# Characterizing Alterations in Cortisol Secretion During Cardiac Surgery

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***Abstract*— Cortisol is a neuroendocrine hormone of the hypothalamus-pituitary-adrenal (HPA) axis secreted from adrenal glands in response to stimulation by adrenocorticotropic hormone (ACTH) from the anterior pituitary and corticotropin releasing hormone (CRH) from the hypothalamus. Cortisol has multiple functionalities in maintaining bodily homeostasis - including anti-inflammatory influences - through its diurnal secretion pattern (which has been studied extensively); its secretion is also increased in response to major traumatic events such as surgery. Due to the adverse health consequences of an abnormal immune response, it is crucial to understand the effect of cortisol in modulating inflammation. To address this physiological issue, we characterize the secretion of cortisol using a high temporal resolution dataset of ten patients undergoing coronary arterial bypass grafting (CABG) surgery, in comparison with a control group not undergoing surgery. We find that cortisol exhibits different pulsatile dynamics in those undergoing cardiac surgery compared to the control subjects. We also summarize the causality of cortisol's relationship with different cytokines (which are one type of inflammatory markers) by performing Granger causality analysis.**

***Clinical relevance*— This work documents time-varying patterns of the HPA axis hormone cortisol in the inflammatory response to cardiac surgery and may eventually help improve patients' prognosis post-surgery (or in other conditions) by enabling early detection of an abnormal cortisol or inflammatory response and enabling patient specific remedial interventions.**

## I. INTRODUCTION

Cortisol, a hormone of the hypothalamus-pituitary-adrenal (HPA) axis, is important in many areas of physiology and pathophysiology [1]. Its pulsatile secretion from the adrenal glands is induced in response to the circulating adrenocorticotropic hormone (ACTH) released by the anterior pituitary gland, which in turn is stimulated by corticotropin releasing hormone (CRH) released from the hypothalamus into the anterior pituitary. HPA hormones interact through a sequence of cascaded feedback interactions resulting in downregulation of precursor hormones by cortisol [2]. Such feedback relationships have been recently exploited to deconvolve the underlying pulsatile signaling that result in observed cortisol levels [3]–[5].

Cortisol levels in healthy individuals show a circadian rhythm that includes 15-22 secretory pulses during a 24-hour period. Cortisol secretion is also altered by multiple factors, including stress, consumption of coffee and alcohol, and altered sleep. Abnormal cortisol secretion is associated with diseases such as hypercortisolism, chronic fatigue syndrome, fibromyalgia syndrome and Addison's disease [6]–[8]. Cortisol is also involved in metabolism through interactions with other hormones such as leptin, prolactin, growth hormone, and thyroid hormones [9], [10]; it is a crucial mediator of the human inflammatory response [11]. During challenges that elicit a systemic inflammation response, specific kinds of signaling proteins called cytokines are produced; they signal the HPA axis to stimulate the production of cortisol, which in turn downregulates the cytokines through its negative feedback interaction [11], [12]. During cardiac surgery, the observed plasma cortisol levels are many times higher than during normal healthy functioning [13] and four cytokines (interleukins IL6, IL8 and IL10) and tumor necrosis factor (TNF$\alpha$) have a major influence on the progress of the inflammatory response, and the patient's prognosis [14]. Many factors induce cytokine production including tissue injury from surgery, the interaction of blood with extracorporeal mechanical surfaces, altered plasma cation concentrations, reperfusion ischemia, the stress experienced by the patient, and medication administered to reduce both the pain and the intensity of the inflammation response [13], [15], [16]. An uncontrolled inflammatory response has the potential to cause a deterioration of patient health though sepsis, shock, organ failure and may ultimately cause death [14], [17]. Efforts to modulate the inflammatory reaction has led to the development of many corticosteroidal drugs to treat immune-related conditions [18].

The exact nature of pulsatile cortisol secretion during health and disease has been studied using many methods [19]–[23]. The development of sparse deconvolution algorithms has enabled detection of underlying secretory pulses in the production of cortisol and other physiological signals [6], [7], [10], [19] and has enabled mathematical investigation of its interactions with other hormones, such as leptin and growth hormone [3], [24]–[26]. In this work,

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we seek to characterize the pulsatile production of cortisol in patients undergoing cardiac surgery, as a first step to better understand the physiology and design countermeasures to improve medical outcomes for patients.

### A. Dataset

We use data from the original, published clinical study of ten male patients undergoing coronary arterial bypass grafting (CABG) surgery [15]. The patients (aged 57-75 years, averaging 65 $\pm$ 6.2) had elective surgery with median sternotomy with or without cardiopulmonary bypass (five each). For all the patients, surgery was scheduled at 08:00 AM and their blood was collected for later assay every ten minutes via in-situ vascular catheters for twelve hours with first sample times between 8.15 AM - 9:10 AM.

The data included plasma levels of ACTH, cortisol, and cytokines (e.g., IL1$\alpha$, IL2, IL4, IL6, IL8, IL10 and TNF$\alpha$) from blood sampling performed at ten-minute sampling intervals for twelve hours. For more details on the experiment and data collection, including the chemical assay analysis procedures to obtain the final cortisol levels, we refer the reader to [15]. The data of the control group comprising three individuals not undergoing surgery used in [15] is directly from an earlier study of healthy males [13], [27]; their eligibility included no history of trans-meridian travel or usage of glucocorticoidal substances. Blood was collected (for later plasma cortisol assay) every ten minutes for 24 hours, during which they were provided with three meals at 08:00 AM, 12.30 PM and 5:30 PM, and had the lights turned off according to their regular daily routine, between 10:00 PM and 12:00 AM. The data of patients undergoing surgery is over a duration of twelve hours, while that of control subjects is over 24 hours; we therefore analyzed the latter dataset only for data starting from 9:10 AM $\pm$ 5 minutes for 9 hours and 50 minutes, the longest overlapping time window between patients and the control group. We note that the surgery onset time for two patients at 8:58 AM preceded this analysis period.

## II. MODEL

In our work, we perform the modeling, deconvolution and sparse pulsatile recovery of cortisol separately. At this level, we seek to infer the stimulating pulses culminated from the direct stimulation of the HPA axis by cytokines, as well as the result of any medication. This model is similar to prior work [10], and although minimal in its description (as it does not account for other feedback pathways including direct interactions with other hormones, cytokines and medications), it helps infer the underlying secretory pulses that cause the observed cortisol levels. This is intended as a first step analysis with which to determine the timing, amplitude and number of each stimulus, and determine the causal interactions between other inflammatory markers and HPA axis hormones.

We use the following second order ordinary differential equation model to describe the cortisol *de novo* secretion process during surgery, as in earlier work [6]:

$$\dot{x}_1(t) = -\theta_1 x_1(t) + u(t) \tag{1}$$

$$\dot{x}_2(t) = \theta_1 x_1(t) - \theta_2 x_2(t) \tag{2}$$

$$y(t_i) = x_2(t_i) + \eta_{t_i} \tag{3}$$

where $x_1(t)$ is the cortisol produced in the adrenal glands, $x_2(t)$ is the serum cortisol level infused from the adrenal glands into the serum, $u(t) = \sum_{i=1}^{N} q_i \delta(t - \tau_i)$ is the train of underlying hormone secretory stimuli that result in cortisol production in the adrenal gland, with $q_i$, $\tau_i$ and $N$ denoting respectively the amplitude, timing and total number of the neural pulses. Here, $N = 720$, since we represent cortisol with a one-minute time resolution. $\theta_1$ and $\theta_2$ refer to the rate of infusion of the cortisol produced in the adrenal gland into serum, and the clearance rate from the serum, respectively. The use of the rate parameters affords a time-scale separation in our model accounting for the varying rates of cortisol production in the adrenal gland and its subsequent infusion into the blood, and its clearance from the body. The measurements every ten minutes are represented in equation (3). The sampled plasma level of cortisol is due to the time-varying cortisol production in the adrenal gland infused into the plasma and is subject to a measurement noise $\eta(t_i)$. Although earlier work [13] has hypothesized a potential basal secretion associated with the immune challenge to account for the increased cortisol secretion, we do not incorporate it explicitly in our model. We assume that each measurement is subject to an additive noise, modeled by an independent, Gaussian distributed random variable.

Given that the dataset reports the measured cortisol levels with ten-minute sampling intervals, and we require our model to perform sparse recovery of the neural pulses at a one-minute sampling rate, we solve the system of equations (1)-(2) and obtain the measurements at the 10-minute sampling rate. Thus, the deconvolution algorithm serves two purposes: recovery of the underlying secretory pulses, and reconstruction of the smoothed cortisol levels at a higher sampling frequency than afforded by the measurements. This is especially crucial since the ability to infer the transient temporal dynamics of the inflammatory response decreases with larger sampling intervals [28].

The measurements at various time instants can be aggregated in the following expression as in [3], which describes the influence of the initial condition $X_d[0] = [0\ y(t_0)]^T$, the underlying pulses $\mathbf{u}$ and the measurement noise $\eta$:

$$\mathbf{y} = \mathbf{F}_\theta X_d[0] + \mathbf{D}_\theta \mathbf{u} + \eta \tag{4}$$

### A. Deconvolution

In order to recover the underlying pulses and reconstruct the cortisol signal at a higher time resolution than that afforded by the measurement sampling interval, we formulate a numerical optimization problem that seeks to minimize the cost [3], [25]:

$$\text{minimize } \frac{1}{2}||\mathbf{y} - \mathbf{F}_\theta X_d[0] - \mathbf{D}_\theta \mathbf{u}||_2^2 \tag{5}$$

TABLE I: Infusion rate ($\theta_1$), clearance rate ($\theta_2$), number of non-zero elements, i.e., number of pulsatile secretory events ($||\mathbf{u}||_0$), sum of absolute values of the pulse amplitudes ($||\mathbf{u}||_1$) and energy of the pulsatile secretory events ($||\mathbf{u}||_2$) in patients and control subjects, and multiple correlation coefficient ($R^2$).

| **Subject No.** | **Subject Type** | $\theta_1$ ($\text{min}^{-1}$) | $\theta_2$ ($\text{min}^{-1}$) | $\|\|\mathbf{u}\|\|_0$ (Number) | $\|\|\mathbf{u}\|\|_1$ ($10^4$ nM.$\text{min}^{-1}$) | $\|\|\mathbf{u}\|\|_2$ ($10^4$ nM.$\text{min}^{-1}$) | $R^2$ |
|---|---|---|---|---|---|---|---|
| 1 | Patient | 0.06 | 0.014 | 12 | 0.42 | 0.14 | 0.94 |
| 2 | Patient | 0.13 | 0.006 | 10 | 0.25 | 0.08 | 0.99 |
| 3 | Patient | 0.03 | 0.008 | 7 | 0.30 | 0.12 | 0.99 |
| 4 | Patient | 0.11 | 0.010 | 11 | 0.26 | 0.09 | 0.96 |
| 5 | Patient | 0.10 | 0.005 | 8 | 0.22 | 0.08 | 0.98 |
| 6 | Patient | 0.14 | 0.010 | 8 | 0.24 | 0.09 | 0.96 |
| 7 | Patient | 0.03 | 0.009 | 6 | 0.34 | 0.16 | 0.97 |
| 8 | Patient | 0.11 | 0.007 | 10 | 0.27 | 0.10 | 0.99 |
| 9 | Patient | 0.12 | 0.003 | 10 | 0.18 | 0.06 | 0.97 |
| 10 | Patient | 0.05 | 0.011 | 10 | 0.45 | 0.16 | 0.99 |
| *Median* | *Patients* | *0.10* | *0.008* | *10* | *0.27* | *0.094* | *0.98* |
| *Std. Dev.* | *Patients* | *0.04* | *0.003* | *1.9* | *0.10* | *0.03* | *0.02* |
| 11 | Control | 0.10 | 0.014 | 9 | 0.18 | 0.06 | 0.78 |
| 12 | Control | 0.17 | 0.01 | 7 | 0.11 | 0.05 | 0.95 |
| 13 | Control | 0.15 | 0.009 | 6 | 0.08 | 0.035 | 0.93 |
| *Median* | *Controls* | *0.15* | *0.010* | *7* | *0.11* | *0.05* | *0.93* |
| *Std. Dev.* | *Controls* | *0.01* | *0.006* | *1.5* | *0.05* | *0.01* | *0.1* |

in order to solve for (i) the infusion and clearance rates $\theta = [\theta_1\ \theta_2]^T$ that determine $\mathbf{F}_\theta$ and $\mathbf{D}_\theta$, and (ii) underlying secretory stimuli $\mathbf{u}$. We constrain this optimization problem by specifying the maximum number of cortisol secretory pulses in a day [3]. Due to the numerical complexity of the optimization problem, we add a soft constraint on the total number of underlying secretory pulses to impose a sparsity criterion, thereby reformulating the cost to be minimized as [3]:

$$\text{minimize } J_\lambda(\theta, \mathbf{u}) = \frac{1}{2}||\mathbf{y} - \mathbf{F}_\theta X_d[0] - \mathbf{D}_\theta \mathbf{u}||_2^2 + \lambda ||\mathbf{u}||_p^p \tag{6}$$

$$\text{subject to: } \mathbf{C}\theta \leq \mathbf{b},\ \mathbf{u} \geq 0,\ 0 \leq ||\mathbf{u}_0|| \leq 11 \tag{7}$$

where $\lambda$ is a regularization parameter and $p = 0.5$ is chosen to enforce the sparsity constraint. We have imposed three constraints based on earlier work [3], [6] to ensure biological plausibility of the solution. The first, $\mathbf{C}\theta \leq \mathbf{b}$, with

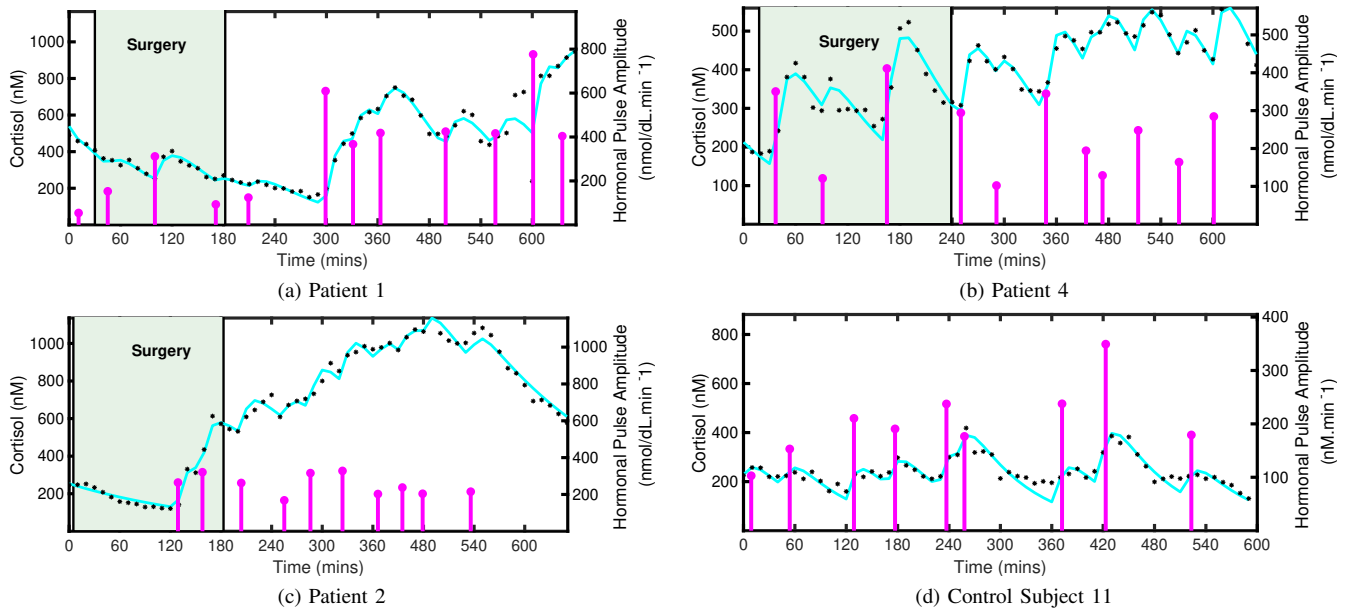
$$\mathbf{C} = \begin{bmatrix} -1 & 4 \\ -1 & 0 \\ 0 & -1 \end{bmatrix},\ \mathbf{b} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} \tag{8}$$

ensures that the infusion rate is at least four times higher than the clearance rate and that both the parameters are positive. Additional constraints on the pulse train $\mathbf{u}$ enforces non-negativity and an upper bound on the total number of the recovered secretory events.

In healthy individuals, the total number of cortisol pulses has been determined in earlier work to be 15-22 per day [2], [3]. In the present case, it is unclear what the upper bound must be, under the conditions of cardiac surgery. Given the higher observed levels of cortisol in patients (in comparison to that measured in the control group) [15] and based on the maximum number of underlying secretory events inferred in healthy (female) subjects in prior studies [3], [7], the maximum number of recovered pulses is chosen to be 15 pulses over the 12-hour sampling period of data collection. Prior work has suggested that the number of underlying pulses in patients undergoing surgery is lower [13], even if overall levels of cortisol are higher, and we expect our sparse deconvolution algorithm to resolve this. We initialize the rate parameters by first sampling a uniform random variable $w \in [10^{-4},\ 0.8]$ and then setting $[\theta_1\ \theta_2] = [w\ w/4]$. We perform a spline interpolation to determine the value of any missing data points in the dataset. The optimization problem is solved using a coordinate descent approach involving the FOCUSS+ and GCV algorithms [3], [29], [30] to obtain the infusion and clearance rates, as well as to recover the underlying secretory pulses. This step is run for 200 iterations to ensure robustness of solutions, and the optimal set of underlying secretory pulses and parameters are finally obtained from this set. A more detailed discussion of this algorithm can be found in [3], [25]. Since the dataset reports the unit of cortisol levels in $nM$, we divided the cortisol levels by 10 to recover the underlying secretory pulses. After performing deconvolution, we converted the cortisol levels and secretory amplitudes back to nM and nM.$\text{min}^{-1}$, respectively. This step is not required when using the original algorithm for cortisol data in $\mu$g/dl unit [3].

### *B. Granger causality analysis between cortisol and cytokines*

We perform Granger causality test [31] to understand the causal interactions between cortisol and each of the cytokines from [15], for the 12 hour data collection period. We determine whether the linear relationship given below between the two physiological signals under consideration,




(a) Patient 1 (b) Patient 4

(c) Patient 2 (d) Control Subject 11

Fig. 1: Cortisol deconvolution results for three patients [panels (a), (b), (c)] undergoing coronary arterial bypass grafting (CABG) surgery and a control subject [panel (d)]. Figure depicts the cortisol levels measured every ten minutes (black *), cortisol levels reconstructed every minute using our analysis (blue line) and the calculated timing and amplitude of underlying secretory pulses (pink bars) for (a) patient 1 (b) patient 4 (c) patient 2 (d) control subject 11. The duration of surgery for patients is annotated in green. The data for patients starts within a ten minute interval centered at 9:10 AM $\pm$ 5 minutes and data for the control group starts at 9:10 AM. Note the different y-axis scales for each panel, with higher overall and maximal values for the patients compared with the control.

say $y_A$ and $y_B$, is valid with statistical significance:

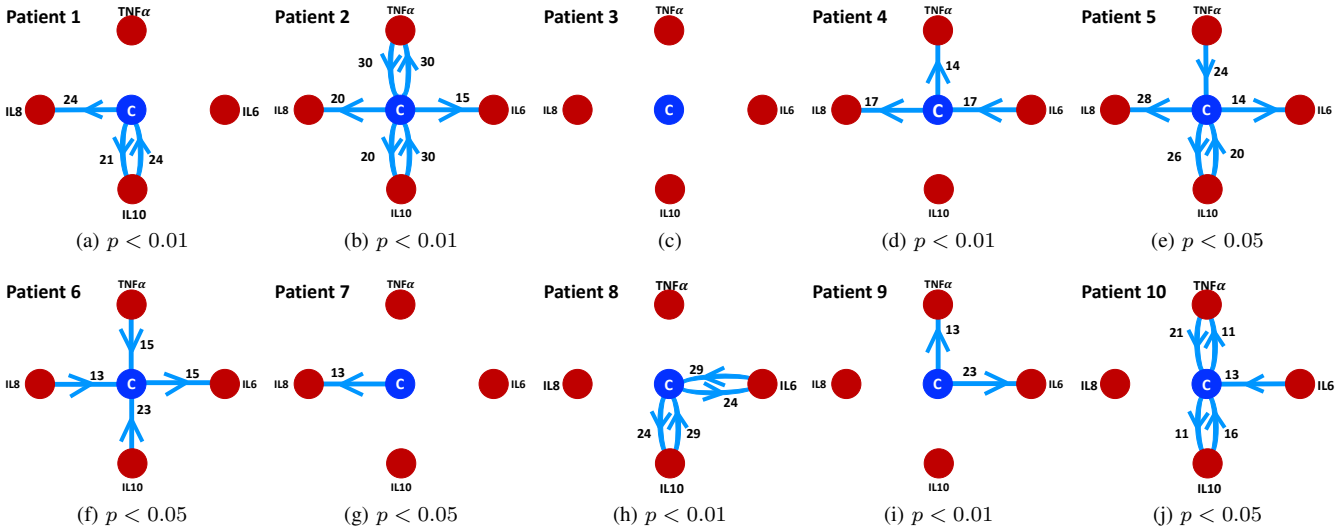
$$y_A(t_k) = \sum_{j=1}^{N_{A,A}} \alpha_{A,j} y_A(t_k - j) + \sum_{j=1}^{N_{A,B}} \beta_{A,j} y_B(t_k - j) + \epsilon(t_k) \tag{9}$$

Here, $y_A$ at time instant $t_k$ is represented as a linear combination of its past values, the past values of $y_B$, with $N_{A,A}$ and $N_{A,B}$ denoting the lag parameters and $\epsilon(t_k)$ representing an error term. If at least one of the coefficients $\beta_{A,j}$ is non-zero with statistical significance, then we say that $y_B$ causes $y_A$. In our analysis, we consider the causality relationships between the reconstructed cortisol levels with those of cytokines obtained from [15]. This is since, (i) raw measurements are subject to stochasticity from imprecise measurements, (ii) the dataset contains only a few measurements to allow for direct causality analysis based on them, and (iii) the hormone reconstruction using our methods retain physiological plausibility even in this simple setting. We set the range of $N_{A,A}$ and $N_{A,B}$ to be a maximum of thirty minutes and calculate the lag parameters' exact value determined by minimization of the Akaike Information Criterion (AIC) by using the MATLAB function *gctest* [32]. This gives us an optimal model that minimizes the residual error over the lag parameters. Then, *gctest* is employed to solve the hypothesis testing problem.

## III. RESULTS AND DISCUSSION

We performed deconvolution for all ten patients undergoing surgery (numbered 1-10) for the 12 hour duration and for the three control subjects (numbered 11-13) over 24 hours of data collection, with the maximum number of underlying secretory events set to 15 and 22 respectively for patients and controls. We perform our analysis over a 9 hour 50 minute time window starting from 9:10 AM $\pm$ 5 minutes, the longest overlapping time window across all patients and control subjects. The infusion and clearance rate parameters as well as the number of recovered underlying secretory pulses over this time period are shown in Table I, and representative results of the cortisol deconvolution and the recovered underlying secretory pulses are presented in Figure 1. The number of recovered secretory pulses for patients ranges between 7-12 with a median value of 10 while the control subjects all have this number less than 10. The levels of cortisol in patients are comparatively higher, and continue to rise in the hours after surgery. For the control subjects, we observe a median value of 7 underlying secretory pulses for the same time duration, with lower levels of cortisol.

For patients undergoing cardiac surgery, the median infusion and clearance parameters were lower than for controls (Table I). In case of patient 1, we observe large amplitude secretory pulses (pink bars) at the corresponding rise times of the cortisol levels (black dots representing measured data, blue line representing the reconstructed cortisol levels at one-minute sampling rate), followed by some smaller pulses




(a) $p < 0.01$ (b) $p < 0.01$ (c) (d) $p < 0.01$ (e) $p < 0.05$

(f) $p < 0.05$ (g) $p < 0.05$ (h) $p < 0.01$ (i) $p < 0.01$ (j) $p < 0.05$

Fig. 2: Causality analysis for deconvolved cortisol and cytokines (inflammatory markers). Each panel depicts the statistically significant causal relationships between cortisol (blue node) and different cytokines (red nodes) obtained from performing Granger causality test as a directed graph with edge weights portraying the optimal lag parameter in minutes and arrows indicating directionality of this relationship. The four inflammatory cytokines tested are proinflammatory interleukins (IL6, IL8) and TNF$\alpha$, and anti-inflammatory interleukin (IL10). Range of significance values of recovered relationships are indicated for each patient.

that result in slower cortisol clearance. In patient 4, the secretory pulse amplitudes were smaller in comparison to patient 1, which eventually decreased towards the end of the analysis period. For patient 2, we noticed secretory pulses with smaller inter-arrival times and similar amplitudes in comparison to the control subject. We find that the norms of the secretory pulses, 0-norm ($||u||_0$, indicating the number of secretory events), 1-norm ($||u||_1$ indicating the sum of underlying secretory event amplitudes) and 2-norm ($||u||_2$, indicating the *energy* of the signal) also indicate comparatively higher cortisol secretory burst amplitudes for patients undergoing surgery compared to control subjects. The median 1-norm and 2-norm of the secretory pulses are at least doubled for patients (Table I).

The results of Granger causality test between the reconstructed cortisol and the inflammatory cytokine levels from [15] are shown in Figure 2; the causality relationship is shown by means of a directed graph, and the lag parameter (in minutes) in the aforementioned expression is represented as edge weights in Figure 2. Here, we consider the proinflammatory interleukins (IL6, IL8) and TNF $\alpha$ and the anti-inflammatory interleukin (IL10). All lag parameters were below 30 except for the IL10-cortisol and TNF$\alpha$-cortisol relationships for patient 2. Six patients show a statistically significant causal relationship between cortisol and IL10, both of which serve to diminish the relative abundance of proinflammatory cytokines, although the directionality of this relationship is not uniform across these subjects. Seven patients show a direct relationship with IL6, six with IL8 and six with TNF$\alpha$. Patient 3 showed no causal relationships in our analysis. Patients 2, 5 and 6 showed a direct relationship between cortisol and all the cytokines. Bidirectional relationships between IL10 and cortisol were recovered for five subjects, between TNF$\alpha$ and cortisol for two subjects and between IL6 and cortisol for one subject, indicating the presence of feedback relationships.

## IV. CONCLUSIONS AND FUTURE WORK

In this work, we have quantified cortisol patterns over a near-ten-hour period for ten patients undergoing cardiac surgery and three controls. We observe using our minimal model that patients exhibited altered cortisol secretion due to surgery, with higher amplitudes of the underlying secretory pulses. After characterizing the observed cortisol levels in [15] using secretory events recovered in our deconvolution analysis, we also investigated the causality of cortisol interactions with the inflammatory cytokines. We plan to incorporate the dynamics of ACTH to perform concurrent deconvolution so that the response of the HPA axis, and sensitivity of cortisol production to secreted ACTH may shed light on the mediatory role played by the HPA axis hormones in the observed inflammatory response. Further work should also quantify the relationship between these results and clinical outcomes.

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