its higher value around 9 AM. Afterwards, it decreases slowly such that it obtains its lowest value at midnight. Observations from panel (c) demonstrate that the cortisol level and the inputs are optimal over 48 h. Although in this example the obtained impulse inputs keep the cortisol levels within the given bounds, the number of pulses are not within the physiologically range of 15-22 pulses reported for healthy subjects [1, 33]. This may indicate a case of cortisol deficiency. We have recorded the cortisol level every 10 minutes, added a zero mean Gaussian measurement error with a standard deviation of $\sigma = 0.45$ to

each simulated data point, and hence plotted panel (d) which resembles cortisol human data depicted in [7].

IV. DISCUSSION

Many dynamical processes, such as pharmacokinetics systems, optimal control problems in economics, biological phenomena involving thresholds, and bursting rhythm models in medicine and biology, are characterized by the fact that they experience a rapid change in their states at certain moments of time. In such processes there exist short-term perturbations whose duration with respect to the duration of the entire evolution is negligible [18]. Therefore, one can mathematically formulate such perturbations in the form of impulses, and then analyze the corresponding models by the tools and techniques developed for impulsive dynamical systems (see, e.g., [11, 12, 18, 39]).

It is widely known that several hormones such as cortisol, insulin, growth, and testosterone are released in pulses. Moreover, changes in the pulsatility of such hormones are related to, e.g., obesity, aging, and metabolic and psychiatric diseases [31, 40, 41]. Therefore, understanding the pulsatile secretion mechanisms and the modeling underlying such systems are of great interest.

Motivated by the applications of analyzing pulsatile release of hormones, our goal in this work has been to study the impulsive control mechanisms underlying the HPA axis. Correspondingly, we have proposed a minimal model which describes the pulsatile release of cortisol. Our model has been built on the two-compartmental stochastic differential equation model of cortisol's diurnal patterns proposed in [1]. The model is based on the first-order kinetics for cortisol infusion and clearance. Owing to the fact that ACTH is released in pulses, in our model we have postulated that the system is impulsive. We have assumed that the circadian rhythms on the cortisol level are two-harmonic time-varying functions with periods of 12 and 24 h, which are the most important periods in the cortisol release. In order to describe the pulsatile release of cortisol, in some previous works (see e.g., [1, 7, 8, 9, 19]) the process is formulated as a deterministic or stochastic model, and then the sparsity of hormone pulses are taken into account to calculate the impulse inputs (i.e., the number, timing, and amplitude of the secretory events), giving an approximation of such inputs. In sharp contrast to previous works, in this paper we have presented an impulsive differential equation model and proposed an *analytical approach* to the calculation of the impulse inputs in presence of circadian demand and holding cost constraints.

We have hypothesized in Remark 8 that human body minimizes the number of times when control is used over 24 hours for cortisol secretion. Hence, if the pulsatile control input is designed such that it takes the cortisol blood levels to the upper bound and the next pulsatile control input is not secreted until the circulatory cortisol is at the lower bound, the number of times when control is used will be minimized. So we have tried to minimize the number of times control input is used. Illustrated by two examples, we have shown that our proposed model and approach yield the optimal solution in the sense that the cortisol level, started at the upper bound, decreases until it reaches the lower bound at which point the obtained inputs exert jumps into the system and as a result, the cortisol level arrives exactly at the upper bound again; this process is repeated for the desired time.

For the examples presented in Section III, we have used the parameters, and the upper and lower bounds provided in [9]; note that such information has been identified based on cortisol measurements from healthy female subjects in [7]. In the case when no human data are available, in order to validate the model by experiments one can first calculate the infusion and clearance rates from a rat model, and also obtain the upper and lower bounds on cortisol levels from a healthy rat. Second, by making the adrenal glands of the rat dysfunctional, the rat can become Addisonian such that it cannot secret cortisol anymore. Lastly, by designing an intermittent controller using the algorithm provided in this study, one can obtain a time-

varying cortisol level which remains within the upper and lower bounds that had been found when the rat was healthy [9].

Now, we compare our model and results with those in [9]: (i) The main difference between the model presented in this paper and the one in [9] is that in the latter, the model is continuous, i.e., without explicitly assuming the system is impulsive, the goal was to obtain impulse control inputs. However, based on the physiology underlying the HPA axis, in our work we have explicitly assumed that the nature of the system is impulsive, and the goal has been to design an intermittent controller for calculating the number, timing, and amplitude of the secretory events. (ii) The optimization formulation in [9] is mainly an ℓ_0 -norm problem. Since such problems are NP-hard, an alternative approach (considering ℓ_1 -norm as a relaxation of the ℓ_0 -norm) was used to solve the problem. Next, using the iterative algorithm proposed in [2], the ℓ_1 -norm optimization problem was solved to find the impulse inputs. The iterative algorithm in [2, 9] cannot always find the exact value of the impulse inputs such that the trajectory $x_2(t)$ reaches the upper bound and can lead to finding suboptimal solutions, while Algorithm 1 can deliver the precise amount of such inputs. For instance, comparing Example 2 with the corresponding one in [9], one observes that the obtained cortisol level and inputs are improved over the whole 24 h, while the corresponding one in [9] gives better cortisol level over the first 19 h, and renders suboptimal outcomes for the last 5 h.

In this work we have presented a simple yet instructive impulsive model to describe the pulsatile cortisol release. There are some other scenarios under which the system can obtain the impulse control. In this work, we have assumed that the infusion and clearance rates are constant. However, these parameters can change after every jump, and hence the problem can be formulated as a switched system, i.e., matrix A in (5) is not fixed anymore and might vary after every jumps. Instantaneous changes in one or both of the infusion and clearance rates may lead to impulse control [9]. First, assume that the clearance rate is fixed, while the infusion rate of cortisol starts from a constant level at wake, and decreases suddenly to a new constant level. In order to compensate such a degradation, a large level of cortisol should be produced in a short time such that the desired cortisol level can be obtained [9]. Second, consider the case when the infusion rate is fixed, while the clearance rate of cortisol starts from a constant level at wake and increases instantaneously to another constant level. Then in a short time a large level of cortisol should be produced such that the desired cortisol level can be achieved [9]. Lastly, assume that both the clearance and infusion rates start from a constant level and change abruptly to different levels periodically. As a result, the overall effect on cortisol is that it gets infused to the blood more slowly, or gets cleared from the blood faster [9]. In such a case, as long as there is no upper bound on control variable, the impulse control can be obtained. For an example with a time-varying rate which obtains the impulse control, the interested reader is referred to [23], where the “maximum principle” is used to find the optimal solution. Another possibility for obtaining the impulse control for neurohormone systems is to

explicitly assume that the system is impulsive, and the timing and amplitude of the secretory events are functions of the states; such a mathematical model for testosterone regulation is presented in [3, 4, 21, 28].

In this work, as a prototype, we have mainly focused on the HPA axis and proposed a physiological plausible model for cortisol secretion in the pituitary-adrenal system. As the control mechanism of the pulsatile feedback in cortisol is similar to the other neuroendocrine hormones such as gonadal hormone, insulin hormone and thyroid hormone [15, 16, 21, 26, 28, 29], a similar approach can be taken to study the pulsatile release of some other neuroendocrine hormones. Since pulsatile secretion is considerably different from basal (continuous) secretion, and some hormonal disorders are associated with hormone pulsatility, one can obtain insight into some hormonal disorders and pathological neuroendocrine states through mathematical models. For instance, one of the disorders which is caused by the adrenal deficiency is Addison's disease. A patient suffering from this disease takes cortisone one or twice a day in order to control their cortisol deficiency which does not seem optimal, because there are 15–22 secretory events in a healthy subject over 24 h. Using the methods presented in this study, it is possible to personalize the medications and use an impulsive controller to control the cortisol levels optimally.

V. CONCLUSION

In this work, we have developed a model of cortisol's diurnal patterns by taking the release of cortisol as a part of an impulsive control feedback system as opposed to a continuous one. Further, by maintaining the blood cortisol levels within a specific circadian range, we have established an analytical approach along with an algorithm to identify the number, timing, and amplitude of secretory events. Employing our approach to two examples, we have shown that the obtained cortisol levels are in line with the known physiology of cortisol secretion.

Inspired by the intermittent controller proposed in this study, one can design such controllers as opposed to continuous ones to improve the battery life of the brain implant in brain-machine interface design, and reduce the number of surgeries required for changing the battery of the implant controller [9]. In addition, this type of bio-inspired pulse controller can potentially be used to control major depression, addiction, and post-traumatic stress disorder. We emphasize that the potential applications of the intermittent controllers go beyond the neuroendocrine and mental disorders presented here, and potentially can be used for some other disorders which arise in neuroscience.

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