A Data-Driven Model for Optimizing Therapy Duration for Septic Patients

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Abstract

Sepsis is a potentially fatal whole-body inflammation caused by severe infection. Blood purification therapy, known as hemoadsorption (HA), was found to be beneficial in animal models of sepsis. However, HA administration is a challenging problem since late and inadequate therapy results in high mortality rate. In this study we propose a data-driven model predictive control to find a suitable duration of the HA therapy application. In our experiments of 5000 virtual patients, for about 41% of the cured patients the proposed data-driven model predictive control was likely to cure using shorter therapy and for some patients it only required 2 hour therapy instead of 12 hours, previously shown to be the optimal continuous HA application. Moreover, the proposed method applies the therapy in non-continuous fashion, which results in saving 14% more patients than the standard continuous therapy, as evident by our experiments in a population of 5000 virtual patients.

1 Introduction

Sepsis is a potentially fatal whole-body inflammation caused by severe infection. It is considered as one of the main death causes in US [1]. Prompt diagnosis is crucial to the management of sepsis, as initiation of early-goal-directed therapy is key to reducing mortality [2]. Late and inadequate therapy results in a mortality rate of 30-35%, and for every hour that the administration of appropriate therapy is delayed, the mortality rate increases by about 7% [3]. Therefore, developing models for providing early and adequate therapy for inflammation treatments is crucial for practicians.

It has been shown that one form of extracorporeal blood purification, known as hemoadsorption (HA), is beneficial in animal models of sepsis, including endotoxic shock [4] and cecal ligation and puncture (CLP) [5]. Published results provide evidence that HA therapy helps cure septic patients by eliminating: activated neutrophils (Na), pro-inflammatory mediators (PI), and anti-inflammatory mediators (AI) during the treatment period (from 18 hours to 22 hours after CLP) [6].

Recently, it has been shown that application of HA therapy for 12 continuous hours at the 18th hour after CLP results in saving more patients' lives than the application of 4 continuous hours therapy [7]. We hypothesize that although the application of 12 continuous hours is effective, the application of the therapy in non-continuous fashion might be even more effective than the application of continuous therapy.

One of the methods that could be used to find the optimal therapy is model predictive control (MPC). MPC uses an explicit process model (based on domain knowledge) to predict the future patient's response during chosen period, known as prediction horizon. The MPC algorithm optimizes a function in the prediction horizon to obtain an optimal sequence of future control (treatment).

As noted at [9], "*The quality of MPC directly depends on the ability of the predictive model to accurately predict the future states.*". Using domain knowledge-based model (like ordinary differential equations) to predict patient's response often fails when dealing with complex biological systems like sepsis. Contrarily, data-driven MPC (DDMPC) utilizes data driven predictive methods to predict the future patient's response. Data driven predictive methods are used to learn the patients' response from the historical data without any knowledge about the underlying dynamical system. DDMPC has been successfully applied in several studies, including an exploration of optimal dosing of anticancer agents [10], and defining an optimal anesthesia [11].

In this paper, we propose DDMPC to provide non-continuous application of HA therapy for septic patients. In a set of 5000 virtual non-survivor septic patients, we show the advantages of using our proposed DDMPC. Application of up to 12 non-continuous hours therapy provided by DDMPC cures 14% more patients than the application of the standard 12 continuous hours therapy, which supports our hypothesis. In addition, in our application DDMPC cures some of the patients using even less than 12 hours of non-continuous therapy.

The structure of the paper is organized as follows: Section 2 describes the data used in our study. Standard therapy (HA) is described in Section 3. MPC and DDMPC are explained in Section 4 while the evaluation and discussion of the results are provided in Section 5. Finally, the conclusion is given in Section 6.

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2 Virtual Patients

The mathematical model for inflammatory response to an infection is derived in [6]. This model defines the dynamics of concentration of 19 variables (states) among which 8 are observable (Lsel - Lselectin; HMGB1 - high-mobility group protein B-1; CRT - creatinine; ALT - alanine aminotransferase; TNFα - tumor necrosis factor-α; IL-1 - interleukin-1β; IL-6 - interleukin-6; IL-10 - interleukin-10) and 11 are hidden (CLP - cecal ligation and puncture; B - bacteria; Nt - peritoneal neutrophil; Nr - resting blood neutrophil; Np - primed blood neutrophil; Na - activated blood neutrophil; PI - systemic proinflammatory response; AI - systemic anti-inflammatory response; Ns - neutrophil sequestered in lung capillaries; Nl - lung neutrophil).

In this model, the patient is connected to the device such that the blood flows in the device. The device simulates blood purification by removing the pro- and anti-inflammatory particles from the blood as shown in Figure 1. We assume that the device has two states - ON and OFF. ON state means that the device is attached to the patient and that it cleans blood with the rate specified in [6]. OFF state means that device is detached from the patient. The ON/OFF states of the blood purification device are controllable by clinicians.

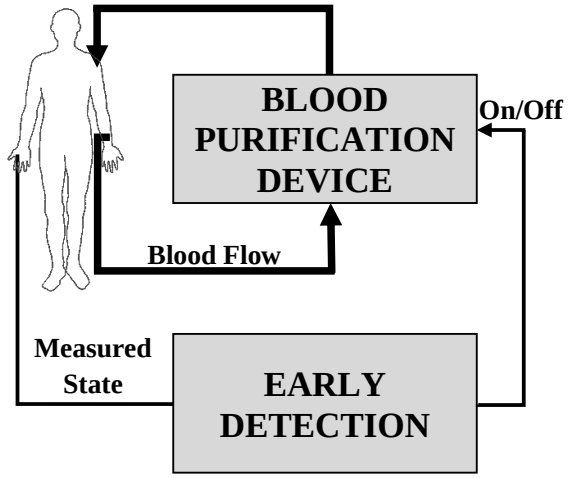

Figure 1: Schematic diagram of dialysis-like blood purification device accompanied with early detection module.

The ordinary differential equations (ODE) model is used to generate a population of virtual patients by random initialization of some parameters in ODE and by random initialization of the states' initial conditions [6]. In all of the simulations, t is an hourly step that starts from $t = 0$ when patient state and parameters are initialized. Then, patient state evolves according to ODE through the simulation time of 200 hours. According to [6], there are two possible outcomes at the end of simulation time. A patient is in the survival group if (1) the number of bacteria (B) is less than $Bmin$, which was set to $1.0e5$, and (2) the value of systemic inflammation (PI) is less than 0.5. Otherwise, a patient is in the non-survival group. Evolution of the patient to the final state can be modulated by applying the blood purification device.

2.1 Real Data To calibrate the model, real data is obtained in [6]. A set of 23 rats was used to evaluate long term (one week) survival rate. The rats were induced by sepsis using the modified cecal ligation and puncture (CLP) protocol, 25% ligated length of cecum and 20-gauge needle. Eight observable states were measured: Plasma cytokines (tumor necrosis factor (TNF), interleukin(IL)-1b, IL-6 and IL-10), Lselectin (Lsel), high mobility group box1 (HMGB1), creatinine (CRT) and alanine aminotransferase (ALT). The states are measured at 18, 22, 48, 72, 120, 144, and 168 hours after CLP. No treatment was applied to any of 23 rats. Seven rats out of these 23 survived up to 7 days, being considered as the survivor population; the remaining 16 animals died and were considered as the non-survivor population.

2.2 Generation of Virtual Patients in Accordance with Real Data We use the real data to generate virtual patients in accordance with real data [6]. The virtual patients are generated according to the following 3-step protocol:

1. The parameters of a mathematical model are randomly sampled in consistence with valid ranges described in [6].

2. For the chosen parameters, the evolution of 19-states over time is simulated and the outcome (survival or non-survival) is determined.

3. The likelihood that evolution of 8 observable states follows evolution of real data is calculated [6]. If the likelihood is high then the virtual patient has been "accepted" as valid. Otherwise, a generated patient has been rejected.

Following this protocol, we have generated a population of sham (no treatment) virtual patients. A group of 5000 virtual patients belonged to the survival population, while another group of 5000 virtual patients belonged to the non-survival population. Statistics of simulated data for eight states together with observations from real data are presented in Figure 2.

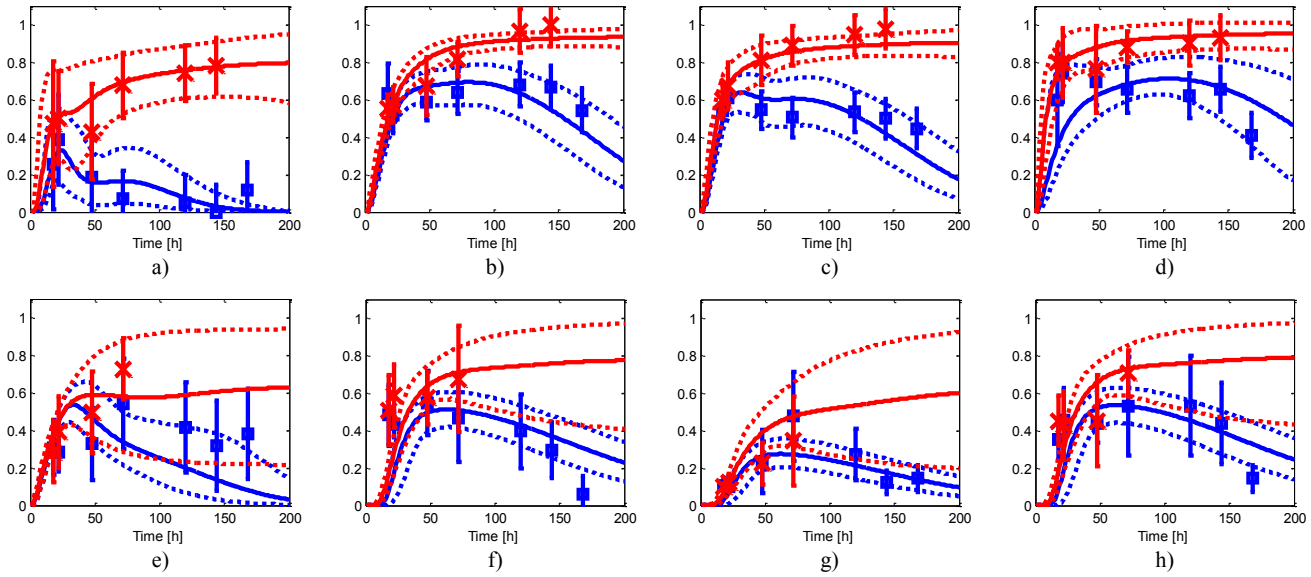

Figure 2: An agreement between simulated and real data. a) TNFα, b) IL-1, c) IL-6, d) IL-10, e) Lsel, f) HMGB1, g) CRT, h) ALT. Solid lines - mean values of simulation outputs of 5000 virtual patients in survival (blue) and non-survival (red) groups. Dotted lines - region of 95% simulation uncertainty (95% of virtual patients are within the region). Error bars - real observations from animal study experiments.

3 Realistic Standard Therapy

According to [6], the device is turned ON from 18 hours to 22 hours after CLP. Following our previous work [7, 9], we found that applying the therapy for 12 continuous hours cures more patients than applying the therapy for 4 continuous hours as shown in Figure 3.

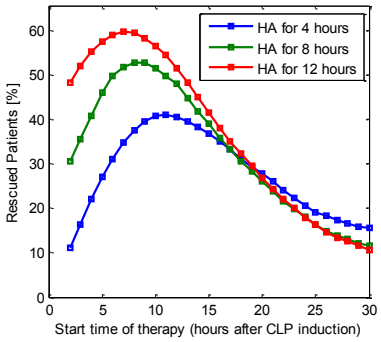

Figure 3: Efficacy of continuous blood purification therapy (percentage of rescued patients) with respect to starting time of therapy and the duration of treatment.

However, these procedures assume that the CLP-sepsis induction time is known, common in laboratory conditions but is uncommon in clinical practice. In other words, the device is turned ON at a known hour after inducing CLP-sepsis to the patients. In clinical practice the sepsis induction time is unknown. To simulate this the time when the patient visits the intensive care unit (ICU) was sampled uniformly from 5-12 hours after the sepsis induction. Then, the therapy is applied for 12 continuous hours at the 18th hour after the patient shows up in the ICU. Using the realistic scenario, the standard therapy was able to cure approximately 15% of the non-survivor patients in our experiments (Section 5).

The time when the therapy is applied is critical for the success of the therapy. In previous work [7], we have shown that using an early classification method, called Multivariate Shapelet Detection (MSD) [12], to predict the start time of the 12-hour therapy cures more patients (21%) than applying the therapy at the 18th hour from ICU admission.

Very recently, a method called Interpretable Patterns for Early Diagnosis (IPED) is proposed for early classification of multivariate time series [13]. It has been shown that the IPED method is more accurate than the MSD method. In our experiments, we have applied the IPED method on the non-survivor patients group to predict the start time to apply the 12 hour continuous therapy. Indeed, IPED cured more patients (28%) than MSD did, as shown in Table 1.

Described methods (standard therapy, MSD- , IPED-initiation based therapy) are aimed to optimize the initiation time of application of the 12 continuous hours therapy to the patients. In the current study we

	Standard	MSD	IPED
Cured Patients[%]	14.8(0.16)	21.0(12.8)	28.2(4.5)

Table 1: The mean and standard deviation (between paranthesis) of the percentage of cured patients by applying the continuous 12-hour therapy either at the 18th hour (Standard), or based on prediction of MSD or IPED, respectively. The performance is computed over 3 runs by sasmpling 30 patients for training and evaluatinng the model on the remaining 4970 patients.

hypothesize that the continuous therapy is not optimal. In other words, we allow non-continuous application of the HA therapy. To administer non-continuous HA therapy we need to build a data driven model that automatically learns when and how long the therapy should be applied to cure the patient. In the next section, we describe the proposed model that allows non-continuous therapy application.

4 Model Predictive Control (MPC)

The objective of MPC is to optimize the duration of HA sepsis therapy application aimed to cure the patient. In order to do that, we need to define a reference trajectory such that minimizing the difference between the estimated future patient state (output of predictive model) and reference trajectory increases likelihood of therapy success [9].

Since PI and B are used to quantify the state of the patient (survival versus no survival) (Section 2), they render themselves as good candidates for the optimization as reference states. However, PI and B are non-observable variables which render the whole model as useless in reality and limit its application in the clinical domain. Therefore, we inspected the training data and found that the high-mobility group protein B-1 (HMGB1) could be used as an early indicator for the therapy efficiency when it is smaller than 0.2 or it is decreasing, which is our optimization objective.

In order to generate training data for the data-driven MPC model, we have randomly sampled 30 patients for training. Then, at each time point the ordinary differential equation was used to predict the patient's response for 10 time points ahead (prediction horizon). A set of different therapy duration is optimized to find the optimal therapy that minimizes our optimization objective at the end of the prediction horizon.

Following the principles of MPC [8], we apply to the patient just the first hour of the therapy from the optimal therapy obtained by the optimization function. Then, we observe the new state and repeat the optimization procedure to obtain new more optimal therapy.

4.1 Data Driven MPC To build a data driven MPC, we do not assume any knowledge about the mathematical models used to generate the data. A model aimed to predict the future states of the patient is learned. Non-linear models need more training samples to prevent overfitting. In early-stage medical studies, often a small number of patients are involved (in our case 30 patients were used for training). Due to data limitation, we have therefore used linear regression models to predict the future states of the patients based on the current observation and the previous two observations. In particular, we have used an independent regression model for each observable variable to predict 10 time points ahead (iteratively one-step-ahead prediction).

4.1.1 Predictive Model Assume that $Y_t = [y_t^1, y_t^2, \ldots, y_t^8]$ is a vector of the 8 observable states at time t, and u_t is the control (therapy is ON or OFF) applied at time t. Then, we learn 8 independent regression models $R^j; j = \{1, 2, \ldots, 8\}$. Each model R^j predicts the j^{th} state at the next time point using the current and the previous two observations: $\hat{y}_{t+1}^j = R^j(Y_t, Y_{t-1}, Y_{t-2}, \hat{u}_t, u_{t-1}, u_{t-2})$ where $\hat{y}_{t+1}^j$ is the predicted value of the state j at time t+1 and $\hat{u}_t$ is the control suggested at time t (see next paragraph). The state at time $t+2$ is predicted as: $\hat{y}_{t+2}^j = R^j(\hat{Y}_{t+1}, Y_t, Y_{t-1}, \hat{u}_{t+1}, \hat{u}_t, u_{t-1})$ where $\hat{u}_{t+1}$ is the optimized control (the control that has been chosen using the optimization function) at time t+1. So, we use the model R^j to predict 10 time points ahead in iterative mode.

At each time point t, we applied our learned data driven MPC model to find the optimal HA therapy that should be applied at time t. Then, if the therapy is recommended ($\hat{u}_t$) by the model, we apply only one hour of therapy and then observe the patient at the next time point. We repeat that process at each time point, and no therapy is applied after the 100^{th} hour.

4.1.2 Constraints To get a fair comparison with the standard 12-hour continuous therapy, we added constraints requiring that the therapy is not applied for more than 4 continuous hours and no more than 12 hours in total during the first 100 hours. We note that the total duration of the resulted therapy application induced by our DDMPC could be less 12 hours but not more than 12 hours. Therefore, some patients might be cured using less than 12 hours of non-continuous therapy application.

5 Evaluation

We generated a population of 5000 non-survivor patients as described in Section 2. We sampled 30 pa-

tient for training DDMPC. In particular, at each time point we find the optimal therapy using the differential equations as explained in Section 4. Then, we apply only one hour therapy if the therapy is recommended. Therefore, we obtain a population of patients along with the temporal therapy provided to the patients. Finally, we trained linear regression models (one for each variable) on the data obtained by the MPC. We evaluated the DDMPC on the remaining 4970 patients. At each time point, the optimal therapy is recommended using the linear regression model (instead of differential equations) used to predict the future states of the patient. Then, we proceed by applying one hour of therapy and then observing the next state of the patient and repeating the process.

We repeated the entire process (sampling 30 patients for training data driven MPC and evaluating the model on the remaining 4970 patients) three times and reported the mean and the standard deviation of each statistic.

It has been shown in Table 1 that IPED is more accurate than three continuous methods to predict the appropriate start time of the 12-hour HA sepsis therapy application. To compare the optimal therapy provided by DDMPC with the IPED 12-hour therapy, we apply the DDMPC therapy starting from the time when the patient visits the ICU (assuming the induction time is unknown). The patient's visit time is uniformally sampled from 5-12 hours from sepsis induction (we use the same patients' visit time as the one used in evaluating the early classification methods to get fair comparisons). The results are shown in Figure 4.

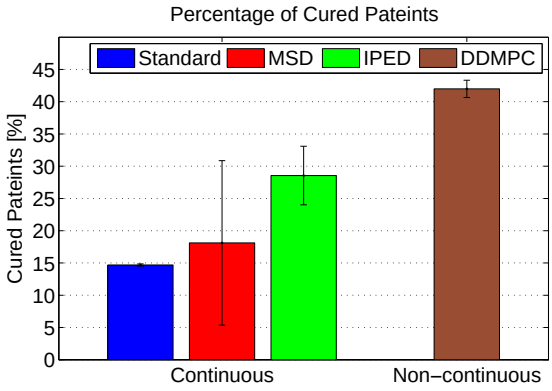

Figure 4: Percentage of cured patients when the induction time is unknwon. The 12 hours non-continuous therapy obtained by DDMPC model has cured more patients than any other 12 hours continuous therapy-based method.

DDMPC-based therapy has cured significantly more patients (42%) than any other method (standard 12-hour, MSD-inititation, IPED-initiation based 12-hour therapy). This result provides evidence that the application of non-continuous therapy (obtained by data driven MPC) is more effective than the continuous therapy.

Figure 5 shows the cumulative distribution of patients who have been cured using different therapy duration intake. It is clear from the figure that the majority of the patients were cured using 12 hour therapy and approximately half of the patients cured using less than 12 hours therapy. These results are consistent with the results shown at Figure 3.

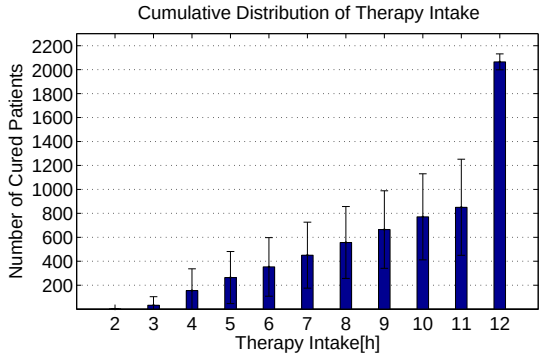

Figure 5: The cumulative distribution of therapy intake. X-axis represnts the total duration of the therapy that have been applied to the patients. Y-axis is the cumulative distribution of patients who have been cured by the therapy.

The application of non-continuous HA therapy on sepsis patients is shown at Figure 6. The figure shows the therapy application for all cured patients (∼2,100 of 5,000 patients). The majority of the therapies were applied at early stages, around hour 15-25 and in few cases additional therapy is applied later if needed (the figure is based on CLP induction time for representation simplicity). We also could see that the therapy is applied in non-continuous fashion, which resulted in more cured patients.

6 Conclusion

We proposed a data-driven model predictive control for optimizing the duration of the HA therapy provided to non-survivor virtual patients. Two benefits of using DDMPC are shown by our experiments in a population of 5,000 virtual patients. The proposed non-continuous therapy cured about 41% of the cured patients with less than 12 hours of HA administrations, and for some patients only two hours of non-continuous HA therapy were sufficient vs. alternative 12 hours of continuous application. The learned DDMPC non-continuous HA administration cured 14% (or more) more patients than any alternative continuous therapy application-based methods.

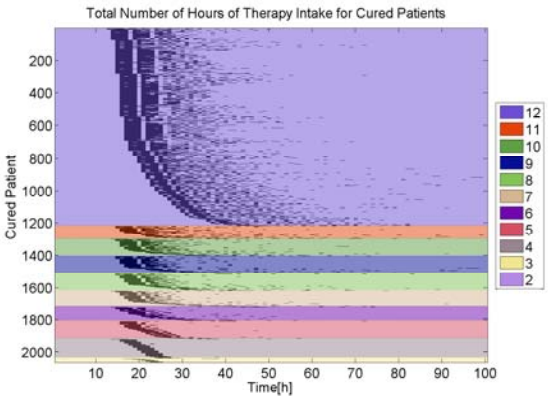

Figure 6: The continuous black horizontal line segment represents time and duration of application of continuous therapy. The majority of the therapies were applied at early stages, around hour 20 (relative to the induction time) and in few cases therapy is applied later if needed.

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