Counterfactual Time Series

Junhao (Bear) Xiong

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1 Introduction

1.1 Setting

For a given patient, we are given some **irregularly** measured values of a signal (e.g. INR) on some **discrete** time points, as well as values of some contexts, including **treatments** (binary, e.g. whether the patient is given anticoagulant at those time points) and **chronic conditions** (binary, e.g. whether the patient has chronic kidney failure), at some time points.
We are interested in the future trajectory of a signal when we change the values of the contexts. As an example, we can ask questions like "how would the patient's INR progress after time t had we stop administering anticoagulant, while in reality we did administer it to him/her?"

1.2 Goal

We want to be able to predict counterfactually the trajectory of any signal, given the past trajectory and some contexts.

2 Model Specification

2.1 Definition

- Treatments
  $\boldsymbol{x}_t = (x_{t1}, ..., x_{tN})$ an N-dimensional vector, where x_{tn} is a binary value indicating whether treatment n is given at time t.
- Chronic condition
  $\boldsymbol{c} = (c_1, ..., c_M)$ an M-dimensional vector, where c_m is a binary value representing whether a patient has chronic condition m. Note $\boldsymbol{c}$ is the same for all time points.
- Signal
  y_t a scalar representing the value of the signal at time t.

2.2 Model Form

Our model is a dynamic linear model (DLM), which is a state-space model where the transition and emission functions are linear (represented by matrices) and the noises are Gaussian.

- Transition

$$z_t = z_{t-1} + \epsilon_t \tag{1}$$

  where

  - z_t is a scalar representing the latent state value at time t. The interpretation of z_t is the underlying value of a marker with some natural fluctuations, without the interference of any treatments, chronic conditions, etc.
  - $z_0 \sim \mathcal{N}(z_{init}, \sigma_0^2)$
  - $\epsilon_t \sim \mathcal{N}(0, \sigma_1^2)$ are i.i.d

- Emission

$$y_t = z_t + \sum_{j=1}^{J} \boldsymbol{a}_j \cdot \boldsymbol{x}_{t-j} + \boldsymbol{b} \cdot \boldsymbol{c} + \delta_t \tag{2}$$

  where

  - y_t is the observed value of a marker, determined by its underlying value, treatments received, chronic conditions, etc.
  - $\boldsymbol{a}_j$ is an I-dimensional coefficient vector. Note that $\boldsymbol{a}_j$ captures the effect of treatment at time $t-j$. For example, $\boldsymbol{a}_1$ always captures the effect of treatment given at the time point prior to the current one, so it's reasonable to assume $\boldsymbol{a}_1$ to be constant. We only consider the effect of the previous J treatments and we sum over J to capture the effects of past treatments.
  - $\boldsymbol{b}$ is a **time-invariant** vector of coefficients of dimensions M
  - $\delta_t \sim \mathcal{N}(0, \sigma_2^2)$ are i.i.d

2.3 Learning and Inference

- Inference
  Since the model is DLM, we can use Kalman Filter to perform exact inference. Murphy 18.3.1.6 includes derivation of the Kalman Filter updates for a model of similar form.

- Learning
  Parameters to be learned are $\boldsymbol{a_j}$, $\boldsymbol{b}$, z_{init}, σ_0^2, σ_1^2, σ_2^2. We can use EM to learn these parameters. The derivations of EM for Kalman Filter are in Ghahramani and Hinton 1996b. We can modify the derivation for our model.

2.4 Prediction

After parameters are learned, we can then recursively compute the means and covariance of $P(y_{t+k}|y_1, ..., y_t)$ for k-step ahead prediction. Counterfactual prediction can be attained by setting $\boldsymbol{x}_t$ to different values at each predicted time point.
Examples prediction plots on real INR data are shown in the last section.

2.5 Missingness

The observational data is irregularly sampled and the sampling time points may be different among individuals, which motivates "binning" the data, i.e. putting the time series into the same time interval. After binning, there would inevitably be time intervals in which there are no observations. Kalman filter has a natural way to deal with missingness by essentially treating the emission matrix at the missing time points as zero and using the usual updates.

3 Data Pipeline

To enable quicker testing iterations on multiple signals, we built an end-to-end data pipeline, which starts from the cdm files, preprocesses the data, runs the model on the data and generates results, e.g. estimated parameters, prediction MSE, prediction plots, etc.

The pipeline is built using pandas and is relatively flexible to modify. Figure 1 shows the pipeline in a flowchart. Figure 2 and Figure 3 show a segment of the creatinine dataframe prior to and after preprocessing, respectively.

The pipeline also enables quick data analysis at any point during preprocessing. For examples, we can ask questions such as "what is the difference of mean signal values between those who have a certain chronic condition vs. those who don't?", "what is the average standard deviation of signal values for patients who don't receive any treatment?", etc. These types of analysis can lend insights into the characteristics of any particular dataset we are dealing with.

To start the pipeline, one only needs to specify a few hyperparameters and the relating fields one wishes to include as context for a given signal. We will first introduce the hyperparameters, then we will describe the specification of fields using creatinine as an example.

3.1 Hyperparameters

- Cutoff: the least number of signal observations a patient must have to be included in the preprocessed data (default=5)

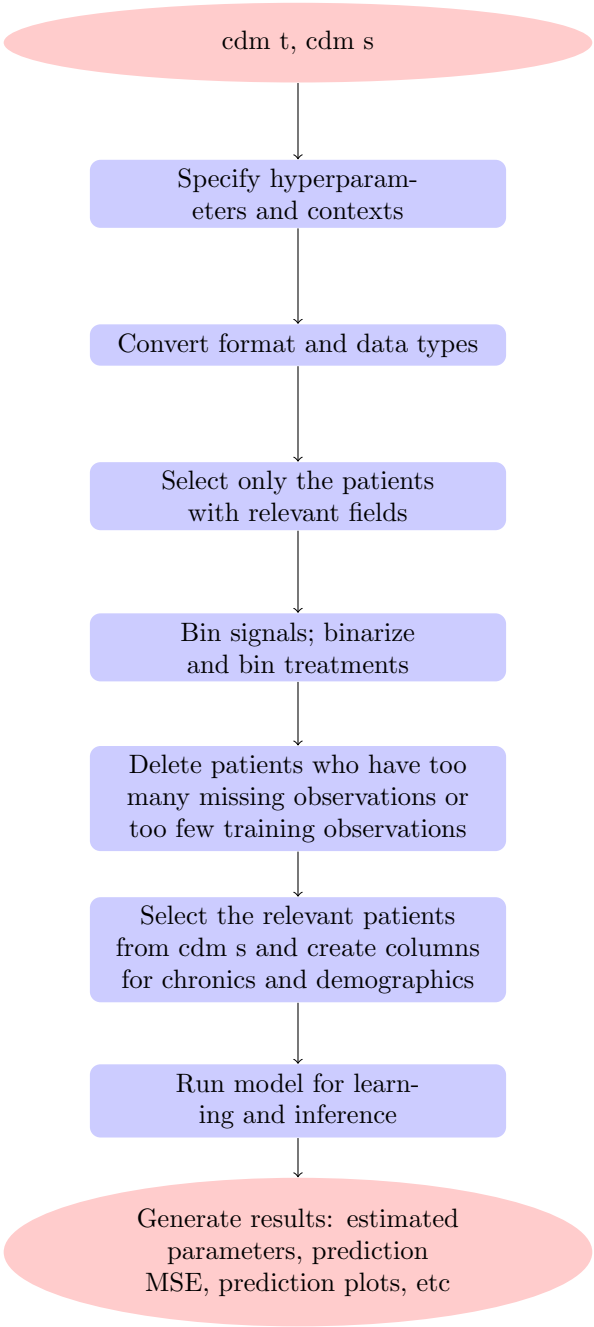

Figure 1: Pipeline Flow Diagram

	dataset_id	enc_id	tsp	fid	value	confidence	tsp_adjusted
129	3	5	2016-01-11 11:38:00	ketorolac_dose	{"dose": 30.0, "order_tsp": "2016-01-11 11:31:...	1	-4 days +22:34:00
225	3	5	2016-01-11 17:46:00	ketorolac_dose	{"dose": 30.0, "order_tsp": "2016-01-11 11:31:...	1	-3 days +04:42:00
240	3	5	2016-01-12 00:32:00	ketorolac_dose	{"dose": 30.0, "order_tsp": "2016-01-11 11:31:...	1	-3 days +11:28:00
265	3	5	2016-01-12 07:58:00	ketorolac_dose	{"dose": 30.0, "order_tsp": "2016-01-11 11:31:...	1	-3 days +18:54:00
270	3	5	2016-01-12 14:47:00	ibuprofen_dose	{"dose": 600.0, "order_tsp": "2016-01-11 11:31...	1	-2 days +01:43:00

Figure 2: Data prior to preprocessing

	enc_id	creatinine	time	dialysis	nephrotoxic_drugs	dronedarone	diuretic	ace_i	arb
38	964	0.7	0 days 00:00:00	0.0	0.0	0.0	0.0	0.0	0.0
39	964	0.8	0 days 12:00:00	0.0	0.0	0.0	0.0	0.0	0.0
40	964	NaN	1 days 00:00:00	0.0	0.0	0.0	0.0	0.0	0.0
41	964	0.7	1 days 12:00:00	0.0	0.0	0.0	0.0	0.0	0.0
42	964	0.6	2 days 00:00:00	0.0	0.0	0.0	0.0	0.0	0.0

Figure 3: Data after preprocessing

- Bin size: the length of time (hrs) we use to bin the signal time series (default=12)
- Maximum missing percentage: the maximum percentage of missingness in the binned observation time series allowed for each individual (default=0.4)
- Least number of training observations: the least number of training observations allowed for each individual (default=4)
- Number of past effects: the number of past time points (the time interval between two adjacent time points is the bin size) where treatment effects are considered (default=2)
- Training percentage: the percentage of each observation time series used for training (default=0.8)

The default hyperparameters are selected to balance the tradeoff between granularity and size of training data, while keeping the missingness relatively low to ensure model performance. The default setting is set to ensure low missingness and high number of data points for each example, so sometimes it can result in the overall size of training dataset being small. In that case, one can try increasing the bin size or decreasing the least number of training observation to include more examples in the training dataset.

3.2 Context Specifications

Finding the relating fields of a signal usually involves some initial online research, but this is only a one-time effort. Here we demonstrate the context specification using creatinine as an example.

3.2.1 Treatments

We first specify a treatment category, e.g. diuretics, which we know may directly affect creatinine level. Then we find a list of drugs, e.g. acetaminophen, which are included under this treatment category through online research. The pipeline then selects the fields which are present in the cdm files which correspond to the drugs, e.g. "acetaminophen dose". This is done for multiple treatment categories.

3.2.2 Chronics

We specify keywords of the chronic conditions and demographics information that may directly affect creatinine level, e.g. "chronic kidney", "admit weights". The pipeline then selects the fields in the cdm files which include these keywords.

4 Experiments

For the experiments, we tested the model on five different signals: creatinine, BUN, INR, lactate, platelets. The hyperparameters for each signal is specified in the result section.

4.1 Special Note – Initialization

We noticed that the estimated chronic coefficients is sensitive to the initialization of the initial state variance, i.e. initialization of the initial state variance that is too large can cause the chronic coefficients to be unidentifiable. This is likely because both initial state variance and chronic coefficients attempt to capture the intercept of a trajectory. When initial state variance is initialized to be large, it leads the model to ignore the effect of the chronic coefficients by explaining away the variation of intercepts among individuals. Through control experiments, we found that initializing the initial state variance to be randomly drawn from $|\mathcal{N}(0, 0.001)|$ gives the best performance.

Estimated chronic coefficients can also be sensitive to the their own initialization. We found that initializing each chronic coefficients to be randomly drawn from $\mathcal{N}(0, 0.001)$ gives the best results.

4.2 Results

To test the performance of the model, we examined the estimated treatment and chronic coefficients and check whether their signs and magnitudes correspond to the effect we expect them to have on a given signal. We also evaluate the prediction MSE of the model as iteration increases.

We found that the model is generally able to the correctly identify the directions and relative magnitudes of the coefficients of various treatments and chronic conditions. The prediction MSE generally decreases as iteration increases. Figure 4 shows the results of creatinine as an example. For creatinine, hyperparameters were set to defaults. Results for other signals are included in the appendix.

The expected effect is compiled through online research on sites such as UpToDate and clinical literatures. Some treatments/chronics (refer together as 'contexts') have known and clear effects on some signals, e.g. dialysis and ESRD on creatinine, to which we denote 'Decrease' and 'Increase' respectively. There are also some contexts which **may** affect some signals, due to individuals' heterogeneous responses to treatment, a lack understanding of physiological mechanisms, or insufficient clinical evidence, etc. For those contexts, we denoted 'May Increase'/'May Decrease'. There are also contexts for which there could be increasing or decreasing effect on a signal through different mechanisms, or there is suspected yet unclear effect. For those contexts, we denoted the expected effect as 'Unclear', but included for the sake of completeness.

The estimated parameters are averaged over eight runs of the model. '$\pm$' denotes the standard deviation of each parameter estimated over these runs.

5 Discussion and Future Work

The goal of this study is to build a model which can generate counterfactual time series for multiple signals. To this end, once the model is trained, we can use the model to generate various counterfactual trajectories by setting different values of treatments and chronic conditions and evaluating the resulting state value z_t.

The model and data pipeline can be used to quickly generate counterfactual trajectories for multiple signals, since they don't require a large amount of manual tuning. We can now incorporate the generated counterfactual trajectories into the sepsis prediction model and see if including counterfactual trajectories improves prediction.

Creatinine			
Variable	**Expected Effect**	**Estimated Coefficient (0-12hrs)**	**Estimated Coefficient (12-24hrs)**
Treatments			
Dialysis	Decrease	-1.325±0.0036	-0.7755±0.014
Diuretics	May increase	0.0417±0.0012	0.0161±0.001
ACE-inhibitors	May increase	0.0077±0.0013	-0.0062±0.0017
ARB	May increase	0.0897±0.0016	0.0508±0.0012
Nephrotoxic drugs	May increase	-0.0164±0.0002	-0.025±0.0002
Dronedarone	May increase	-0.0623±0.0026	0.1103±0.0031
Chronics			
CKD	Increase	1.5065±0.1771	
Kidney cancer	Increase	0.376±0.1616	
Renal insufficiency	Increase	0.3312±0.0375	
ESRD	Increase	4.0354±0.6468	
Sickle cell	May increase	0.8465±0.0975	
Demographics			
Gender	May increase	0.3112±0.1604	
Admitted weight	Increase	0.0023±0.0023	
Other Parameters			
Initial State Mean		0.8242±0.2983	
Initial State Standard Deviation		1.6337±0.03	
Transition Standard Deviation		0.4159±0.01	
Observation Standard Deviation		0.1282±0.0257	

Figure 4: Estimated Coefficients of Creatinine

6 Appendix

BUN: hyperparameters set to default.

BUN			
Variable	**Expected Effect**	**Estimated Coefficient (0-12hrs)**	**Estimated Coefficient (12-24hrs)**
Treatments			
Dialysis	Decrease	-13.688±0.0105	-8.9857±0.0238
Diuretics	May increase	0.5387±0.0068	0.4377±0.0059
Certain antibiotics	May increase	-0.5351±0.0026	-0.4038±0.0016
Chronics			
CKD	Increase	22.0651±2.9861	
Kidney cancer	Increase	9.1157±2.0536	
Renal insufficiency	Increase	10.0298±1.7138	
ESRD	Increase	15.1922±2.8438	
Liver failure	May decrease	6.6227±2.5723	
Heart failure	May increase	8.4475±2.2311	
Other Parameters			
Initial State Mean		20.0116±1.6128	
Initial State Standard Deviation		20.2954±0.1548	
Transition Standard Deviation		5.9132±0.0127	
Observation Standard Deviation		0.4716±0.1479	

Figure 5: Estimated Coefficients of BUN

INR: bin size=18, number of past effects=3, other hyperparameters set to default.

INR				
Variable	**Expected Effect**	**Estimated Coefficient (0-18hrs)**	**Estimated Coefficient (18-36hrs)**	**Estimated Coefficient (36-54hrs)**
Treatments				
NSAID	Unclear	-0.0745±0.0005	-0.1191±0.0001	-0.1172±0.0005
Anticoagulants	Increase	-0.012±0.0029	0.213±0.0011	0.1423±0.0008
Platelets transfusion	Decrease	-0.1623±0.0024	-0.2517±0.0029	-0.1565±0.0018
Chronics				
Liver disease	Unclear	0.247±0.0624		
Sickle cell	May decrease	-0.0367±0.0383		
Other Parameters				
Initial State Mean		2.2168±0.0031		
Initial State Standard Deviation		1.3538±0.0063		
Transition Standard Deviation		0.6617±0.0047		
Observation Standard Deviation		0.3101±0.008		

Figure 6: Estimated Coefficients of INR

Lactate: bin size=18, least number of training observation=2, other hyperparameters set to default.

Lactate			
Variable	**Expected Effect**	**Estimated Coefficient (0-12hrs)**	**Estimated Coefficient (12-24hrs)**
Treatments			
IV fliuds	Unclear	-0.1358±0.0002	0.2267±0.0
Antibiotics	May decrease	-0.3197±0.0001	-0.3919±0.0001
Certain drugs	May increase	0.0146±0.0001	0.0712±0.0001
Chronics			
Liver failure	Increase	1.36±0.0004	
CKD	May increase	-0.2556±0.0002	
Kidney cancer	May increase	-2.1013±0.0006	
Renal insufficiency	May increase	0.0293±0.0004	
ESRD	May increase	0.3696±0.0003	
Diabetes	May increase	-0.004±0.0004	
Other Parameters			
Initial State Mean		3.8943±0.0005	
Initial State Standard Deviation		1.6614±0.0002	
Transition Standard Deviation		1.6493±0.0003	
Observation Standard Deviation		1.6033±0.0002	

Figure 7: Estimated Coefficients of Lactate

Platelets: hyperparameters set to default.

Platelets			
Variable	**Expected Effect**	**Estimated Coefficient (0-12hrs)**	**Estimated Coefficient (12-24hrs)**
Treatments			
Platelets transfusion	Increase	6.9197±0.0	1.2143±0.0
DITP*	May decrease	-17.5464±0.0	-7.8111±0.0
Chronics			
Liver failure	May decrease	-76.475±0.0076	
Sickle cell	May increase	63.9293±0.1267	
Other Parameters			
Initial State Mean		226.1669±0.0009	
Initial State Standard Deviation		99.6645±0.0	
Transition Standard Deviation		23.3053±0.0	
Observation Standard Deviation		16.6558±0.0	
*Drug-induced immune thrombocytopenia			

Figure 8: Estimated Coefficients of Platelets