What-If Reasoning with Counterfactual Gaussian Processes

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Abstract

Answering “What if?” questions is important in many domains. For example, would a patient’s disease progression slow down if I were to give them a dose of drug $A$? Ideally, we answer our question using an experiment, but this is not always possible (e.g., it may be unethical). As an alternative, we can use non-experimental data to learn models that make counterfactual predictions of what we would observe had we run an experiment. In this paper, we propose the counterfactual GP, a counterfactual model of continuous-time trajectories (time series) under sequences of actions taken in continuous-time. We develop our model within the potential outcomes framework of Neyman [1990] and Rubin [1978]. The counterfactual GP is trained using a joint maximum likelihood objective that adjusts for dependencies between observed actions and outcomes in the training data. We report two sets of experimental results using the counterfactual GP. The first shows that it can be used to learn the natural progression (i.e. untreated progression) of biomarker trajectories from observational data. In the second, we show how the counterfactual GP can be used for medical decision support by learning counterfactual models of renal health under different types of dialysis.

1 Introduction

What change to a click prediction model will have the largest impact on an online advertising firm’s revenue? Which drug, dosage, and frequency should a physician recommend to a patient with a chronic disease? These types of questions are commonly formalized using counterfactual queries about observable outcomes (see e.g., Pearl 2009, Bottou et al. 2013), such as “How many more users per day will click an ad if I include this feature in the model?”. Ideally, we would get our answer by running an experiment and measuring the outcome under the different actions.

Experiments, however, are not always feasible. An alternative is to learn models from observational (non-experimental) data that can make counterfactual predictions of the outcomes we would have observed had we run an experiment (see e.g., Pearl 2009). The key challenge when learning counterfactual models from observational data is that it is difficult to distinguish between statistical dependence and causal relationships. For instance, consider a drug that is often given to sicker patients who are also more likely to die. Without accounting for this bias in the treatment policy, a statistical model would predict that the drug kills patients even if it is actually beneficial.

This challenge is commonly addressed using the potential outcomes framework [Neyman 1990, Rubin 1978], which models outcomes under different actions using a collection of random variables $\{Y(a) : a \in C\}$ indexed by actions $a$ from a set of choices $C$. Within this framework, we can clearly state assumptions that equate statistical models of observed data to counterfactual models of outcomes under hypothetical interventions (we will review these ideas in more detail later).
In this paper, we use the potential outcomes framework to develop the counterfactual Gaussian process (CGP), an approach to modeling counterfactual continuous-time trajectories (i.e., time series). Many authors have studied counterfactual models for discrete time series data. For instance, in health care and epidemiology, Robins (1997) develop counterfactual models of a single outcome measured after a sequence of actions in discrete time. Brodersen et al. (2015) build counterfactual models to estimate the impact that a single, discrete event has on a discrete time series of interest (e.g., daily sales after a product launch). Others have modeled the effect of actions taken in continuous time on a single outcome (e.g., Arjas and Parner 2004, Lok 2008). The CGP is unique in that it allows us to predict how future trajectories in continuous-time will change in response to sequences of interventions.

Figure 1 illustrates this idea with an example from health care. We show an individual with a lung disease, and would like to predict how her lung capacity (y-axis) will progress in response to different treatment plans. Panel (a) shows the history in the red box, which contains previous lung capacity measurements (black dots) and previous treatments (green and blue bars). Panels (b) and (c) illustrate the type of predictions we would like to make: given the history, what is the likely future trajectory of lung capacity under a single dose of Drug B (green) vs. under two doses of drug A (blue)?

**Contributions.** The potential outcomes framework allows us to derive statistical learning algorithms that recover counterfactual predictive models from non-experimental (i.e., observational) data. Our key methodological contribution is an adjusted maximum likelihood algorithm for Gaussian processes that allows us to learn counterfactual models of continuous-time trajectories from observational traces: irregularly sampled sequences of actions and outcomes denoted using $D = \{(y_{ij}, a_{ij}, t_{ij})\}_{j=1}^{m}$, where $y_{ij} \in \mathbb{R} \cup \{\varnothing\}$, $a_{ij} \in \mathcal{C} \cup \{\varnothing\}$, and $t_{ij} \in [0, \tau]^J$. We derive the objective by jointly modeling actions and outcomes using a marked point process (MPP; see e.g., Daley and Vere-Jones 2007), where the GP acts as a conditional distribution for the marks. We refer to GPs trained using the typical maximum likelihood objective as regression GPs (RGP; see e.g., Section 5.4.1 of Rasmussen and Williams 2006), and to GPs trained using our adjusted objective as counterfactual GPs (CGP). When using potential outcomes, several assumptions are typically required to show that the learned statistical model is equivalent to the target counterfactual model. We describe one set of assumptions sufficient to show equivalence for the counterfactual GP.

We report two sets of experimental results on health care applications. First, we use the CGP to predict the natural progression—that is, untreated progression—of simulated clinical marker time series (e.g., similar to that shown in Figure 1). This is a challenging problem in health care because clinical data is almost always collected from patients who are being actively treated, but a prediction of the natural progression can be helpful to judge whether an intervention is necessary. We use simulated data because it is otherwise impossible to evaluate the CGP without a true randomized experiment (simulations are often used to evaluate counterfactual models; for example, in Brodersen et al. 2015). In the second experiment, we show how the CGP can be used as a medical decision support tool by modeling the effects of dialysis on creatinine concentrations for ICU patients.

1.1 Related Work

The difference between counterfactual predictions of an outcome if an action had been taken and if it had not been taken is defined as the causal effect of the action in the causal inference community (see e.g., Pearl 2009 or Morgan and Winship 2014). Potential outcomes are commonly used to formalize
counterfactual predictions and obtain causal effect estimates \cite{Neyman1990, Rubin1978}; we will review them shortly. Potential outcomes are often applied to cross-sectional data (e.g., Bottou et al. 2013, Johansson et al. 2016), but have also been used to estimate the causal effect of a sequence of actions in discrete time on a final outcome (e.g. \cite{Robins1997}). Conversely, Brodersen et al. \cite{Brodersen2015} estimate the effect that a single discrete intervention has on a discrete time series.

Recent work on optimal dynamic treatment regimes uses the sequential potential outcomes framework proposed by \cite{Robins1997} to learn lists of discrete-time treatment rules that optimize a scalar outcome. Algorithms for learning these rules often use value-function approximations (Q-learning; e.g., Nahum-Shani et al. \cite{Nahum-Shani2012}). Alternatively, A-learning directly learns the relative differences between competing policies \cite{Murphy2003}.

Others have extended the potential outcomes framework in \cite{Robins1997} to learn causal effects of actions taken in continuous-time on a single final outcome using observational data. \cite{Lok2008} proposes an estimator based on structural nested models \cite{Robins1992} that learns the instantaneous effect of administering a single type of treatment. \cite{Arjas2004} develop an alternative framework for causal inference using Bayesian posterior predictive distributions to estimate the effects of actions in continuous time on a final outcome. \cite{Xu2016} also learn effects of actions in continuous-time on outcomes measured in continuous-time, but make one-step-ahead scalar predictions instead of trajectory-valued predictions. Both \cite{Lok2008} and \cite{Arjas2004} use marked point processes to formalize assumptions that make it possible to learn causal effects from continuous-time observational data. We build on these ideas to learn causal effects of actions on continuous-time trajectories instead of a single outcome.

Causal effects in continuous-time have also been studied using differential equations. Mooij et al. \cite{Mooij2013} formalize an analog of Pearl’s “do” operation for deterministic ordinary differential equations. Sokol and Hansen \cite{Sokol2014} make similar contributions for stochastic differential equations by studying limits of discrete-time non-parametric structural equation models \cite{Pearl2009}.

Reinforcement learning (RL) algorithms learn from data where actions and observations are interleaved in discrete time (see e.g., \cite{Sutton1998}). In RL, however, the focus is on learning a policy (a map from states to actions) that optimizes the expected reward, rather than a model that predicts the effects of the agent’s actions on future observations. In model-based RL, a model of an action’s effect on the subsequent state is produced as a by-product either offline before optimizing the policy (e.g., \cite{Ng2006}) or incrementally as the agent interacts with its environment. In most RL problems, however, learning algorithms rely on active experimentation to collect samples. This is not always possible, for example in health care we cannot actively experiment on patients, and so we must rely on retrospective observational data.

In RL, a related problem known as off-policy evaluation also uses retrospective observational data (see e.g., \cite{Dudik2011, Jiang2016, Paduraru2012}). The goal is to use state-action-reward sequences generated by an agent operating under an unknown policy to estimate the expected reward of a target policy. Off-policy algorithms typically use value-function approximations, importance reweighting, or doubly robust combinations of the two to estimate the expected reward.

### 2 Counterfactual Models from Observational Traces

Counterfactual GPs build on ideas from potential outcomes \cite{Neyman1990, Rubin1978}, Gaussian processes \cite{Rasmussen2006}, and marked point processes \cite{Daley2007}. In the interest of space, we review potential outcomes and marked point processes, but refer the interested reader to Rasmussen and Williams \cite{Rasmussen2006} for background on GPs.

**Background: Potential Outcomes.** To formalize counterfactuals, we adopt the potential outcomes framework \cite{Neyman1990, Rubin1978}, which uses a collection of random variables \(Y[a] : a \in C\) to model the distribution over outcomes under each action \(a\) from a set of choices \(C\). To make counterfactual predictions, we must learn the distribution \(P(Y[a])\) for each action \(a \in C\). If we can freely experiment by repeatedly taking actions and recording the effects, then it is straightforward to learn a probabilistic model for each potential outcome \(Y[a]\). Conducting experiments, however, may not be possible. Alternatively, we can use observational data, where we have example actions \(A\) and outcomes \(Y\), but do not know how actions were chosen. Note the difference between the action \(a\) and the random variable \(A\) that models the observed actions in our data. The notation \(Y[a]\) serves to distinguish between the observed distribution \(P(Y \mid A = a)\) and the target distribution \(P(Y[a])\).
In general, we can use observational data to estimate \( P(Y \mid A = a) \). Under two assumptions, however, we can show that this conditional distribution is equivalent to the counterfactual model \( P(Y[a]) \). The first is known as the Consistency Assumption.

**Assumption 1 (Consistency).** Let \( Y \) be the observed outcome, \( A \in C \) be the observed action, and \( Y[a] \) be the potential outcome for action \( a \in C \), then: \( (Y \not= Y[a]) \mid A = a \).

Under consistency, we have that \( P(Y \mid A = a) = P(Y[a] \mid A = a) \). Now, the potential outcome \( Y[a] \) may depend on the action \( A \), so in general \( P(Y[a] \mid A = a) \neq P(Y[a]) \). The next assumption posits that we have additional observed variables \( X \) known as confounders [Morgan and Winship, 2014] that are sufficient to d-separate \( Y[a] \) and \( A \).

**Assumption 2 (No Unmeasured Confounders (NUC)).** Let \( Y \) be the observed outcome, \( A \in C \) be the observed action, \( X = x \) be a vector containing potential confounders, and \( Y[a] \) be the potential outcome under action \( a \in C \), then: \((Y[a] \perp A) \mid X = x\). Under Assumptions 1 and 2 \( P(Y \mid A = a, X = x) = P(Y[a] \mid X = x) \). By marginalizing with respect to \( P(X) \) we can estimate \( P(Y[a]) \).

An extension of Assumption 2 introduced by Robins [1997] known as sequential NUC allows us to estimate the effect of a sequence of actions in discrete time on a single outcome. In continuous-time settings, where both the type and timing of actions may be statistically dependent on the potential outcomes, Assumption 2 and sequential NUC cannot be applied as-is. We will describe an alternative that serves a similar role for CGPs.

**Background: Marked Point Processes.** Point processes are distributions over sequences of timestamps \( \{T_i\}_{i=1}^N \), which we call points, and a marked point process (MPP) is a point process where each point is annotated with an additional random variable \( X \), called its mark. For example, a point \( T \) might represent the arrival time of a customer, and \( X \) the amount that she spent at the store. We emphasize that both the annotated points \( (T_i, X_i) \) and the number of points \( N \) are random variables.

A point process can be characterized as a counting process \( \{N_t : t \geq 0\} \) that counts the number of points that occurred up to and including time \( t \): \( N_t = \sum_{i=1}^N \mathbb{1}_{(T_i \leq t)} \). By definition, this process can only take integer values, and \( N_t \geq N_s \) if \( t \geq s \). In addition, it is commonly assumed that \( N_0 = 0 \) and that \( \Delta N_t \equiv \lim_{s \to 0^+} N_t - N_{t-s} \in [0,1] \). We can parameterize a point process using a probabilistic model of \( \Delta N_t \) given the history of the process \( H_t \) up to but not including time \( t \) (we use \( t^- \) to denote the left limit of \( t \)). Using the Doob-Meyer decomposition [Daley and Vere-Jones, 2007], we can write \( \Delta N_t = \Delta M_t + \Delta \lambda_t \), where \( M_t \) is a martingale, \( \lambda_t \) is a cumulative intensity function, and

\[
P(\Delta N_t = 1 \mid H_{t^-}) = E[\Delta N_t \mid H_{t^-}] = E[\Delta M_t \mid H_{t^-}] + \Delta \lambda_t(H_{t^-}) = 0 + \Delta \lambda_t(H_{t^-}),
\]

which shows that we can parameterize the point process using the conditional intensity function \( \lambda^*(t)dt \equiv \Delta \lambda_t(H_{t^-}) \). The star superscript on the intensity function serves as a reminder that it depends on the history \( H_{t^-} \). For example, in non-homogeneous Poisson processes \( \lambda^*(t) \) is a function of time that does not depend on the history. On the other hand, a Hawkes process is an example of a point process where \( \lambda^*(t) \) does depend on the history [Hawkes, 1971]. MPPs are defined by an intensity that is a function of both the time \( t \) and the mark \( x \): \( \lambda^*(t,x) = \lambda^*(t)p^*(x \mid t) \). We have written the joint intensity in a factored form, where \( \lambda^*(t) \) is the intensity of any point occurring (that is, the mark is unspecified), and \( p^*(x \mid t) \) is the pdf of the observed mark given the point’s time. For an MPP, the history \( H_t \) contains all prior point’s time and mark.

### 2.1 Counterfactual Gaussian Processes

Let \( \{Y_t : t \in [0, \tau]\} \) denote a continuous-time stochastic process, where \( Y_t \in \mathbb{R} \), and \( [0, \tau] \) defines the interval over which the process is defined. We will assume that the process is observed at a discrete set of irregular and random times \( \{(y_j, t_j)\}_{j=1}^n \). We use \( C \) to denote the set of possible action types, \( a \in C \) to denote the elements of the set, and define an action to be a 2-tuple \( (a, t) \) specifying an action type \( a \in C \) and a time \( t \in [0, \tau] \) at which it is taken. To refer to multiple actions, we use \( a = \{(a_1, t_1), \ldots, (a_n, t_n)\} \). Finally, we define the history \( H_t \) at a time \( t \in [0, \tau] \) to be a list of all previous observations of the process and all previous actions. Our goal is to model the counterfactual:

\[
P(\{Y_s[a] : s > t\} \mid H_t), \quad a = \{(a_j, t_j) : t_j > t\}_{j=1}^m.
\]  

(1)

To learn the counterfactual model, we will use traces \( \mathcal{D} \equiv \{h_i = \{(t_{ij}, y_{ij}, a_{ij})\}_{j=1}^{n_i} : i = 1, \ldots, m\} \), where \( y_{ij} \in \mathbb{R} \cup \{\emptyset\}, a_{ij} \in C \cup \{\emptyset\} \), and \( t_{ij} \in [0, \tau] \). Our approach is to model \( \mathcal{D} \) using a marked point
We define the MPP mark space as the Cartesian product of the outcome space and the set of action types $C$. To allow either the outcome or the action (but not both) to be the null variable $\emptyset$, we introduce binary random variables $z_y \in \{0, 1\}$ and $z_a \in \{0, 1\}$ to indicate when the outcome $y$ and action $a$ are not $\emptyset$. Formally, the mark space is $X = (\mathbb{R} \cup \{\emptyset\}) \times (C \cup \{\emptyset\}) \times \{0, 1\} \times \{0, 1\}$. We can then write the MPP intensity as

$$
\lambda^*(t, y, a, z_y, z_a) = \lambda^*(t)p^*(z_y, z_a \mid t) p^*(y \mid t, z_y) p^*(a \mid y, t, z_a),
$$

where we have again used the superscript as a reminder that the hazard function and densities above are implicitly conditioned on the history $H_{t-}$. The parameterization of the event and action models can be chosen to reflect domain knowledge about how the timing of events and choice of action depend on the history. The outcome model is parameterized using a GP (or any elaboration such as a hierarchical GP, or mixture of GPs), and can be simply designed as a regression model that predicts how the future trajectory will progress given the previous actions and outcome observations.

**Learning.** To learn the CGP, we maximize the likelihood of observational traces over a fixed interval $[0, \tau]$. Let $\theta$ denote the model parameters, then the likelihood for a single trace is

$$
\ell(\theta) = \sum_{j=1}^{n} \log p_0^*(y_j \mid t_j, z_{yj}) + \sum_{j=1}^{n} \lambda^*(t) p_0^*(a_j, z_{yj}, z_{aj} \mid t_j, y_j) - \int_{0}^{\tau} \lambda_0^*(s) \, ds.
$$

We assume that traces are independent, and so can learn from multiple traces by maximizing the sum of the individual-trace log likelihoods with respect to $\theta$. We refer to Equation 2 as the adjusted maximum likelihood objective. We see that the first term fits the GP to the outcome data, and the second term acts as an adjustment to account for dependencies between future outcomes and the timing and types of actions that were observed in the training data.

**Connection to target counterfactual.** By maximizing Equation 3, we obtain a statistical model of the observational traces $D$. In general, the statistical model may not recover the target counterfactual model (Equation 1). To connect the CGP to Equation 1 we describe two sufficient assumptions. The first assumption is an alternative to Assumption 2.

**Assumption 3 (Continuous-Time NUC).** For all times $t$ and all histories $H_{t-}$, the densities $\lambda^*(t)$, $p^*(z_y, z_a \mid t)$, and $p^*(a \mid y, t, z_a)$ do not depend on $Y_s[a]$ for all times $s > t$ and all actions $a$.

The key implication of this assumption is that the policy used to choose actions in the observational data did not depend on any unobserved information that is predictive of the future potential outcomes.

**Assumption 4 (Non-Informative Measurement Times).** For all times $t$ and any history $H_{t-}$, the following holds: $p^*(y \mid t, z_y = 1) = d_y = P(Y_t \in d_y \mid H_{t-})$.

Under Assumptions 1, 3, and 4, we can show that Equation 1 is equivalent to the GP used to model $p^*(y \mid t, z_y = 1)$. In the interest of space, the argument for this equivalence is in Section A of the supplement. Note that these assumptions are not statistically testable (see e.g., Pearl 2009).

## 3 Experiments

The key strength of the CGP is that it is able to learn counterfactual models from observational data. On the other hand, a regression GP (RGP), in general, will not recover a counterfactual model from observational data, and will therefore make poor predictions about trajectories under interventions. Our first set of experimental results demonstrates this difference using simulated data. We use simulated data because it is otherwise impossible to evaluate a counterfactual model without running a randomized experiment (this is common practice when evaluating counterfactual models; for example, in Brodersen et al. 2015). A counterfactual model is useful because it allows decision-makers to guide their actions using estimates of likely outcomes under different choices. In our second experiment, we demonstrate how the CGP can be used in a medical decision-making context by using real data to learn counterfactual models of kidney function under treatment.

### 3.1 Predicting Natural Progression

In our first experiment, we simulate ICU time series, and use the CGP to predict the natural progression (i.e. untreated progression) of lab test trajectories measured over a period of 24 hours.
Observational

Unobserved Confounders

| Hours | Experimental RGP | CGP | Δ | Observational RGP | CGP | Δ | Unobserved Confounders RGP | CGP | Δ |
|-------|-----------------|-----|---|-------------------|-----|---|--------------------------|-----|---|
| (12, 16) | 1.71 | 1.71 | 0.0 | 2.25 | 1.72 | *0.53 (0.41, 0.66) | 2.44 | 2.37 | *0.07 (0.02, 0.12) |
| (16, 20) | 1.86 | 1.86 | 0.0 | 3.28 | 1.87 | *1.41 (1.23, 1.60) | 2.89 | 2.55 | *0.34 (0.23, 0.45) |
| (20, 24) | 2.51 | 2.51 | 0.0 | 3.92 | 2.52 | *1.40 (1.17, 1.63) | 3.25 | 2.85 | *0.41 (0.27, 0.54) |

Table 1: Simulated disease trajectory prediction accuracy measured using mean absolute error. The columns labeled Δ report the mean paired differences of absolute residuals between the RGP and CGP (positive numbers show that the CGP has lower error). 95% confidence intervals are shown in parentheses (computed using pivotal bootstrap), * indicates significant difference (i.e. 0 \( \not\in \) CI).

Specifically, we model how an individual’s test results will progress if left untreated after the first 12 hours, which is formalized by the counterfactual distribution \( P(\{Y_t | \omega : t > 12\} | H_{12}) \). This is a hard problem in health care because real clinical data is nearly always collected from patients who are being actively treated, and the natural progression is therefore unobserved and counterfactual.

Simulation. Using the model described in Equation[2] we simulate observational lab test result traces assuming a single type of intervention. The event model \( \lambda^* (t) p^s (z_y, z_a | t) \) is implemented as follows. The hazard \( \lambda^* (t) = 15 \) is a constant function set so that there are 15 events on average per patient. The outcome indicator \( z_y \) is always equal to 1 (i.e. we always observe a marker at an event time), and \( z_a \) is drawn from a Bernoulli distribution with parameter \( p = \sigma (\bar{y}_{t-2:t} / \bar{z} t) \), where \( \sigma \) is the inverse logit function and \( \bar{y}_{t-2:t} \) is the average of the observed markers in the last two hours (individuals with lower recent histories are more likely to be treated). There is only a single action type, so \( p^s (a | y, t, z_a) = 1 \). Finally, the outcomes are modeled using a mixture of GPs with three classes. The covariance is shared between all classes, and is defined using a Matérn 3/2 kernel (variance 0.2^2, lengthscale 8.0) and independent Gaussian noise (scale 0.1) added to each observation. Each class has a distinct mean function parameterized using a 5-dimensional, order-3 B-spline. The first class has a declining mean trajectory, the second has a trajectory that declines then stabilizes, and the third has a stable trajectory[2]. The actions affect the mean function for each class by increasing it by a constant amount for 2 hours. If two or more actions occur within 2 hours of one another, the effects do not compound. We simulate 200 trajectories for training, and 200 for testing. This simulation model satisfies Assumptions[1,3] and[4].

Model. As a baseline, we consider a classical GP regression approach (e.g. Rasmussen and Williams[2006]) which models the distribution \( P(\{Y_t : t > 12\} | H_{12}) \) by regressing the trajectories beyond hour 12 on to the histories. We refer to this as the regression GP (RGP). For both the RGP and CGP outcome model, we use a mixture of three GPs (as was used to simulate the data). We assume that the mean function coefficients, the covariance parameters, and the treatment effect size are unknown and must be learned. We emphasize that both the CGP and RGP have identical forms, but are trained using different objectives; the RGP marginalizes over future actions, inducing an implicit dependence on the treatment policy in the training data, while the CGP explicitly controls for them while learning. Predictions for both are made using the posterior predictive mean given data and interventions up until 12 hours.

Results. Table[1] reports mean absolute errors (MAE) scaled by the observation noise \( \sigma = 0.1 \) for the RGP and CGP in three scenarios. In the “Experimental” scenario, we modify the simulation model to never produce actions after 12 hours. This is equivalent to obtaining experimental data for the counterfactual of interest. This implies that the RGP will recover the counterfactual distribution, and so there is no advantage to using CGP (indeed we see no difference between the two models in Table[1]). In the “Observational” scenario, we simulate training data from the simulation model as described above. This represents the type of observational traces that are available in practice, where clinicians treat patients as usual. In Table[1] we see that the CGP performs just as well as in the experimental scenario, but the RGP’s performance has degraded considerably. This highlights that the CGP is able to learn a counterfactual predictive model as though we had run a proper experiment. Finally, in the “Unobserved Confounders” scenario we change the simulation by introducing a dependence between an individual’s latent mixture class and the treatment model so that the declining class is unresponsive to treatment and less likely to receive it. This modification violates Assumption[8] and we see that the CGP is no longer able to generalize from the observational data.

[2] The exact B-spline coefficients can be found in the simulation code included in the supplement.
These results have broad consequences for the practice of building predictive models from observational data. In our example setting of disease trajectory models, for instance, state-of-the-art approaches do not explicitly control for future actions (see e.g., [Li-wei et al. 2015], [Schulam and Saria 2015], [Alaa et al. 2016], [Wiens et al. 2016], [Cheng et al. 2017]), and are therefore sensitive to the treatment policy in the training data. This compromises their reliability, which is critical in health care. Counterfactual GPs sidestep this issue, and offer a new, more reliable way to train predictive models for data in continuous-time.

3.2 CGPs for Medical Decision Support

Creatinine is a compound produced as a by-product of the chemical reaction in the body that breaks down creatine to fuel muscles. Healthy kidneys normally filter creatinine out of the body, which can otherwise be toxic in large concentrations. During kidney failure, however, creatinine levels rise and the compound must be extracted using a medical procedure called dialysis. Patients in the intensive care unit (ICU) often experience kidney failure, and therefore need to undergo dialysis. The procedure, however, is expensive and, if given unnecessarily, can waste critical resources (e.g. staff and equipment). It is therefore important that managing physicians have access to estimates of how an individual’s creatinine levels will progress so they can decide whether treatment is appropriate or whether an individual’s therapy can be stopped without putting the patient at risk.

To demonstrate how the CGP can be used as a decision support tool, we extract observational creatinine traces from the publicly available MIMIC-II database [Saeed et al., 2011]. The cohort is defined by identifying patients in the database who tested positive for abnormal creatinine levels, which is a sign of kidney failure. We also extract the times at which three different types of dialysis were given to each individual: intermittent hemodialysis (IHD), continuous veno-venous hemofiltration (CVVH), and continuous veno-venous hemodialysis (CVVHD). The data set includes a total of 428 individuals, with an average of 34 (±12) creatinine observations each. We shuffle the data and use 300 traces for training, 50 for validation and model selection, and 78 for testing.

Model. We parameterize the outcome model of the CGP using a mixture of GPs. We always condition on the initial creatinine measurement and model the deviation from that initial value. The mean for each class is zero (i.e. there is no deviation from the initial value on average). We parameterize the covariance function using two non-stationary kernel functions. Let \( \phi : t \rightarrow [1, t, t^2]^\top \in \mathbb{R}^3 \) denote the quadratic polynomial basis, then the first kernel is \( k_1(t_1, t_2) = \phi^\top(t_1)\Sigma\phi(t_2) \), where \( \Sigma \in \mathbb{R}^{3 \times 3} \) is a positive-definite symmetric matrix parameterizing the kernel. The second kernel is the covariance function of the integrated Ornstein-Uhlenbeck (IOU) process (see e.g., [Taylor et al. 1994]), which is parameterized by two scalars \( \alpha \) and \( \nu \) and defined as

\[
\begin{align*}
    k_{\text{IOU}}(t_1, t_2) &= \frac{\nu^2}{2\pi^2} \left( 2\alpha \min(t_1, t_2) + e^{-\alpha t_1} + e^{-\alpha t_2} - 1 - e^{-\alpha |t_1 - t_2|} \right),
\end{align*}
\]

The IOU covariance corresponds to the random trajectory of a particle whose velocity drifts according to an OU process. We assume that each creatinine measurement is observed with independent Gaussian noise with scale \( \sigma \). Each class in the mixture has a unique set of covariance parameters. To model the treatment effects in the outcome model, we define a short-term function and long-term response function. If an action is taken at time \( t_0 \), the outcome \( \delta = t - t_0 \) hours later will be additively affected by the response function \( g(\delta; h_1, a, b, h_2, r) = g_s(\delta; h_1, a, b) + g_l(\delta; h_2, r) \), where \( h_1, h_2 \in \mathbb{R} \) and \( a, b, r \in \mathbb{R}_+ \). The short-term and long-term response functions are defined as \( g_s(\delta; h_1, a, b) = \frac{h_1}{a-b} \left( e^{-b \delta} - e^{-a \delta} \right) \), and \( g_l(\delta; h_2, r) = h_2 \cdot (1.0 - e^{-r \delta}) \). Each class in the mixture has a unique set of response function parameters. We assume that Assumptions 1-8 hold, and that the event and action models have separate parameters, so can remain unspecified when estimating the outcome model. We fit the CGP outcome model using Equation [3] and select the number of classes in the mixture using fit on the validation data (we choose three components).
**Results.** Figure 2 demonstrates how the CGP can be used for medical decision support. Each panel in the figure shows data for an individual drawn from the test set. The green points show measurements on which we condition to obtain a posterior distribution over mixture class membership and the individual's latent trajectory under each class. The red points are unobserved, future measurements. In grey, we show predictions under the factual sequence of actions extracted from the MIMIC-II database. Treatment times are shown using vertical bars marked with an “x” (color indicates which type of treatment was given). In blue, we show the CGP’s counterfactual predictions under an alternative sequence of actions. The posterior predictive trajectory is shown for the MAP mixture class (mean is shown by a solid grey/blue line, 95% credible intervals are shaded).

We qualitatively discuss the CGP’s counterfactual predictions, but cannot quantitatively evaluate them without prospective experimental data from the ICU. We can, however, measure fit on the factual data and compare to baselines to evaluate our modeling decisions. Our CGP’s outcome model allows for heterogeneity in the covariance parameters and the response functions. We compare this choice to two alternatives. The first is a mixture of three GPs that does not model treatment effects. The second is a single GP that does model treatment effects. Over a 24-hour horizon, the CGP’s mean absolute error (MAE) is 0.39 (95% CI: 0.38-0.40) and for predictions between 24 and 48 hours in the future the MAE is 0.62 (95% CI: 0.60-0.64). The pairwise mean difference between the first baseline’s absolute errors and the CGP’s is 0.07 (0.06, 0.08) for 24 hours, and 0.09 (0.08, 0.10) for 24-48 hours. The mean difference between the second baseline’s absolute errors and the CGP’s is 0.04 (0.04, 0.05) for 24 hours and 0.03 (0.02, 0.04) for 24-48 hours. The improvements over the baselines suggest that modeling treatments and heterogeneity with a mixture of GPs for the outcome model are useful for this problem.

Figure 2 shows factual and counterfactual predictions made by the CGP. In the first (left-most) panel, the patient is factually administered IHD about once a day, and is responsive to the treatment (creatinine steadily improves). We query the CGP to estimate how the individual would have responded had the IHD treatment been stopped early. The model reasonably predicts that we would have seen no further improvement in creatinine. In the third panel, an individual with erratic creatinine levels receives CVVHD for the last 100 hours and is responsive to the treatment. As before, the CGP counterfactually predicts that she would not have improved had CVVHD not been given. Interestingly, panel four shows the opposite situation: the individual did not receive treatment and did not improve for the last 100 hours, but the CGP counterfactually predicts an improvement in creatinine similar to that in panel 3 if daily CVVHD had been administered.

4 Discussion

We proposed the counterfactual Gaussian process (CGP) to model the effects of actions taken in continuous-time on continuous-time trajectories (time series). The CGP builds on previous ideas in continuous-time causal inference (e.g., [Robins 1997], [Arjas and Parner 2004], [Lok 2008]), but is unique in that it can predict the full counterfactual trajectory; we combined marked point processes (MPP) with GPs to model observational traces, and described three assumptions that are sufficient to connect the statistical model to the target counterfactual model. We presented two sets of experimental results. In the first, we used the CGP to model the natural progression (i.e. untreated progression) of a clinical marker trajectory. This task is challenging because observational clinical data is almost always collected from patients who are being actively treated, so the natural progression is unobserved and counterfactual. We demonstrated that the CGP can recover an accurate natural progression model from observational data, but that a GP trained using a standard approach is severely biased by the interventions in the training data. In the second experiment, we used the CGP to model the progression of creatinine and its response to dialysis using data from the MIMIC-II repository ([Saeed et al., 2011]). We quantitatively evaluated the CGP’s fit to the factual data against two baselines, and demonstrated how the CGP’s counterfactual predictions can be used for medical decision support. Our work points to several exciting future research directions. First, the validity of conclusions drawn from the CGP are conditioned upon a set of assumptions that are, in general, not testable. The reliability of our approach therefore critically depends on the plausibility of those assumptions in light of domain knowledge. Formal procedures, such as sensitivity analyses (e.g., [Robins et al., 2000], [Scharfstein et al., 2014]), that can identify when causal assumptions conflict with a data set will help to make our method more easily applied in practice. Alternatively, there may be other sufficient assumptions that allow us to learn counterfactual GPs and are also easier to validate.

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395% confidence intervals computed using the pivotal bootstrap are shown in parentheses.
A  Equivalence of MPP Outcome Model and Counterfactual Model

At a given time \( t \), we want to make predictions about the potential outcomes that we will measure at a set of future query times \( q = [s_1, \ldots, s_m] \) given a specified future sequence of actions \( a \). This can be written formally as

\[
P(\{Y_s[a] : s \in q \} \mid \mathcal{H}_t)
\]  

(4)

Without loss of generality, we can use the chain rule to factor this joint distribution over the potential outcomes. We choose a factorization in time order; that is, a potential outcome is conditioned on all potential outcomes at earlier times. We now describe a sequence of steps that we can apply to each factor in the product.

\[
P(\{Y_s[a] : s \in q \} \mid \mathcal{H}_t) = \prod_{i=1}^{m} P(Y_{s_i}[a] \mid \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t).
\]  

(5)

Using Assumption 3, we can introduce random variables for marked points that have the same timing and actions as the proposed sequence of actions without changing the probability. Recall our assumption that actions can only affect future values of the outcome, so we only need to introduce marked points for actions taken at earlier times. Formally, we introduce the set of marked points for the potential outcome at each time \( s_i \)

\[
\mathbf{A}_i = \{(t', \emptyset, a, 0, 1) : (t', a) \in a, t' < s_i \}.
\]  

(6)

We can then write

\[
P(Y_{s_i}[a] \mid \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t) = P(Y_{s_i}[a] \mid \mathbf{A}_i, \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t).
\]  

(7)

To show that \( P(Y[a] \mid A = a, X = x) = P(Y[a] \mid X = x) \) in Section 2, we use Assumption 2 to remove the random variable \( A \) from the conditioning information without changing the probability statement. We reverse that logic here by adding \( \mathbf{A}_i \).

Now, under Assumption 1 after conditioning on \( \mathbf{A}_i \), we can replace the potential outcome \( Y_{s_i}[a] \) with \( Y_{s_i} \). We therefore have

\[
P(Y_{s_i}[a] \mid \mathbf{A}_i, \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t) = P(Y_{s_i} \mid \mathbf{A}_i, \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t).
\]  

(8)

Similarly, because the set of proposed actions affecting the outcome at time \( s_i \) contain all actions that affect the outcome at earlier times \( s < s_i \), we can invoke Assumption 1 again and replace all potential outcomes at earlier times with the value of the observed process at that time.

\[
P(Y_{s_i} \mid \mathbf{A}_i, \{Y_s[a] : s \in q, s < s_i \}, \mathcal{H}_t) = P(Y_{s_i} \mid \mathbf{A}_i, \{Y_s : s \in q, s < s_i \}, \mathcal{H}_t).
\]  

Next, Assumption 4 posits that the outcome model \( p^*(y \mid t', z_y = 1) \) is the density of \( P(Y_{t'} \mid \mathcal{H}_t) \), which implies that the mark \( (t', y, \emptyset, 1, 0) \) is equivalent to the event \( (Y_{t'} \in dy) \). Therefore, for each \( s_i \) define

\[
\mathbf{O}_i = \{(s, Y_s, \emptyset, 1, 0) : s \in q, s < s_i \}.
\]  

(9)

Using this definition, we can write

\[
P(Y_{s_i} \mid \mathbf{A}_i, \{Y_s : s \in q, s < s_i \}, \mathcal{H}_t) = (Y_{s_i} \mid \mathbf{A}_i, \mathbf{O}_i, \mathcal{H}_t).
\]

The set of information \( (\mathbf{A}_i, \mathbf{O}_i, \mathcal{H}_t) \) is a valid history of the marked point process \( \mathcal{H}_{s_i}^- \) up to but not including time \( s_i \). We can therefore replace all information after the conditioning bar in each factor of Equation 7 with \( \mathcal{H}_{s_i}^- \).

\[
P(Y_{s_i} \mid \mathbf{A}_i, \mathbf{O}_i, \mathcal{H}_t) = P(Y_{s_i} \mid \mathcal{H}_{s_i}^-).
\]  

(10)

Finally, by applying Assumption 4 again, we have

\[
P(Y_{s_i} \in dy \mid \mathcal{H}_{s_i}^-) = p^*(y \mid s_i, z_y = 1) \, dy.
\]  

(11)

The potential outcome query can therefore be answered using the outcome model, which we can estimate from data.
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