Causal Effect Estimation using LODE

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Abstract

This paper details our approach in estimating causal effects of full interventions or treatments on ICU patients with Sepsis. Sepsis is a condition that is determined using specific lab values and vitals of the patient. These are the same lab values and vitals that can be intervened on to potentially improve the patient's condition. As Sepsis affects both the treatment that can be given to improve the patient's condition, as well as the outcome (i.e. death), it is a confounder.As Sepsis is a function of the pre-outcome variables that can be intervened on, it is a functional confounder. Our goal is to estimate the effects of full interventions on a septic patient's time to death. Positivity is an assumption that is required to hold true when trying to estimate the causal effects of treatments/interventions.This assumption of positivity is violated in the case of functional confounders like Sepsis.To tackle this violation of positivity in the case of functional confounders, we follow the LODE algorithm introduced in Puli et al. (2021). We use LODE to estimate causal effects of full interventions on patients with Sepsis.We use the MIMIC-IV dataset (Johnson et al., 2021) for our experiments.

Keywords: Sepsis, Functional Confounders, Causal Effect Estimation, Positivity, LODE, MIMIC

1. Introduction

Sepsis is a life threatening condition and is one of the leading causes of death amongst ICU patients. As sepsis gets more severe, it results in septic shock, and ultimately death. There have been several formal definitions of sepsis and septic shock. We will be following the organ dysfunction based definition of Sepsis3 that was determined in Singer et al. (2016).Based on the analysis done in Johnson et al. (2018), the Sepsis3 definition seems to be the preferred choice amongst a group of different Sepsis definitions. The Sepsis3 definition can be summarised using the equation SOFA ≥ 2 where SOFA stands for the Sequential Organ Failure Assessment score. The SOFA score is computed by thresholding various lab values across 6 categories, and adding the resulting scores from each category that range from 0 to 4, as seen below in Figure 1 from Singer et al. (2016). Sepsis affects the patient's time to death(i.e. outcome), as well as choice of treatment.This makes sepsis a confounder.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

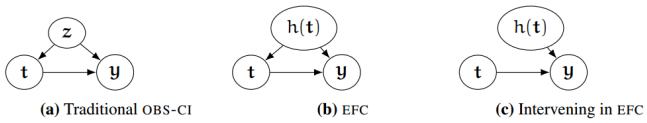
Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Figure 1: SOFA Score Summary for Sepsis3



(a) Traditional OBS-CI (b) EFC (c) Intervening in EFC

Figure 2: Estimation with Functional Confounders $h(t)$

It is also a function of the observed lab values i.e. pre-outcome variables, that can be intervened on to improve the patient's condition. As per Puli et al. (2021), when a function of the pre-outcome variables provides the confounder and these same pre-outcome variables define the intervention, the confounder is said to be a functional confounder. Thus, Sepsis is a functional confounder. Functional confounders violate positivity (Puli et al., 2021), a necessary condition required to perform causal effect estimation. However, with the help of LODE from Puli et al. (2021) we can estimate the effects of full interventions i.e. intervening on all pre-outcome variables. The critical step of LODE involves computing a surrogate intervention - which is a function of the treatment whose effect we want to estimate as well as the confounder value that we want to condition on. We then use this surrogate intervention for estimating the conditional (on the given confounder) effect, and then the average treatment effect.New sufficient conditions like C-Redundancy and Surrogate Positivity are established in Puli et al. (2021) and causal effect estimation when dealing with functional confounders like Sepsis can then be done using the constructed surrogate interventions.

As we can see from the causal graphs in Figure 2 (that has been taken from Puli et al. (2021)), there are some differences in how we can (and should) do causal effect estimation in traditional observational causal inference (a), and when estimating with functional confounders (b) and (c). in (a) of Figure 2, y denotes the outcome , z denotes the confounder and t denotes the treatment/intervention. Positivity is violated in the case of functional confounders because $\forall t_1, t_2 \in \text{supp}(t)$ s.t. $h(t_2) \neq h(t_1)$, $p(z = h(t_2)|t = t_1) = 0 \neq p(z = h(t_2)) > 0$. In our case, $z = h(t) = Sepsis$, t is the full intervention on pre outcome variables

and y is a patient's time to death. To deal with the violation of positivity which occurs in the case of functional confounders like Sepsis, we will follow LODE under the same assumptions as defined in Puli et al. (2021).The first step is to obtain a survival regression model to predict a septic patient's time to death. This model can be represented using $f(t) = y$ where y denotes the patient's time to death and t denotes the patient's pre-outcome variables - including lab values and vitals that determine sepsis - which can be denoted as t_{Sepsis} such that $t_{Sepsis} \in t$. We will then compute a surrogate $t'(t*, t2*)$ intervention using the given treatment $t*$ and confounder $h(t2*)$ values. Then with the obtained surrogate intervention and the survival regression model, we will estimate the conditional treatment effect $f(t')$ and the average treatment effect $E_{p(h(t2*)}[f(t')]$.

2. Related Work

Our project involves an intersection of topics like survival analysis (time to patient death prediction in particular) and causal effect estimation. Extensive work has been done in both these fields and although we will not be able to enlist all the existing literature on these topics, we will focus on the papers that have worked on problems involving Sepsis - as those are closely related to our problem statement.Based on review papers by Moor et al. (2020) and Fle, Henry et al. (2015) appears to predict the onset of septic shock most number of hours in advance.Thus,the approach in this paper by Henry et al. (2015) is something we will loosely follow whilst building our regression model for predicting a septic patient's time to death, as the earlier we can predict the time to death (from detection of sepsis), the earlier one can intervene and potentially improve the patient's condition.Time to septic shock prediction (which is what Henry et al. (2015) do) is equivalent to the time to death prediction problem with respect to the aspect that both are predicting time to an event for septic patients in the ICU.

3. Method

3.1 Data Extraction and Pre-processing

The dataset that we will be working with is the MIMIC-IV dataset by Johnson et al. (2021). This dataset of electronic health records has been a vital tool in enabling various computational tasks for healthcare, and we would like to thank its creators for giving us access to the same. We will be mainly looking at ICU patients with Sepsis. We explored and queried the required data using the BigQuery api provided as part of the Google Cloud Platform. There exist readily available tables like Sepsis3 and Sofa in the MIMIC database of tables. There are 27139 unique patients with Sepsis in the data filtered by us, using a patient's latest stay in the ICU. Missing data was filled for a patient by taking an average over the recorded values for that column for that particular stay (same stay_id) in the ICU. If the average was also null i.e. no values were recorded for that column in that particular ICU stay, we sampled from a distribution for that column that was generated using values from ICU patients with similar scores for that category. Please see the data pre-processing pipeline linked **here** for implementation details.The SQL queries that were used for data extraction can be found in the same repository.
We extracted and (whenever necessary) computed over 50 pre-outcome variables of a pa-

SOFA Category	Lab Values that determine Sepsis
Coagulation	platelet_min
CNS	gcs_min
Liver	bilirubin_max
Renal	creatinine_max
Renal	uo_24hr
Respiration	pao2fio2ratio_vent
Respiration	pao2fio2ratio_novent
Cardiovascular	rate_dopamine
Cardiovascular	rate_eipinephrine
Cardiovascular	rate_norepinephrine
Cardiovascular	rate_dobutamine
Cardiovascular	meanbp_min

Figure 3: Pre-outcome variables used in determining Sepsis

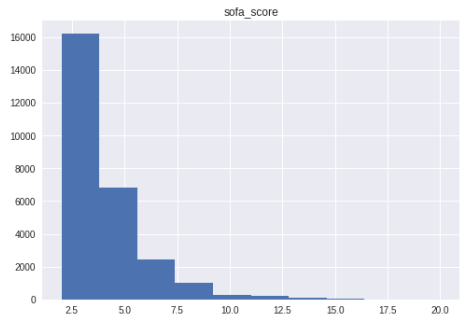


Figure 4: Distribution of SOFA Scores among ICU patients with Sepsis

tient.These included lab values that are used in sepsis determination, vital signs and patient demographics.These pre-outcome variables are consistent with the recommended features to be considered in sepsis prediction tasks as well, as per Reyna and Clifford (2019).Figure 3 shows the patient's pre-outcome variables along with their SOFA category, that are used in determining Sepsis.Figure 4 illustrates the distribution of SOFA scores in our data. As we are only dealing with septic patients, all observed SOFA scores are $>= 2$.

3.2 Survival Regression

The first step of LODE (Puli et al., 2021) requires the computation of $E[Y|t]$. We regress y on t, where y represents a septic patient's time to death, and t represents the patient's pre-outcome variables. As we are following a similar approach to Henry et al. (2015), we will be using a Cox Proportional Hazards (CPH) Model as well. Interval censoring - that was dealt with in Henry et al. (2015) by multiple imputation based approaches, will not be an issue while predicting time to death as we are considering the time to death from the latest time at which the SOFA score is valid. Thus, we can directly use a CPH model(which already handles right censored events i.e. when death has not been observed for a given patient), to estimate the time to death when given a septic patient's pre-outcome variables t.Thus, $E[y|t] = f(t)$ where $f(t)$ is the fitted CPH model.
The CPH model has certain assumptions that it is based on. It requires independence of survival times between distinct individuals in the sample set, a multiplicative relationship between the predictors and the hazard, and a constant hazard ratio over time. We used lasso regularization, similar to Henry et al. (2015).

3.3 Computing Surrogate Intervention

The second step of LODE (Puli et al., 2021) entails computing a surrogate intervention - which is a function of both the confounder we want to condition on, and the treatment whose effect we want to estimate. The first step in doing so would be constructing a continuous and differentiable function $h(t_{Sepsis})$ - which thus denotes the functional confounder. t_{Sepsis} represents those pre-outcome variables of the patient that are used in determining whether they have Sepsis or not. To construct the continuous function(s), we use the exact thresholds and take the same lab values as inputs for each of the categories, as defined in the MIMIC-IV (Johnson et al., 2021) repository that can be found **here.** It is consistent with the definition of $SOFA \geq 2$ and the bounds described in Figure 1.
The procedure would be to compute the category specific SOFA scores, add them to get the overall SOFA score and then threshold it to determine if the patient is septic or not.From both Figure 1 and Figure 3, we can see that there are 6 categories, namely: Respiration, Coagulation, Liver, CNS, Renal and Cardiovascular. As seen from Figure 3, each of these categories depends on a separate set of lab values that are part of the patient's pre-outcome variables.Thus, we would need to construct continuous and differentiable functions to compute the category specific SOFA scores, as $h(t_{Sepsis})$ is then a function of the values returned by the category specific functions, which are in turn functions of the lab values. Each of the category specific scores (as seen from Figure 1) lie in $[0, 4]$. So, the SOFA score lies in the range $[0, 24]$.
To construct $h_{respiration}(pao2fio2ratio\_novent, pao2fio2ratio\_vent)$, a continuous and differentiable function that returns the score for respiration, we transform the discrete formulation for getting the respiration score,with the help of a logistic function and a smooth maximum function. A logistic function is represented by $f_{logistic}(x) = \frac{1}{1+\exp(-\beta(x-x_0))}$. A smooth maximum function that computes the maximum from x and y can be represented by $max_{smooth}(x, y) = \frac{x \exp \alpha x + y \exp \alpha y}{\exp \alpha x + \exp \alpha y}$ (Smo). $\lim_{\alpha \to \inf} max_{smooth}(x, y) = max_{discrete}(x, y)$ where $max_{discrete}(x, y)$ is the standard max function that returns the maximum of the two values passed i.e. x if $x >= y$ else, y. The values of α , β and x_0 in the smooth maximum and logistic functions respectively are tuned while fitting the continuous curves to the corresponding discrete curve.
The discrete formulation for getting the respiration is as follows:
$h_{respiration_{discrete}}(pao2fio2ratio\_novent, pao2fio2ratio\_vent) = \{$
$4, pao2fio2ratio\_vent<100,$
$3, pao2fio2ratio\_vent<200,$
$2, pao2fio2ratio\_novent<300,$
$2, pao2fio2ratio\_vent<300,$
$1, pao2fio2ratio\_novent<400,$
$1, pao2fio2ratio\_vent<400$
None, $pao2fio2ratio\_vent$ is None and $pao2fio2ratio\_novent$ is None
$0\}$
The continuous formulation for respiration can be done as follows:
$h_{respiration_{vent}}(x) = \frac{1}{1+\exp 10((x/100)-1)} + \frac{1}{1+\exp 10((x/100)-2)} + \frac{1}{1+\exp 10((x/100)-3)} + \frac{1}{1+\exp 10((x/100)-4)}$
$h_{respiration_{novent}}(x) = \frac{1}{1+\exp 10((x/100)-3)} + \frac{1}{1+\exp 10((x/100)-4)}$
$h_{respiration}(pao2fio2ratio\_novent, pao2fio2ratio\_vent) = \frac{r_1 \exp 5r_1 + r_2 \exp 5r_2}{\exp 5r_1 + \exp 5r_2}$

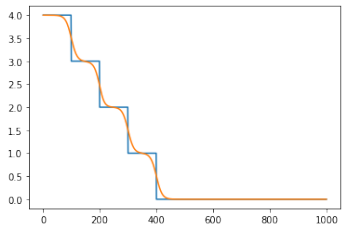


Figure 5: Discrete (blue) and Continuous (orange)

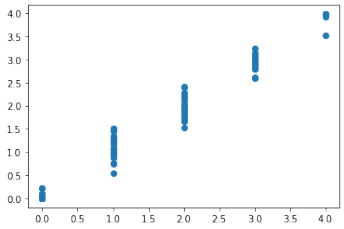


Figure 6: Discrete Respiration Score on X v/s Continuous Respiration Score on Y

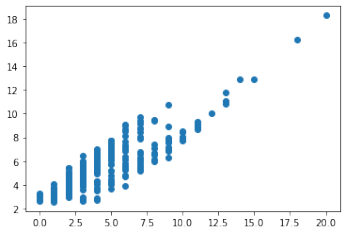


Figure 7: Discrete SOFA Score on X v/s Continuous SOFA Score on Y

where,
$r_1 = h_{respiration_{vent}}(pao2fio2ratio\_vent))$
$r_2 = h_{respiration_{novent}}(pao2fio2ratio\_novent)$

Figure 5 shows the fit of the continuous plot (in orange) with respect to the discrete plot(in blue) for computing the respiration score.For ease of plotting and illustrating the fit, the pao2fio2ratio readings - with and without ventilator, were kept the same for generating Figure 5, as it doesn't affect how well the continuous plot fits the discrete one. Figure 6 gives a more true picture in the sense of comparing discrete and continuous scores computed using actual lab values.A similar recipe was followed to formulate the continuous functions of the other categories as well. To see their visualizations, please refer to the Appendix.Figure 7 shows the SOFA score computed via discrete functions on X v/s the SOFA score computed via continuous functions on Y.

$\text{SOFA} = h_{respiration}(pao2fio2ratio\_novent, pao2fio2ratio\_vent) +$
$h_{coagulation}(platelet\_min) +$
$h_{liver}(bilirubin\_max) +$
$h_{cardiovascular}(rate\_dopamine, rate\_epinephrine, rate\_norepinephrine, rate\_dobutamine, meanbp\_min) +$
$h_{cns}(gcs\_min) +$
$h_{renal}(creatinine\_max, uo\_24hr).$

$\text{SEPSIS} = \frac{1}{(1+\exp(-(\text{SOFA}-2))}$ which returns values in the range $[0, 1]$ where a return value that tends to 1 denotes that the patient has Sepsis and a return value that tends to 0 denotes the patient doesn't have Sepsis.

Once the continuous function $h(t_{Sepsis})$ has been constructed, we can compute the surrogate intervention by finding the limiting solution to the following gradient flow equation, as instructed by **Theorem 1** in Puli et al. (2021). When confounder value is $h(t2_{Sepsis})$ and we want to estimate the effect of treatment $t*$, the gradient flow equation is as follows:
$\frac{dt(s)}{ds} = \nabla(h(t_{Sepsis}(s)) - h(t2_{Sepsis}))^2$ with $t_{Sepsis}(0) = t*_{Sepsis}$

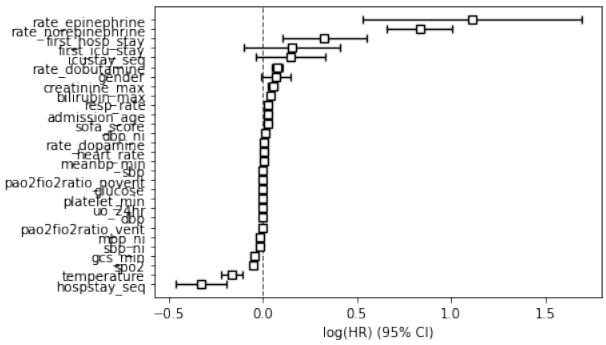


Figure 8: Summary of trained CPH Model

The gradient flow equation was solved using the Euler's method for solving ordinary differential equations (Eul). Please see **this notebook** for implementation details. The pre-outcome variables that are not used in determining Sepsis can be directly copied from $t*$ to the surrogate treatment t', and thus the surrogate treatment is computed.
There are two variations of $h(t_{Sepsis})$ that we can consider. One, where we get the Sepsis label, 1 (or tending to 1) for Sesis, 0 (or tending to 0) for not Sepsis) as output, and the second where we get the SOFA score as output. Please see the Experiments and Results section below for a comparitive analysis.

4. Experiments and Results

The CPH model was trained using the time to death (time of death - SOFA time (i.e. latest time the SOFA score is valid)) as the supervising label.If the patient had not died, their death flag was set to 0 and the difference between their discharge time and SOFA time was stored as the time to death. We narrowed down to 30 pre-outcome variables of the patient (including the lab values that determine Sepsis).Please see the Appendix for the complete list of covariates used for survival regression. We split the dataset containing 27139 unique patients into the training set (80%) and test set (20%). A summary of the fitted CPH model can be seen in Figure 8. The concordance of the fitted model was 0.76.

The computed surrogate intervention for different confounder $h(t2)$ and treatment $t*$ pairs is summarised in Figure 9. It shows the resulting surrogate interventions for same input pair (confounder, treatment), when functional confounder $h(t)$ represents the sepsis label (t'_{sepsis}) and when it represents the SOFA score (t'_{sofa}).

The effect of the computed surrogate treatments on a patient are shown via survival plots (where x is time in days and y is probability of survival) in Figure 10. The three plots represent three different septic patients (i.e. three different confounder values) and a corresponding randomly chosen treatment $t*$ such that confounder $t2 \neq t*$. The surrogate treatments for these three pairs of $(t2, t*)$ are then computed in the manner described above. As mentioned before, there are two types of surrogate treatment computed for each given pair of $(t2, t*)$ - one where the functional confounder returns a sepsis label (represented

	pao2fio2ratio_novent	pao2fio2ratio_vent	rate_dobutamine	rate_epinephrine	rate_norepinephrine	rate_dopamine	meanbp_min	gcs_min	uo_24hr	bilirubin_max	creatinine_max	platelet_min
t2 - Confounder	485.3078427	450.4110754	0	0	0.04002934293	0	70	15	2060.785205	0.3	0.8	222
t* - Treatment	470.3772053	345	0	0	0.03000693869	0	47	15	2060.648911	0.1641088494	1.4	199
t'_sepsis - Surrogate Treatment	470.3771973	345	0.02066872828	-0.636085391	-0.6360104084	0.002370961942	47	15.22567463	2060.648926	-0.08709504455	0.5284837484	199
t'_sofa - Surrogate Treatment	470.3771973	345.0019531	0.02008323744	-0.660629034	-0.660625577	0.002010066994	46.99998093	15.23828602	2060.648926	-0.1016044989	0.4879199266	199.0000916
t2 - Confounder	232.2222222	299.0083333	0	0	0.2272980618	2.751099761	69	10	1659.007846	0.5777777778	0.7632653061	262.6410256
t* - Treatment	499.2799483	149.7083333	0	0.08355475317	0.3000075223	0	54	15	2071.259747	23.2	3.9	50
t'_sepsis - Surrogate Treatment	499.2799377	149.7083282	8.81E-09	0.08355475217	0.3000075221	2.42E-09	54	15	2071.259766	23.20000076	3.900000095	50
t'_sofa - Surrogate Treatment	499.2799377	149.8922882	-1.293113232	-2.107043743	-2.107043743	-7.641557693	54.00183487	17.17286682	2071.259766	23.20000076	-1.725429058	55.11245346

Figure 9: Surrogate Treatments

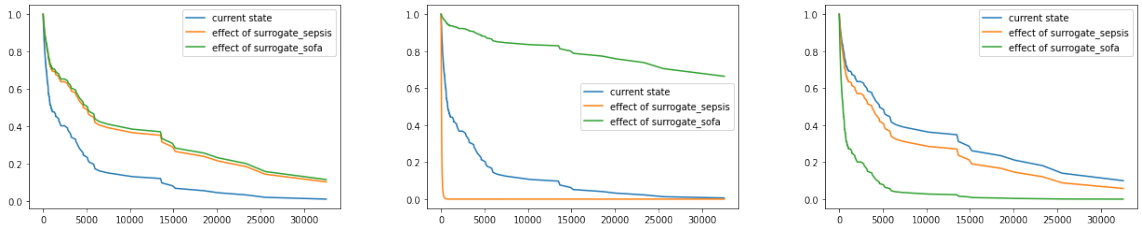


Figure 10: Individual Treatment Effect on survival for different pairs of confounder $t2$ (patient) and treatment $t*$

as surrogate_sepsis) or t'_sepsis in Figure 9, and one where the functional confounder returns the sofa score (represented as surrogate_sofa or t'_sofa in Figure 9. We thus compare the individual treatment effects from both these surrogate treatments for a given $(t2, t*)$ as well as the current state of survival of the patient that is indicated by confounder in the graph.Thus, we were able to compute the individual treatment effects with the help of LODE. As shown, there is huge variance in which surrogate intervention (t'_sepsis or t'_sofa) proves to be more beneficial for the patient, and further analysis needs to be done on that.

All the code used in this project can be found **here.**

5. Conclusion and Future Work

Sepsis is a life threatening condition that is a major cause of death amongst ICU patients. To be able to increase the chances of a patient's survival will be immensely beneficial, given the criticality and urgency of the condition. As we saw, when trying to estimate the effects of treatments on Septic patients, we would be doing causal effect estimation with functional confounders, as Sepsis is a functional confounder. Positivity - an essential condition to perform causal effect estimation, is violated in the case of functional confounders. To deal with this violation of positivity (in the case of functional confounders), we use LODE (Puli et al., 2021). With the help of the LODE algorithm, we were able to construct surrogate treatments and establish sufficient conditions like C-Redundancy and Surrogate-Positivity (Puli et al., 2021), which thus enabled to do causal effect estimation using these constructed surrogate treatments. A surrogate treatment t' is constructed for a given functional con-

founder $h(t2)$ and treatment $t*$ pair. Using the constructed surrogate treatment, we were able to estimate the individual treatment effect (for $h(t2)$) of the given treatment $t*$. Two types of surrogate treatments were computed - one where the functional confounder returned the sepsis label and one where the functional confounder returned the SOFA score. The individual treatment effects (on a patient's survival) were then computed using the surrogate treatments. The results are shown in Figure 10.

The authors would like to add that more work needs to be done on how the estimated effects would change, with the change in the modelling of the functional confounder. For instance, if we were to use DEEP SOFA by Shickel et al. (2019) as our functional confounder or another type of continuous modelling. Moreover, more analysis needs to be done on the difference in the treatment effects when the surrogate treatment is computed using Sepsis as the functional confounder, and when it is computed using SOFA score as the functional confounder.

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Appendix

The visualizations below are comparing the discrete and continuous formulations for different categories that are needed for computing the SOFA score.Please keep in mind that the plots were constructed using artificial values and the x axis shows the value that was used to generate the multi-dimensional input in cases like Cardiovascular and Renal.

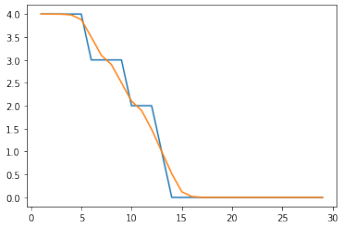

Figure 12: CNS

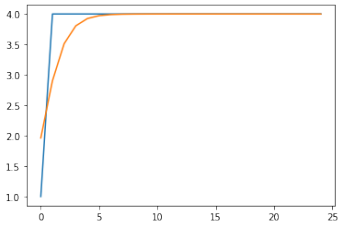

Figure 13: Cardiovascular

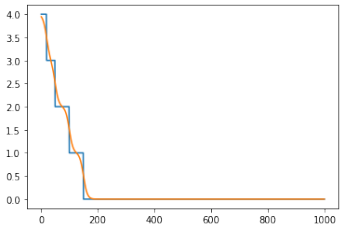

Figure 14: Coagulation

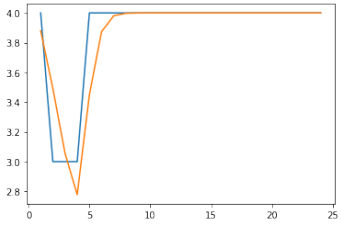

Figure 15: Renal

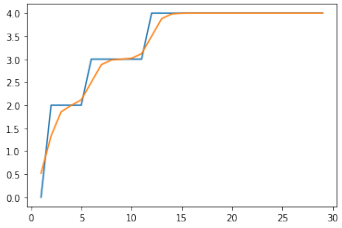

Figure 16: Liver

```
0   pao2fio2ratio_novent
1   pao2fio2ratio_vent
2   rate_dobutamine
3   rate_epinephrine
4   rate_norepinephrine
5   rate_dopamine
6   meanbp_min
7   gcs_min
8   uo_24hr
9   bilirubin_max
10  creatinine_max
11  platelet_min
12  sofa_score
13  death_flag
14  heart_rate
15  sbp
16  dbp
17  sbp_ni
18  mbp_ni
19  dbp_ni
20  temperature
21  glucose
22  spo2
23  resp_rate
24  gender
25  admission_age
26  hospstay_seq
27  first_hosp_stay
28  icustay_seq
29  first_icu_stay
```

Figure 17: Patient's Covariates used for Survival Regression