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Constrained Gaussian process with application in tissue-engineering scaffold biodegradation

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ABSTRACT

In many biomanufacturing areas, such as tissue-engineering scaffold fabrication, the biodegradation performance of products is a key to producing products with desirable properties. The prediction of biodegradation often encounters the challenge of how to incorporate expert knowledge. This article proposes a Constrained Gaussian Process (CGP) method for predictive modeling with application to scaffold biodegradation. It provides a unified framework of using appropriate constraints to accommodate various types of expert knowledge in predictive modeling, including censoring, monotonicity, and bounds requirements. Efficient Bayesian sampling procedures for prediction are also developed. The performance of the proposed method is demonstrated in a case study on a novel scaffold fabrication process. Compared with the unconstrained GP and artificial neural networks, the proposed method can provide more accurate and meaningful prediction. A simulation study is also conducted to further reveal the properties of the CGP.

1. Introduction

Biomanufacturing is an emerging area that is experiencing rapid growth (Grant and Settles, 2009). In biomanufacturing, biodegradation is an important performance aspect of products (Buchanan, 2008), especially for those integrated into human systems and made by degradable biomaterials. Figure 1 depicts the complicated biodegradation process caused by hydrolysis: in the human body environment, water molecules penetrate into the matrix of the product, causing it to swell. This triggers the breakdown of chemical chains, leading to weight loss, which continues until complete dissolution of the product.

For many biomanufacturing processes, the biodegradation rate of the product needs to be designed to meet the requirements of a specific application. One typical example is scaffold fabrication in tissue engineering, as illustrated in Figure 2, in an attempt to develop biological substitutes for failing tissues/organs (Fisher et al., 2007; Chu and Liu, 2008; Sultana, 2013). First, relevant cells are grown in vitro to form a three-dimensional tissue/organ. To enable the cells to grow in favored orientations—i.e., those in the native tissue—the cells are seeded onto the scaffold, which is a highly porous matrix made from degradable biomaterials. The pores on the scaffold provide space for flow transport of nutrients and metabolic wastes, thus forming a temporary substrate and microenvironment for cells. Then the cell–scaffold composite is implanted into the human body, where the scaffold eventually degrades, leaving only the new tissue/organ. As the scaffold plays a critical role in the success of this development, it is crucial to match the degradation rate of the scaffold to the cell growth rate in the application of interest (Burdick and Mauck, 2011). If the degradation rate is too fast, there can be insufficient support to the cells, whereas if the degradation rate is too slow, the scaffold may impede the growth of the new tissue.

In scaffold fabrication, the biodegradation performance of products is usually characterized by an experiment setup as shown in Figure 3 (Henry et al., 2007; Dey et al., 2008; Nicodemus and Bryant, 2008). Scaffold specimens are incubated in phosphate-buffered saline (PBS)—i.e., salt solution—used to mimic the environment found in the human body for a period of time; at each predetermined time point, one specimen is taken out, dried, measured for weight loss, and then discarded. Scaffold products with desired biodegradation performances can be obtained by adjusting the process variables of scaffold fabrication, such as those in material synthesis (e.g., compositions of the biomaterial and their percentages) and those in pore construction (e.g., pore size and processing conditions; Liao et al. (2002); Cui et al. (2015)).

Achieving the desired biodegradation performance is, however, a challenge, due to the lack of an understanding of the relationship between process variables and biodegradation performance of products. Analytical models of the relationship are often not available, due to the effects of process variables on scaffold biodegradation being very complicated. As a result, the trial-and-error approach predominates in this field (Burdick and Mauck, 2011). In this study, we focus on data-driven methods for predictive modeling of scaffold biodegradation. The objective is to establish an empirical model for biodegradation prediction in scaffold fabrication such that it will enable process optimization to produce scaffolds with a required biodegradation performance.
It is worth pointing out that the problem considered in this article is different from degradation modeling in reliability studies (Chen and Tsui, 2013; Bian and Gebrael, 2014; Ranfiee et al., 2014). First, the biodegradation of scaffolds is treated as a controllable performance aspect of products in this study, which is different from the degradation of engineering components that is a reliability concern. Second, the modeling of biodegradation concerns the characterization of the relationship between product biodegradation performance and process variables in scaffold fabrication, whereas degradation modeling in reliability studies concerns the characterization of the time evolution of degradation. Finally, the data used in this study are scaffold biodegradation measurements (as shown in Fig. 3) under different settings of process variables. Often the measurements are collected at a small number of time points (e.g., five in the case study), as quantification of biodegradation is very time-consuming (taking months or years in some cases). In contrast, classic time-series data tend to be used in reliability studies.

Surrogate models are common methods for predictive modeling of complex relationships between process variables/design parameters (predictors) and product performance (response) in manufacturing applications (Chen et al., 2006; Tsai et al., 2012; Arendt et al., 2015). Among various surrogate models, Gaussian Process (GP) and Artificial Neural Networks (ANNs) are two popular approaches that are widely used in problems similar to the one studied in this article. For example, GP modeling is used in the prediction of a product’s mechanical performance in nanomanufacturing (Pourhabib et al., 2015) and of wafer geometric quality in semiconductor manufacturing (Jin et al., 2012). ANNs are used in the prediction of surface roughness and other quality measures in machining (Feng and Wang, 2003, 2004; Feng et al., 2006).

However, the aforementioned surrogate methods may not work well for modeling scaffold biodegradation, as expert knowledge needs to be incorporated to ensure meaningful prediction. Such knowledge includes the following:

1. **Full-degradation censoring**: Once the point of full degradation is reached, the weight loss measurement will be a constant 100%.
2. **Monotonicity**: Intrinsically, the biodegradation of scaffolds is monotonically increasing with respect to time and to some process variables in scaffold fabrication.
3. **Bounds of weight loss**: The percentage of weight loss is bounded by 0% and 100%.

Without guidelines from expert knowledge, those methods are likely to result in poor predictions and interpretation. Thus, a novel modeling method is called for, one that is able to accommodate these three types of expert knowledge.

Zeng et al. (2016) develop a constrained hierarchical model for the problem of modeling scaffold biodegradation, where one type of expert knowledge is incorporated as a constraint on model parameters. This approach is easy to implement and creates a good interpretation; however, it only works for monotonicity constraints. In the literature, some nonparametric-constrained modeling methods, such as shape-constrained function estimation methods (e.g., Shively et al., 2011; Wang and Ghosh, 2012; Chatterjee et al., 2015), have been shown to be useful for this problem. However, they also can only deal with monotonicity constraints. Moreover, they are designed for the one-dimensional case (i.e., a single predictor) as opposed to the

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**Figure 1.** An illustration of the biodegradation of products made from degradable biomaterials.

**Figure 2.** The development of biological substitutes for failing tissue/organs in tissue engineering.

**Figure 3.** Experimental setup to characterize biodegradation in scaffold fabrication.
multi-dimensional case (i.e., more than one predictor) assumed in this study. There are also some papers that consider shape constraints in GP modeling (Riihimäki and Vehtari, 2010; Wang, 2012; Lin and Dunson, 2014; Wang and Berger, 2016; Lenk and Choi, 2017). These methods may incorporate constraints conveniently and do work for multi-dimensional cases but, again, they are limited to monotonicity and other shape constraints.

In this article, we propose a Constrained GP (CGP) method for the predictive modeling of scaffold biodegradation. It provides a unified framework to accommodate the aforementioned three types of expert knowledge in the form of constraints. Efficient Bayesian algorithms are developed and used for model estimation and prediction. The algorithms address several procedures to implement the CGP method are summarized in Section 3. Section 3 describes the proposed CGP method to impose each definition of the scaffold biodegradation modeling problem. Appendix C, for the convenience of practitioners.

2. Background and problem definition

In this section, we will briefly review the basics of GP modeling and prediction. Then we define the problem of modeling scaffold biodegradation.

2.1. GP model

Suppose the observed data are \((x_i, y_i), i = 1, \ldots, n\), where \(x_i = [x_{i1}, \ldots, x_{id}]\) is the \(i\)th realization of the \(d\)-dimensional predictor and \(y_i\) is the corresponding response. Following the GP literature (Santner et al., 2003; Fang et al., 2005), we call \(x_1, \ldots, x_n\) locations. To model the relationship between the response and predictors, the GP modeling considers

\[
y_i = \mu + f(x_i) + \epsilon_i,
\]

where \(\mu\) is the mean, \(f(x_i)\) is a random function of \(x_i\), and \(\epsilon_i \sim N(0, \sigma^2)\) is the random error, called the nugget effect, which is independent of \(f(x_i)\). Here the random function \(f(x)\) follows a GP with zero mean and covariance function \(\sigma_f^2 R(x)\). That is, the vector \([f(x_1), f(x_2), \ldots, f(x_n)]'\) follows a multivariate normal distribution with \(f(x_i) \sim N(0, \sigma_f^2)\) and \(\text{cov}(f(x_i), f(x_j)) = \sigma_f^2 R_{ij}\) for \(i \neq j\). A popular choice for the correlation function is the Gaussian correlation function (Rasmussen and Williams, 2006) such that

\[
R_{ij} = \prod_{n=1}^{d} \exp \left[-\theta_n (x_{in} - x_{jn})^2\right],
\]

where \(\theta = \{\theta_1, \ldots, \theta_d\}\) are scale parameters on each dimension of the predictor. Thus, the correlation of \(f(x_1)\) and \(f(x_2)\) depends on the distance between the two locations \(x_1\) and \(x_2\).

By denoting \(y = [y_1, y_2, \ldots, y_n]'\), \(X = [x_1, x_2, \ldots, x_n]'\), \(\epsilon = [\epsilon_1, \epsilon_2, \ldots, \epsilon_n]'\), it is easy to see that

\[
y \sim N \left(\mu I_n, \sigma_f^2 R(X, X) + \sigma_\epsilon^2 I_n\right),
\]

where \(I_n\) is an \(n\)-dimensional column vector of ones and \(R(X, X)\) is the correlation matrix of \(f(X) = [f(x_1), f(x_2), \ldots, f(x_n)]'\) with the \((i, j)\)th entry \(R_{ij}\) and \(I_n\) is the \(n \times n\) identity matrix. For notational convenience, we denote the covariance function by

\[
K_{00}^0(X, X) = \sigma_f^2 R(X, X) = (K_{00}^0(x_i, x_j))_{n \times n},
\]

where \(K_{00}^0(x_i, x_j) = \text{cov}(f(x_i), f(x_j)) = \sigma_f^2 R_{ij}\). Here the superscript “00” is to distinguish the covariance function of the GP from other covariance functions, such as those given in Section 3.2.

The prediction based on GP modeling is straightforward as follows. Let \(X = [x_1', x_2', \ldots, x_n']'\) be the vector of locations for prediction and \(f(X') = [f(x_1'), f(x_2'), \ldots, f(x_n')]'\) be the function values at these locations. Since \(f(x)\) follows a GP, it is easy to find that \((f(X'), f(X'))'\) follows a multivariate normal, and \(f(X')\) given \(y\) also follows a multivariate normal with mean and variance–covariance matrix as follows (Schabenberger and Gotway, 2005):

\[
E[f(X')|y, \psi] = \mu I_n + K_{00}^0(X', X) [K_{00}^0(X, X) + \sigma_\epsilon^2 I_n]^{-1} \times (y - \mu I_n),
\]

\[
\text{cov}[f(X')|y, \psi] = K_{00}^0(X', X') - K_{00}^0(X', X)
\times [K_{00}^0(X, X) + \sigma_\epsilon^2 I_n]^{-1} K_{00}^0(X, X'),
\]

where \(\psi = [\mu, \theta, \sigma_f^2, \sigma_\epsilon^2]\) contains the parameters of the GP, \(K_{00}^0(X', X) = \text{cov}(f(X'), f(X)) = \sigma_f^2 R(X', X)\), and \(K_{00}^0(X', X')\) is similarly defined. Thus, the conditional mean
E[f(X*)|y, ψ] in Equation (5) can be used as a best linear unbiased predictor of f(X*).

It should be noted that estimation and prediction based on GP modeling are often described in the Bayesian framework. In this framework, the distributions based on the basic setup of the GP—e.g., Equation (3)—are called prior distributions, whereas those updated distributions given data—e.g., Equation (5)—are called posterior distributions. This framework is followed in this article.

### 2.2. Predictive modeling of scaffold biodegradation

There are two sets of predictors in scaffold biodegradation: (i) time and (ii) the process variables used in the fabrication of the scaffold. For convenience, we will use the two-dimensional case, with time \( t \) and a process variable \( z \) as predictors, to illustrate the problem of modeling biodegradation; however, the proposed CGP is a generic method that can be applied to multi-dimensional cases. Suppose the biodegradation experiment is conducted at a grid of \( n \) time points \((t_1 < t_2 < \cdots < t_n)\) and \( n_z \) values of the process variable \((z_1 < z_2 < \cdots < z_{n_z})\).

We denote \( \{x_1, \ldots, x_i\} \) as these \( n = n_t \times n_z \) different settings of the predictors. The corresponding responses are the weight loss measurements \( \{y_1, \ldots, y_n\} \). Figure 4 illustrates the structure of the data (not real data), where each stream of solid dots represents biodegradation measurements under the same value of the process variable. The objective of this work is to model the relationship between the response and the predictors and thus enable us to predict the weight loss at new locations \( x_1^*, x_2^*, \ldots, x_i^* \). In the modeling, the three types of expert knowledge described in the Introduction (i.e., censored, monotonicity, and bounds requirements) are taken into account.

It is worth pointing out that a new location can represent (i) an unsampled time point under a sampled value of \( z \) (e.g., a time point between \( t_1 \) and \( t_2 \) under \( z = z_1 \)); or (ii) a sampled time point under an unsampled value of \( z \) (e.g., \( t_2 \) under a \( z \) value between \( z_1 \) and \( z_2 \)); or (iii) an unsampled time point under an unsampled value of \( z \) (e.g., a time point between \( t_1 \) and \( t_2 \) under a \( z \) value between \( z_1 \) and \( z_2 \)).

In addition, the \( t \) value and/or \( z \) value of a new location can be within or outside of the observed data region; the estimation of weight loss in these two cases is called interpolation and extrapolation, respectively. For simplicity, both cases are called “prediction” in this article, and the performance of the proposed method in each case will be investigated in the case study.

### 3. The proposed method

This section describes the proposed CGP method for scaffold biodegradation modeling, where the three types of expert knowledge will be incorporated in the form of constraints, referred to as the censored constraint, monotonicity constraint, and bound constraint. The method simultaneously imposes multiple constraints of these three types. To facilitate understanding, how to impose each type of constraint will be presented in the following subsections.

#### 3.1. Imposing the censoring constraint

Censored measurements are often encountered in scaffold biodegradation experiments, as shown in Figure 5, where the censored measurement occurs at \( x_n = [t_n, z_n]^T \). This measurement indicates that full degradation is reached at or before \( t_n \) under \( z = z_n \). Obviously, the measured value “100%” cannot be directly used as the response at \( x_n \) in the modeling and prediction study. Here we propose a novel method to take this censored measurement into account.

The idea is as follows: Let the dashed line in Figure 5 represent the true biodegradation trajectory during the measurement period. The piece of the line above “100%” is not realizable, due to the full degradation of the scaffold; it is simply an extension of the realizable biodegradation trajectory. Let \( y_n \) be the weight loss at \( x_n \), denoted by the dotted circle in Figure 5. Note that \( y_n \) is not an actual measurement but is rather an imagined quantity. Also, \( y_n \) is a random variable, which cannot be lower than 100% based on the actual measurement at this location. Consequently, we can impose a constraint “\( y_n \geq 100\)” in the modeling study. The CGP method following this idea is described below.

Let us first consider the case with one censored measurement as shown in Figure 5. Denoting the uncensored data as \( y^{(n-1)} = [y_1, y_2, \ldots, y_{n-1}]^T, X^{(n-1)} = [x_1, x_2, \ldots, x_{n-1}]^T \), the whole data set is \( y = [y^{(n-1)}; y_n], X = [X^{(n-1)}; x_n] \). From Equation (3), the prior of \( y_n \) is a truncated Gaussian:

$$
\pi(y_n) = N(\mu, \sigma_\mu^2 + \sigma_\epsilon^2) \cdot I(y_n \geq 100).
$$

where \( I(\cdot) \) is an indicator function. Given this prior, the joint (conditional) posterior of the prediction \( f(X^*) \) and \( y_n \) can be found, as stated below.

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**Figure 4.** Illustration of the biodegradation data used in this study.

**Figure 5.** Illustration of the censoring constraint.
Proposition 1. Given the prior in Equation (6), the joint posterior distribution of \( f(X^c), y_n \) is
\[
P(f(X^c), y_n | y^{(n-1)}, \psi) = P(f(X^c) | y^{(n-1)}, y_n, \psi) \cdot P(y_n | y^{(n-1)}, \psi) = P(f(X^c) | y, \psi) \cdot P(y_n | y^{(n-1)}, \psi),
\]
where
\[
y_n | y^{(n-1)}, \psi \sim N(m(x_n), V(x_n)) \cdot I(y_n \geq 100),
\]
\[
f(X^c) | y, \psi \sim N(m(X^c), V(X^c)),
\]
with
\[
m(x_n) = \mu + K_{00}^{(0)}(x_n, X^{(n-1)}) \left[ K_{00}^{(0)}(X^{(n-1)}, X^{(n-1)}) + \sigma_x^2 I_{m-1} \right]^{-1} \cdot (y^{(n-1)} - \mu 1_{n-1}),
\]
\[
V(x_n) = K_{00}^{(0)}(X^{(n-1)}, X^{(n-1)}) - K_{00}^{(0)}(x_n, X^{(n-1)}) \cdot \left[ K_{00}^{(0)}(X^{(n-1)}, X^{(n-1)}) + \sigma_x^2 I_{m-1} \right]^{-1} K_{00}^{(0)}(x_n, x_n),
\]
\[
m(X^c) = \mu 1_m + K_{00}^{(0)}(X^c, X^{(n-1)}) K_{00}^{(0)}(X^{(n-1)}, X^{(n-1)})^{-1} (y - \mu 1_n),
\]
\[
V(X^c) = K_{00}^{(0)}(X^c, X^c) - K_{00}^{(0)}(X^c, X^{(n-1)}) \cdot \left[ K_{00}^{(0)}(X^{(n-1)}, X^{(n-1)}) + \sigma_x^2 I_{m-1} \right]^{-1} K_{00}^{(0)}(X^c, X^{(n-1)}).
\]

The proof is given in Appendix A. The above result indicates that the joint posterior of \( f(X^c) \) and \( y_n \) given the uncensored data \( y^{(n-1)} \) and the GP parameter \( \psi \) can be decomposed into two parts: the conditional posterior of \( y_n \) given \( y^{(n-1)} \) and the conditional posterior of \( f(X^c) \) given \( y^{(n-1)} \) and \( y_n \). The specific forms of the two conditional posteriors are given in Equations (7) and (8). Specifically, the conditional posterior of \( y_n \) is a truncated normal distribution, whereas the conditional posterior of \( f(X^c) \) is a multivariate normal distribution. Consequently, an estimate of the two conditional posteriors are given in Equations (7) and (8).

The above method can be extended in a straightforward manner to deal with cases of more than one censored measurement. Assume there are \( n_c \) censored measurements, with locations \( X^{(c)} = [x^{(1)}, \ldots, x^{(n_c)}] \) and imagined responses \( y^{(c)} = [y^{(1)}, \ldots, y^{(n_c)}] \). Then the prior in Equation (6) becomes
\[
\pi(y^{(c)}) = N(\mu 1_{n_c}, K_{00}^{(0)}(X^{(c)}, X^{(c)}) + \sigma_x^2 I_{n_c}) \cdot I(y^{(1)} \geq 100, \ldots, y^{(n_c)} \geq 100).
\]

Given this prior, the posterior in Equations (7) and (8) still apply, the main difference being that the scalar terms are replaced with their vector counterparts.

### 3.2. Imposing the monotonicity constraint

As mentioned in the Introduction, scaffold biodegradation follows some intrinsic monotonicity properties with respect to time or certain process variable according to expert knowledge. As shown in Fig. 3, each scaffold specimen yields only one data point; the specimen is destroyed during the weight loss measurement and is then discarded. In other words, the data points on the observed biodegradation profile are obtained from different specimens rather than from the same specimen over time. As a result, it is possible that some later measurements are smaller than earlier measurements (e.g., the second data point in the lower part of Fig. 3) due to sample uncertainty among scaffold specimens. Consequently, predictions violating the intrinsic monotonicity may occur. Therefore, in practice, monotonicity constraints are necessary in modeling and prediction of the scaffold biodegradation data.

One advantage of adopting the GP modeling approach is that the derivative process of the GP is also a GP (Rasmussen and Williams, 2006), thus making it convenient to impose monotonicity constraints. Hereafter the two processes will be referred to as the original GP and the derivative GP. For ease of understanding, we will first consider monotonicity with respect to a single predictor and then generalize to both predictors.

**Case I: Monotonicity with respect to a single predictor**

Let us consider imposing monotonicity constraints with respect to time. We first need to specify a set of locations, called the constrained set, where monotonicity is required. Let \( X^A = [x^A_1, x^A_2, \ldots, x^A_{m}] \) be the vector of \( m \) constrained locations and \( f(X^A) = [f(x^A_1), f(x^A_2), \ldots, f(x^A_m)] \) be the first derivatives with respect to time at these locations. Thus, the monotonicity constraints are \( f(x^A_1) \leq 0, \ldots, f(x^A_m) \leq 0 \), as illustrated in Figure 6. Note that the locations in the constrained set do not have to be the observed ones \( \{x_1, \ldots, x_n\} \). The covariance of the derivative GP and the covariance of the derivative GP and the original GP are
\[
K^{00}(X, X^A) = (K^{00}(x_i, x^A_j))_{n \times m},\quad \text{where} \quad K^{00}(x_i, x^A_j) = 2\sigma_x^2 R_{ij} \theta_1 (x_i - x^A_j),
\]
\[
K^{10}(X^A, X) = (K^{10}(x^A_j, x_i))_{m \times n} = (K^{00}(x_i, x^A_j))_{n \times m},
\]
\[
K^{11}(X^A, X^A) = (K^{11}(x^A_j, x^A_k))_{m \times m},
\]
where
\[
k^{11}(x^A_j, x^A_k) = 2\sigma_x^2 R_{jk} \theta_1 \left( 1 - 2\theta_1 (x^A_j - x^A_k)^2 \right),
\]
where \( K^{11}(\cdot, \cdot) \) is the covariance function of the derivative GP, and \( K^{00}(\cdot, \cdot) \) is the covariance function of the original GP and the derivative GP. In the above formulas, \( x_i, x^A_j, x^A_k \) are the time values (among \( t_1, \ldots, t_n \)) of locations \( x_i, x^A_j, \) and \( x^A_k \); \( R_{ij} \) is the correlation function defined in Equation (2) between locations \( x_i \) and \( x^A_j \), and \( \theta_1 \) is the scale parameter for time in the correlation function. Derivations of Equation (9) are provided in Appendix B.

Given the monotonicity constraints, the prior of \( f(X^A) \) is
\[
\pi(f(X^A)) = N(0, K^{11}(X^A, X^A)) \cdot I(f(x^A_1) \geq 0, \ldots, f(x^A_m) \geq 0).
\]
The joint posterior of \( f(X^*) \) and \( f'(X^*) \) can be derived in a similar way as Proposition 1.

**Proposition 2.** Given the prior in Equation (9), the joint posterior distribution of \( (f(X^*), f'(X^*)) \) is

\[
P( f(X^*), f'(X^*) | y, \psi ) = P( f(X^*) | f'(X^*), y, \psi ) \cdot P( f'(X^*) | y, \psi )
\]

where

\[
f(X^*) | f'(X^*), y, \psi \sim N( m(X^*), V(X^*) ), \quad I( f'(x^*_i) \geq 0, \ldots, f'(x^*_n) \geq 0 ) \tag{11}
\]

\[
f(X^*), f'(X^*) | y, \psi \sim N( m(X^*), V(X^*) ) \tag{12}
\]

with

\[
m(X^*) = K^{10}(X^*, X)[\sigma^2_f I + K^{00}(X, X)]^{-1}(y - \mu_{1_n}),
\]

\[
V(X^*) = K^{11}(X^*, X^*) - K^{10}(X^*, X) 
\times [\sigma^2_f I + K^{00}(X, X)]^{-1} K^{01}(X, X^*),
\]

\[
m(X^*) = \mu_{1_n} + A^{-1}(A'_1 B_1^{-1}(y - \mu_{1_n}) + B_2^{-1} A_2 f'(X^*))
\]

\[
V(X^*) = A^{-1}.
\]

In the above terms, the matrix \( A = A'_1 B_1^{-1} A_1 + B_2^{-1} \) and the matrix \( A'_1 B_1^{-1} \) are given by

\[
A'_1 = K^{00}(X, X'), \quad A_1 = K^{01}(X, X'), \quad B_1 = \sigma^2_f I + K^{00}(X, X) - K^{01}(X, X'),
\]

and \( B_2 = K^{00}(X', X) - K^{01}(X', X') \) and \( K^{11}(X^*, X^*) = [K^{11}(X^*, X^*)]^{-1} K^{10}(X^*, X). \)

This result is similar to Lemma 3.1 in the study of Wang (2012). It has a similar interpretation as Proposition 1; that is, we can find an estimate for \( f(X^*) \) by sampling from the joint posterior of \( f(X^*) \) and \( f'(X^*) \): first, draw a sample of \( f'(X^*) \) from the truncated multivariate normal distribution in Equation (11) and, second, draw a sample of \( f(X^*) \) from the multivariate normal distribution in Equation (12).

If the biodegradation increases monotonically as the process variable \( z \) increases according to expert knowledge, monotonicity constraints with respect to \( z \) need to be imposed. All of the formulas will take the same form as above except that \( \theta_1 \) and \( x_{i1} - x^\Delta_{i1} \) are replaced by \( \theta_2 \) and \( x_{i2} - x^\Delta_{i2} \), respectively, in Equation (9).

**Case II: Monotonicity with respect to both predictors**

When the monotonicity constraints are applicable for both of the predictors, we can specify a general constrained set:

\[
X^\Delta = \left[ x^\Delta_1, \ldots, x^\Delta_{m_1}, x^\Delta_{m_1+1}, \ldots, x^\Delta_{m_n} \right],
\]

with their first derivatives being

\[
f(X^\Delta) = \left[ f^- (x^\Delta_1), \ldots, f^- (x^\Delta_{m_1}), f^- (x^\Delta_{m_1+1}), \ldots, f^- (x^\Delta_{m_n}) \right],
\]

where \( f^- (\cdot) = \partial f(\cdot)/\partial t, f^- (\cdot) = \partial f(\cdot)/\partial z \).

The constraints to impose are

\[
f^-(x^\Delta_1) > 0, \ldots, f^-(x^\Delta_{m_1}) > 0, f^- (x^\Delta_{m_1+1}) > 0, \ldots, f^- (x^\Delta_{m_n}) > 0.
\]

That is, there are monotonicity constraints with respect to time at \( m_1 \) locations \( \{x^\Delta_1, \ldots, x^\Delta_{m_1}\} \) and those with respect to the process variable at \( m-m_1 \) locations \( \{x^\Delta_{m_1+1}, \ldots, x^\Delta_{m_n}\} \), as illustrated in Figure 7.

In this case, Proposition 2 still applies, except that the covariance functions—i.e., \( K^{01}(X, X^\Delta) \) and \( K^{11}(X^\Delta, X^\Delta) \) in Equations (11) and (12)—are replaced by

\[
K^{10}(X^\Delta, X) = \begin{bmatrix} K^{10}(X^\Delta, X) & K^{00}(X^\Delta, X) \\ K^{01}(X^\Delta, X^\Delta) & K^{11}(X^\Delta, X^\Delta) \end{bmatrix},
\]

with

\[
x^\Delta_1 = \left[ x^\Delta_1, \ldots, x^\Delta_{m_1} \right], X^\Delta_{m_1+1} = \left[ x^\Delta_{m_1+1}, \ldots, x^\Delta_{m_n} \right], \text{and } X^\Delta = \left[ X^\Delta_1, X^\Delta_{m_1+1} \right].
\]

In the superscripts of the terms at the right side, “0” indicates the original GP, “1” indicates the first derivative with respect to time, and “2” indicates the first derivative with respect to the process variable. Specific formulas of the covariance functions and derivations are given in Appendix B.

**3.3. Imposing the bound constraint**

Bound constraints may exist at one or several locations of a prediction. Let us consider a general case where the predictions must satisfy \( f(x^*_i) \in U_1, \ldots, f(x^*_n) \in U_n \), with \( U_1, \ldots, U_n \) being the bounds of weight loss based on expert knowledge. This equates to a prior for the predictions

\[
\pi( f(X^*) ) = N( 0, K^{00}(X^*, X^*) ) \cdot I( f(x^*_i) \in U_1, \ldots, f(x^*_n) \in U_n ). \tag{14}
\]

The resulting posterior of \( f(X^*) \) is given below.

**Proposition 3.** Given the prior in Equation (14), the posterior of \( f(X^*) \) is

\[
f(X^*) | y, \psi \sim N( m(X^*), V(X^*) ) \cdot I( f(x^*_i) \in U_1, \ldots, f(x^*_n) \in U_n ),
\]

where the mean and variance–covariance matrices of the normal distribution are as defined in Equation (8).

This result is natural based on the results in Propositions 1 and 2. To obtain samples of \( f(X^*) \), we need to draw from the truncated multivariate normal distribution in Equation (15).

**4. Model estimation and inference**

Note that the posterior distributions in Propositions 1 to 3 are conditionally on the parameters of the original GP model \( \psi = [\mu, \theta, \sigma^2_f, \sigma^2_e] \), where \( \mu \) is the mean, \( \theta = [\theta_1, \ldots, \theta_d] \) are parameters of the correlation function, \( \sigma^2_f \) is the process variance, and \( \sigma^2_e \) is the random error variance. Thus, \( \psi \) needs to be estimated from data to generate predictions. Basically, the
implementation of the proposed CGP method involves two steps: (i) estimation of $\hat{\psi}$ and (ii) prediction of $f(\mathbf{x}^*)$ given the estimate of $\hat{\psi}$. A fully Bayesian approach treats $\hat{\psi}$ as a random vector like $f(\mathbf{x}^*)$ and conducts the two steps simultaneously by finding the joint posterior of $\hat{\psi}$ and $f(\mathbf{x}^*)$. However, this creates challenging issues; e.g., specifying priors for components of $\hat{\psi}$ that are intrinsically correlated (Wang, 2012) and sampling of the high-dimensional posterior. In this study, we adopt the idea of empirical Bayesian methods (Robert, 2007) and use the Maximum Likelihood Estimate (MLE) of $\hat{\psi}$. Then we predict $f(\mathbf{x}^*)$ by sampling from its conditional posterior given the MLE of $\hat{\psi}$. Details of the two steps are given in this section. Some other related issues will also be discussed.

### 4.1. Parameter estimation

A commonly used method to find the MLE of $\psi$ will now be briefly described (Ranjan et al., 2011). Defining $\delta = \sigma^2 / \sigma_i^2$, the closed form of the MLEs of $\mu$ and $\sigma^2$ given $\theta$ and $\delta$ is

$$\hat{\mu}(\theta, \delta) = \left[ I_n^T (\mathbf{R}(\mathbf{X}, \mathbf{X}) + \delta I_n)^{-1} I_n^T \right]^{-1} I_n^T (\mathbf{R}(\mathbf{X}, \mathbf{X}) + \delta I_n)^{-1} y,$$

and the variance of $\hat{\mu}(\theta, \delta)$ is

$$\hat{\sigma}^2(\theta, \delta) = \frac{(y - \hat{\mu}(\theta, \delta) I_n^T (\mathbf{R}(\mathbf{X}, \mathbf{X}) + \delta I_n)^{-1} (y - \hat{\mu}(\theta, \delta) I_n))}{n}.$$ 

that is, the MLE of $\mu$ and $\sigma^2$ are functions of other parameters (i.e., $\theta$ and $\delta$). Consequently, the MLEs of $\theta$ and $\delta$ can be found by minimizing the negative profile log-likelihood:

$$-2 \log L \propto \log |\mathbf{R}(\mathbf{X}, \mathbf{X}) + \delta I_n| + n \log \left[ (y - 1_n \hat{\mu}(\theta, \delta))^T (\mathbf{R}(\mathbf{X}, \mathbf{X}) + \delta I_n)^{-1} (y - 1_n \hat{\mu}(\theta, \delta)) \right].$$

where $|\cdot|$ is the determinant of a matrix. To address possible issues with bumpy likelihood surface near boundaries of the parameter space, a new parameterization for $\theta$ (Butler et al., 2014) can be used:

$$\omega_m = \log_{10}(\theta_m w) = 1, \ldots, d.$$

With this parameterization, peaks and dips of the likelihood surface will appear in the middle of the parameter space to facilitate a thorough search for the MLEs of $\theta$ and $\delta$.

### 4.2. Posterior sampling

Sampling from the posteriors given in Propositions 1 to 3 is challenging, due to their high dimension and need for truncation. We propose the following strategy for the posterior sampling, it integrates random generators built-in software (e.g., Matlab) and Markov Chain Monte Carlo (MCMC) algorithms (Robert and Casella, 2004):

- The posterior of $y_m$ in Equation (7), which is a truncated univariate normal distribution, can be sampled simply by drawing from the normal distribution and discarding samples that do not satisfy the constraint. Alternatively, to enhance the efficiency of sampling, we can use popular MCMC algorithms that directly draw from nonstandard distributions, such as truncated normal. One good choice is the slice sampler (Neal, 2003), which is both powerful and convenient to use, as it only needs the posterior to be sampled from and a set of casually picked initial values as inputs.

- The posterior of $f'(\mathbf{x}^*)$ in Equation (11), a truncated multivariate normal distribution, is more complex to sample. In this case, generating all elements of $f'(\mathbf{x}^*)$ simultaneously from the distribution has many issues, including the inefficiency in multivariate truncation. A better method is the Gibbs sampler that generates each element of $f'(\mathbf{x}^*)$—i.e., $f'(\mathbf{x}_1^*)$, $f'(\mathbf{x}_2^*)$—separately from its conditional posterior given other elements (Gelfand et al., 1992). This method will be used in this study for all samplings from truncated multivariate normal distributions.

- The posteriors of $f(\mathbf{x}^*)$ in Equations (8) and (12) are multivariate normal distributions, which can be sampled using software. The posterior of $f(\mathbf{x}^*)$ in Equation (15) is a truncated multivariate distribution, which will be sampled using the abovementioned Gibbs sampler. Note that in calculating the variance matrix $V(\mathbf{x}^*)$ in these equations, a simplification based on the Sherman–Morrison–Woodbury formula—i.e., $A^{-1} = B_2 - B_1 A_1^{-1} (B_1 + A_1 B_2 A_1^{-1})^{-1} A_1 B_2$—can be used for faster and more stable computation.

We now present a short note on the order of sampling when multiple types of constraints are imposed: Whenever the censoring constraint is considered, the sampling of $y_m$ in Equation (7) should be performed first; whenever the bound constraint is considered, the sampling of $f(\mathbf{x}^*)$ in Equation (15) should be done last. Detailed procedures of the posterior sampling in each case are summarized in Appendix C.

### 4.3. Identifying the constrained set

When imposing monotonicity constraints, we need to specify the constrained set $\{\mathbf{x}_1^*, \ldots, \mathbf{x}_d^*\}$. A straightforward method is to use manual techniques to identify a set of locations where the data exhibit a violating trend, but this may miss some locations that should be constrained. Alternatively, one can use all of the training and prediction locations; however, this may include many unnecessary locations. Problems may occur in model estimation and prediction due to the inverse of the covariance matrix of GP becoming more difficult to compute as more locations and/or more nearby locations are involved. Wang (2012) proposes a rigorous procedure to decide the minimal constrained set, which is useful when large samples exist and/or locations are densely distributed. In studies of scaffold biodegradation, limited data are typically available and locations are distributed in a sparse pattern, so we now provide a simplified, easy-to-implement procedure to find a reasonable constrained set with a small number of locations (assuming that the predictions are required to be monotonically increasing).

**Step 1:** Manually identify a set of candidate locations $\{\mathbf{x}_1, \mathbf{x}_2, \ldots\}$ among the training locations. To be conservative, we can just use the whole training set as the candidate set.

**Step 2:** For each location $\mathbf{x}_i$ in the candidate set, since the posterior of the first-derivative at this location is a normal distribution—i.e., $f'(\mathbf{x}_i^*)y, \psi \sim N(m(\mathbf{x}_i^*), V(\mathbf{x}_i^*))$, according to
Equation (11)—we can find the probability of negative first-derivative at this location:

\[ p_{Neg} = P(f'(x^*) < 0 | y, \psi) = \Phi \left( -\frac{m(x^*)}{\sqrt{V(x^*)}} \right). \] (16)

Location(s) with a large \( p_{Neg} \) should be constrained.

Step 3: To make sure the predictions at given locations \( X^* \) satisfy the monotonicity requirement: those locations should also be constrained. This leads to a constrained set as follows:

\[ X^\Delta = \arg \max_{x^* \in [x_{1*}, x_{2*}, \ldots]} [p_{Neg}(x^*) \geq 0.5] \cup \{x_{1*}, \ldots, x_{n*} \}. \]

4.4. Estimating the full degradation time

In the case with full degradation censoring in Section 3.1, scaffold researchers are interested in the full degradation time, which is the time point when full degradation is reached. Let the full degradation time under the process setting that yields the censored data (i.e., \( z = z_{c0} \) in Fig. 5) be \( t_F \). An estimate of this time can be obtained as a by-product of the prediction. Based on Equations (8), (12), and (15), for any \( x^* = [t; z_{n*}]; f(x^*) \square \sim N(m(x^*), V(x^*)) \), where \( \square \) is the conditioning set in those equations. Thus, the probability of full degradation at \( x^* \) is

\[ p_{Full}(x^*) = P(f(x^*) \geq 100|\cdot) = 1 - \Phi \left( \frac{100 - m(x^*)}{\sqrt{V(x^*)}} \right), \] (17)

where \( \Phi \) is the cumulative distribution function of the standard normal distribution. Based on this result, we can define the estimate of the full degradation time as

\[ \hat{t}_F = \arg \left[ p_{Full}(x^*) = 0.5 \right] = \arg \left[ E(f(x^*)) = 100 \right]. \] (18)

Here this estimate has two interpretations: as the time point with a 50% chance of full degradation or as the time point where the expected weight loss is 100%. Since \( f(x^*) \square \) follows a normal distribution, which is symmetric, these two are equivalent. Note that the percentage “50%” in the first definition can be replaced by a higher value—e.g., 60% or 80%—depending on the concern/priority in the specific application.

5. Case study

In this study, the proposed CGP method is applied to data from a novel tissue-engineering scaffold fabrication process (Yang et al., 2004; Dey et al., 2008). This process uses a new class of biomaterials called Crosslinked Urethaned-doped Polyester Elastomers (CUPES) to fabricate scaffolds. Unlike conventional biomaterials that are either stiff and compliant or soft but weak, CUPES are fully elastic and sufficiently strong, making them potential scaffold materials to develop soft tissues such as cardiac tissues and blood vessels. Figure 8 displays a data set from the process, with scaffold weight loss percentages \( \psi \) under different settings of a critical process variable \( z \), the percentage of Polyethylene glycol (PEG) in scaffold material synthesis. Figures 8(a) to 8(c) contain three streams of data under \( z = 75, 25, \) and 0%, which will be used to demonstrate the proposed method in one-dimensional cases. Figure 8(d) contains data at \( t = 3, 7, 14, 21, 28, \) days under \( z = 0, 25, 30, 40, 50, 60, \) and 75%, which will be used to demonstrate the application in a two-dimensional case. Each data point in the figures is the average of five replicates.

Section 5.1 reports results of CGP prediction with each of the three types of constraints described in Sections 3.1 to 3.3 using the three one-dimensional data streams in Figures 8(a) to 8(c). It should be noted that the one-dimensional case often occurs in practice, which involves prediction under an interested setting of process variables. Here these data streams are used to illustrate how to impose the constraints. Section 5.2 shows prediction results on the two-dimensional data in Figure 8(d). We first demonstrate the use and performance of CGP at unsampled time points and/or settings of the process variable (Section 5.2.1). Then a comparative study of CGP, GP, and ANNs is conducted through leave-one-out cross-validation to identify the advantages of CGP over other methods (Section 5.2.2). In the posterior sampling for each prediction, 20 000 samples are generated using Matlab functions with 2000 burn-ins.

5.1. One-dimensional prediction

The data in Figure 8(a) contain a censoring measurement (at \( t = 42 \) days) and thus will be used to demonstrate prediction using the censoring constraint. The data in Figure 8(b) have an “abnormal” measurement (at \( t = 14 \) days), which may lead to predictions violating the monotonicity requirement and thus

![Figure 8. Degradation measurements used in the case study: (a) one-dimensional data with z = 75%, (b) one-dimensional data with z = 30%, (c) one-dimensional data with z = 0%, and (d) two-dimensional data.](image-url)
will be used to demonstrate prediction with the monotonicity constraint. The data in Figure 8(c) will be used to demonstrate the case using the bound constraint. Procedures and results of the predictions are given as follows.

Let us first consider the case in Figure 8(a). Predictions are made at $t = 5, 8, 10, 15, 20, 25, 30, 32, 35, 38, 40$ days using two methods: the (unconstrained) GP based on all the measurements (i.e., $y_6 = 100\%$) and the proposed constrained GP with a censoring constraint at $t = 42$ days. Figure 9(a) shows the resulting predictions. We can see that the two methods yield similar predictions during the uncensored period (3–28 days), whereas their behaviors during the censored period (28–42 days) are clearly different. Specifically, the predictions from the CGP are accurate and adequate, which implies that full degradation occurred before the last time point (i.e., 42 days). The 95% confidence bands of the constrained prediction are narrow during the uncensored period and become wider after that, reflecting the increase of uncertainty as time proceeds. In contrast, the predictions from the unconstrained GP show a linear trend toward 100% in this period, which is expected since the censored measurement “100%” was used directly in this method. These results validate the importance of considering the censoring information in order to make meaningful predictions.

We can also obtain the full degradation probability, $p_{\text{Full}}$ in Equation (17), from the two methods for comparison. Figure 9(b) shows their estimates of the full degradation probability at $t = 4, 5, \ldots, 45$ days. Again, the proposed CGP method yields reasonable results, with $p_{\text{Full}}(42) = 0.86$, which is consistent with reality (i.e., the censoring observed at this time point). Since $p_{\text{Full}}(38) = 0.46$ and $p_{\text{Full}}(39) = 0.57$, a simple estimate of the full degradation time is 38.5 days based on the definition in Equation (18). The unconstrained results appear unreasonable, where the estimated probability of full degradation at 42 days is relatively small (around 50%), though censoring was actually observed. This suggests that imposing the censoring constraint makes sense not only to make predictions but also to make other inferences on scaffold degradation.

In the case of Figure 8(b), the weight loss measurement at $t = 14$ days ($y_3 = 24.7\%$) appears “abnormal,” which is slightly smaller than the measurement at $t = 7$ days ($y_2 = 25.0\%$). Before applying the proposed method, the unconstrained GP is tried to see if there is a need to impose monotonicity constraints. First, the MLEs of the GP parameters are obtained: $\hat{\mu} = 25.4921$, $\hat{\theta} = 0.2658$, $\hat{\sigma}_z = 10.3558$, $\hat{\sigma}_{e} = 6.3509$. Then prediction of weight loss is made at $t = 5, 8, 10, 12, 15, 17, 20, 22, 25$ days. The results, as shown in Figure 10(a), exhibit an increasing trend, indicating that the unconstrained GP yields reasonable predictions.

To further understand the data, we calculate the probability of negative first-derivative—i.e., $p_{\text{Neg}}$ in Equation (16)—during the observed period (3–28 days), which is shown in Figure 10(b).
All of the probabilities are small (<0.5), meaning that monotonicity constraints are probably not needed. One explanation is that despite the mild outlier at \( t = 14 \) days, the whole data set has an increasing trend overall. In this case, due to the smoothing effect of the random error in the GP model, the predictions will follow the overall trend of data and will not be significantly affected by the outlier.

In the case of Figure 8(c), the MLEs of the GP parameters are \( \hat{\mu} = 5.8871, \hat{\theta} = 0.1244, \hat{c} = 9.0483, \hat{\sigma}_e = 0.9289 \). We compare predictions at \( t = 1, 5, 8, 10, 12, 15, 17, 20, 22, 25 \) days using the unconstrained GP and the proposed CGP with a bound constraint "\( f(t) > 0 \)" at \( t = 1 \) day. Note that \( t = 1 \) day is not in the observed time range, so the prediction at this time point is an extrapolation. According to the results shown in Figure 11, the unconstrained prediction at \( t = 1 \) day is negative (−0.4%), which is not meaningful. Such problems are expected for extrapolations. In contrast, the constrained prediction at this time point is positive (0.58%) and the 95% confidence bands are also positive.

5.2. Two-dimensional prediction

5.2.1. Prediction using the proposed CGP

Now we apply the CGP method to the two-dimensional data set in Figure 8(d) to demonstrate its use and performance in a general multi-dimensional case. Unlike in the one-dimensional case, where the three types of constraints are imposed separately, here we will focus on the monotonicity constraints and bound constraints, and all constraints will be imposed simultaneously when needed. In addition, we assume that the degradation is monotonically increasing with respect to both time and the process variable based on expert knowledge. We will consider the two situations of prediction mentioned in Section 2.2; i.e., interpolations where a prediction is made within the observed data region and extrapolations where a prediction is made out of the region. It is well known that the latter situation is challenging in general, and the unconstrained GP tends not to work well in this situation, due to its flexibility.

We first predict weight loss at the observed time points (i.e., \( t = 3, 7, 14, 21, 28 \) days) under three new settings of the process variable: \( z = 15, 32, \) and 70%, which represent the situation of interpolations. Noticing the “abnormal” data point in the dataset (\( t = 14 \) days, \( z = 30\% \)), monotonicity is our concern here. In the first step, the MLEs of the GP parameters are found: \( \hat{\mu} = 23.6849, \hat{\theta}_1 = 0.4451, \hat{\theta}_2 = 1.8604, \hat{c} = 29.3117, \hat{\sigma}_e = 2.3743 \). Then, we check the probability of a negative first derivative with respect to time and the process variable to see if there is a need to impose constraints. The results are shown in Figures 12(a) and 12(b), respectively. In Figure 12(a), the probability is close to zero everywhere within the data region, except for the small neighborhood around the abnormal data point; but even in that neighborhood, the peak is lower than 0.2. This means that the predictions will probably satisfy the monotonicity with respect to \( t \) automatically and thus constraints are not needed. The probability of a negative first derivative in Figure 12(b) shows similar patterns, which is near zero in most part of the data region, with small values in the margins, meaning that once again monotonicity constraints with respect to \( z \) are not needed. Therefore, the unconstrained GP is used in the prediction. The results are shown in Figure 12(c), which are all meaningful, as predicted by the probabilities of a negative first derivative in Figures 12(a) and 12(b). In particular, it seems that the predictions under \( z = 32 \% \) are not affected by the abnormal data point under \( z = 30\% \).

For extrapolations, two cases are considered. In the first case, we focus on predicting weight loss at some unobserved time points, \( t = 30, 35, 40, 42 \) days under \( z = 75\% \). According to Figure 12(a), the probability of negative first derivative at the last observed time point (i.e., \( t = 28 \) days) is rather high, especially under \( z = 75\% \). Thus, monotonicity constraints with respect to time are imposed at all the time points to be predicted. The CGP predictions are given in Figure 13(a), and the corresponding unconstrained predictions are also given in the figure for comparison. Clearly, the constraints are necessary to produce meaningful predictions. It should be pointed out that the predicted weight loss at \( t = 42 \) days under \( z = 75\% \) is 100%—i.e., full degradation is reached—which is consistent with the actual measurement under this setting of \( z \) as shown in Figure 8(a). In the second case, we predict weight loss under two unobserved settings of the process variable, \( z = 80\% \) and 90%. As implied by Figure 12(b), the probability of negative first derivative tends to becoming high around \( z = 75\% \), so monotonicity constraints with respect to \( z \) are imposed at the locations to predict. The results of CGP and unconstrained GP are given in Figure 13(b). The unconstrained predictions are, again, not meaningful; values under \( z = 90\% \) are lower than those under \( z = 80\% \) at some time points, and they are similar to the observations under \( z = 75\% \). These results suggest that the CGP method is particularly useful in extrapolations to enable meaningful predictions.

5.2.2. Comparative study

To further understand the advantages of the CGP method, we compare its prediction performance with the two popular surrogate models mentioned in the Introduction; i.e., the unconstrained GP and ANNs, using data in Figure 8(d). Specifically, two powerful ANN methods are considered, the Feed-forward Neural Network (FNN) and the Radial-basis Neural Network (RNN). There are two key parameters of the ANN methods: the number of neurons (\#neurons) in FNN and the upper bound of mean-squared error in training (\text{trainMSE}) for RNN. In this study, these parameters are tuned by considering different settings of them (\#neurons = 3–20, trainMSE = 8–40), and the settings that lead to the best prediction performance are chosen.
To assess the prediction performance of the methods, we adopt the leave-one-out cross-validation method with respect to values of the process variable (i.e., $z = 0, 25, 30, 40, 50, 60, 75\%$). Specifically, for each value of $z$, data under other values are used for model training, and data under this value are used for weight loss prediction at the five observed time points (i.e., $t = 3, 7, 14, 21, 28$ days). Note that the predictions under $z = 0\%$ and $z = 75\%$ are extrapolations, whereas those under other values of $z$ are interpolations. The performances of the four methods in these two situations will now be discussed.

The predictions in interpolations (i.e., $z = 25, 30, 40, 50, 60$, and $60\%$) are shown in Figure 14, and the corresponding Root-Mean-Squared Prediction Errors (RMSPEs) are summarized in Table 1. In these cases, the predictions from the unconstrained GP are meaningful (i.e., monotonically increasing with time), so constraints are not needed; in other words, the CGP will produce the same results as the GP, as shown in Figure 14. In terms of prediction accuracy, the GP and CGP methods perform quite well: better than FNN and RNN in the cases of $z = 20, 40, 50, 60$, as shown in Table 1. In terms of prediction validity, both GP
and CGP give meaningful predictions, whereas the FNN predictions violate monotonicity in three cases (z = 0, 30, and 40%), and the RNN predictions violate in two cases (z = 0, 75%). In summary, as we have seen in Section 5.2.1, both GP and CGP give promising prediction performance in interpolations.

The prediction results in extrapolations (i.e., z = 0%, 75%) are given in Figure 15 and the corresponding RMSPEs are summarized in Table 1. One can see that constraints are not active for the CGP method under z = 75%, leading to the same performance for both GP and CGP. The results under z = 0% are interesting, where the four methods perform dramatically differently. In fact, prediction in this case is very challenging, due to the lack of training data around z = 0% (the closest are those under z = 25%). The proposed CGP used in this case imposes bound constraints "f(t) > 0" and monotonicity constraints with respect to time at all of the locations to predict. In terms of prediction accuracy, the CGP gives the best prediction accuracy and substantially outperforms the GP, FNN, and RNN methods. In terms of prediction validity, only the CGP predictions are always meaningful; the GP gives negative prediction values at the beginning time points, whereas the two neural networks produce negative prediction at some time points and are not monotonically increasing. These results suggest, again, that the proposed CGP is especially useful in extrapolations to provide meaningful predictions. Moreover, it can also improve the prediction accuracy.

6. Numerical study

To further investigate the properties of the proposed CGP method, we conduct two simulation studies by generating new data sets through slightly modifying the original data sets used in Section 5. Since the CGP's advantages on extrapolations were demonstrated in the case study, here we will create cases of interpolations where the monotonicity is violated and imposing constraints are necessary.

### 6.1. One-dimensional example

In the one-dimensional data in Figure 8(b), we have noted the abnormal data point at t = 14 days and found that since it does not affect the overall monotonic trend of data, constraints are not needed, as shown in Figure 10. Now we replace this data point with a smaller value (e.g., 10%), while keeping the other data points at their original values. The new data set is shown in Figure 16(a), where the modified data point appears to be a serious outlier and has decisive influence on the overall trend of the data. As a result, the probability of a negative first derivative given in Figure 16(b) becomes very different from that in Figure 10(b), with large values at some time points—e.g., t = 11, 12 days—indicating that monotonicity constraints must be imposed. This is validated by the unconstrained GP predictions given in Figure 16(a), which exhibits a dramatically downward trend around the modified data point.

To apply the CGP method, a constrained set is identified following the procedure in Section 4.3. The set found to be {3, 5, 8, 9, 10, 11, 12, 13, 14, 15, 17, 20, 21, 22, 23, 24, 25, 28} days, at each of which a monotonicity constraint is imposed. The resulting predictions are shown in Figure 16(a); they have an increasing trend and seem not to be affected much by the outlier. Another interesting result is that the 95% confidence bands of the CGP is much narrower than the 95% confidence bands of the unconstrained GP, which indicates a lower level of uncertainty. These results suggest that the CGP will be useful in interpolations when the data set contains influential outliers.

### 6.2. Two-dimensional example

The two-dimensional data in Figure 8(d) are similarly modified by replacing the third data point (at t = 14 days) under each setting of z with a value that is a little smaller than the second data point (at t = 7 days). Figure 17(a) shows the new data set, where the modified data points substantially change the overall trend of data. The probability of a negative first derivative with respect to time, shown in Figure 17(b), now looks very different from the one in Figure 12(a). In particular, a high peak can be observed around 0.9, in the neighborhood of the third data point for all values of z. Thus, unlike in Figure 12(c), the unconstrained predictions under z = 15, 32, and 70% violate the monotonicity. In contrast, when monotonicity constraints on related locations are imposed, the predictions become monotonic as shown in Figure 17(a). This validates what we found.

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**Table 1.** RMSPEs of the four methods.

<table>
<thead>
<tr>
<th>Methods</th>
<th>0%</th>
<th>25%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>75%</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>7.1</td>
<td>2.0</td>
<td>3.7</td>
<td>1.4</td>
<td>3.7</td>
<td>4.8</td>
<td>6.0</td>
<td>4.1</td>
</tr>
<tr>
<td>CGP</td>
<td>1.9</td>
<td>2.0</td>
<td>3.7</td>
<td>1.4</td>
<td>3.7</td>
<td>4.8</td>
<td>6.0</td>
<td>3.4</td>
</tr>
<tr>
<td>FNN</td>
<td>10.3</td>
<td>2.7</td>
<td>5.9</td>
<td>8.2</td>
<td>4.4</td>
<td>5.1</td>
<td>6.7</td>
<td>6.2</td>
</tr>
<tr>
<td>RNN</td>
<td>15.9</td>
<td>5.9</td>
<td>3.6</td>
<td>2.3</td>
<td>3.1</td>
<td>6.1</td>
<td>7.0</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*Note: The smallest value under each setting of the process variable is printed in bold.*
in the one-dimensional examples; i.e., the CGP must be used to produce meaningful predictions when substantial outliers exist.

A simulation following the similar strategy of data generation is also conducted to find the advantage of the CGP on prediction accuracy in cases containing outliers. In the simulation, the data point at $t = 14$ days is set to be proportional to that at $t = 7$ days under the same setting of $z$; i.e., $y_3/y_2 = r$, where $0 < r \leq 1$ is an outlying factor, a smaller value of which indicates more serious outlying level of the data set. Values of $r = 1, 0.95, 0.9, 0.85$ are considered, and given each of these values, the RMSPEs of GP and CGP in leave-one-out cross-validation (as reported in Section 5.2.2) are found. The results under $z = 25\%$ and $60\%$ are given in Figure 18. The benefit of CGP in prediction accuracy is clear, which increases approximately linearly as the outlying level increases (i.e., $r$ gets smaller).

![Figure 15. Leave-one-out predictions of the four methods in extrapolations.](image)

![Figure 16. One-dimensional example: (a) data and predictions and (b) probability of negative first-derivative.](image)

![Figure 17. Two-dimensional example: (a) data and predictions and (b) probability of a negative first-derivative.](image)
constant mean (i.e., $\mu$ in Equation (1)). In the universal version of GP, the mean part takes a more complicated form, usually as a function of the predictors. A natural question is how to incorporate those constraints in this case. One idea is that we can model the mean part using shape-constrained splines. Finally, we will also extend the current framework to impose other types of constraints in scaffold fabrication and other biomanufacturing or manufacturing applications.

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**References**


Appendix A: Proof of Proposition 1.

The following is a well-known result on multivariate normal distribution that will be used in the proof: given two vectors \( X_1 \) and \( X_2 \) following a multivariate normal distribution:

\[
\begin{bmatrix}
X_1 \\
X_2
\end{bmatrix}
\sim N
\left(
\begin{bmatrix}
\mu_1 \\
\mu_2
\end{bmatrix},
\begin{bmatrix}
\Sigma_{11} & \Sigma_{12} \\
\Sigma_{21} & \Sigma_{22}
\end{bmatrix}
\right)
\]

then \( X_2 \) given \( X_1 = x \) follows a normal distribution with

\[
E(X_2|X_1 = x) = \mu_2 + \Sigma_{21} \Sigma_{11}^{-1}(x - \mu_1)
\]

\[
\text{cov}(X_2|X_1 = x) = \Sigma_{22} - \Sigma_{21} \Sigma_{11}^{-1} \Sigma_{12}
\]

From the GP model in Equation (1):

\[
\begin{bmatrix}
y(n-1) \\
y_n
\end{bmatrix}
\sim N
\left(
\begin{bmatrix}
\mu_{I,n-1} \\
\mu
\end{bmatrix},
\begin{bmatrix}
\sigma^2_I & \sigma^2_{I,n-1} \\
\sigma^2_{I,n-1} & \sigma^2
\end{bmatrix}
\right),
\]

\[
\times K^{00}(X(n-1), x(n-1)) + \sigma^2_I \Sigma_{I,n-1} \Sigma_{00}(X(n-1), x_n)
\]

Plugging in the terms in the above into Equation (A1) leads to \( m(x_n) \) and \( V(x_n) \) in Equation (7). Considering the constraint \( \gamma_n \geq 100 \), the truncated normal distribution in Equation (7) will be obtained. Similarly, according to the joint distribution of \( f(X^*) \) and:

\[
\begin{bmatrix}
y \\
f(X^*)
\end{bmatrix}
\sim N
\left(
\begin{bmatrix}
\mu_{I*} \\
\mu_{I,n*}
\end{bmatrix},
\begin{bmatrix}
K^{00}(X, X) + \sigma^2_{I*}K^{00}(X^*, X) & K^{00}(X, X^*) \\
K^{00}(X^*, X) & K^{00}(X^*, X^*)
\end{bmatrix}
\right)
\]

and thus \( m(X^*) \) and \( V(X^*) \) in Equation (7) will be obtained.
Appendix B: Derivation of Equations (9) and (13)

Based on the definitions in Rasmussen and Williams (2006), we can find the covariance of the derivative GP and the covariance of the derivative GP and the original GP:

Case I: Monotonicity with respect to t (Equation (9))

\[ K^{01}(x_i, x_n^b) = \text{cov}(f(x_i), f'(x_n^b)) = \frac{\partial \text{cov}(f(x_i), f(x_n^b))}{\partial t} = \sigma_j^2 R_{ij} \cdot 2 \theta_1 (x_{i1} - x_{n1}^b), \]

\[ K^{10}(x_n^b, x_i) = \text{cov}(f'(x_n^b), f(x_i)) = \frac{\partial \text{cov}(f(x_i), f(x_n^b))}{\partial t} = \sigma_j^2 R_{ij} \cdot 2 \theta_1 (x_{i1} - x_{n1}^b), \]

\[ K^{11}(x_n^b, x_n^b) = \text{cov}(f'(x_n^b), f'(x_n^b)) = \frac{\partial^2 \text{cov}(f(x_i), f(x_n^b))}{\partial t^2} = \sigma_j^2 R_{jk} \cdot 2 \theta_1 (1 - 2 \theta_1 (x_{j1}^b - x_{n1}^b)^2). \]

Case II: Monotonicity with respect to both t and z (Equation (13))

\[ K^{20}(x_i, x_n^b) = \text{cov}(f(x_i), f'(x_n^b)) = \frac{\partial \text{cov}(f(x_i), f(x_n^b))}{\partial z} = 2 \sigma_j^2 R_{ij} \theta_1 (x_{i1} - x_{n1}^b), \]

\[ K^{02}(x_i, x_n^b) = \text{cov}(f(x_i), f'(x_n^b)) = \frac{\partial \text{cov}(f(x_i), f(x_n^b))}{\partial z} = 2 \sigma_j^2 R_{ij} \theta_2 (x_{i2} - x_{j2}^b), \]

\[ K^{22}(x_n^b, x_n^b) = \text{cov}(f(x_i), f'(x_n^b)) = \frac{\partial^2 \text{cov}(f(x_i), f(x_n^b))}{\partial z^2} = 2 \sigma_j^2 R_{jk} \theta_2 \left[ 1 - 2 \theta_2 (x_{j2}^b - x_{n2}^b)^2 \right]. \]

Appendix C: Sampling procedures for the CGP method described in Sections 3.1 to 3.3

Section 3.1: Prediction with censoring constraint

Step 1: Find MLEs of the GP parameters \( \hat{\psi} \) using the method described in Section 3.4.1.

Step 2: Draw \( y_n^{(b)} \) from Equation (7). If \( y_n^{(b)} < 100 \), redraw the sample until the constraint is satisfied.

Step 3: Given \( y_n^{(b)} \), draw \( f(X^*)^{(b)} \) from Equation (8).

Repeat Steps 2 and 3 to obtain a stream of the posterior samples \( \{f(X^*)^{(b)} : b = 1, 2, \ldots \} \).

Section 3.2: Prediction with monotonicity constraint

The following is the conditional distribution of each variable in a multivariate normal distribution, which is the basis for sampling from a truncated multivariate normal distribution.

Let \( X = [X_1, \ldots, X_m] \sim N(\mu, \Sigma) \), \( X_{-j} \) is \( X \) excluding \( X_j \), \( j = 1, \ldots, m \), then

\[ X_{-j} \sim N \left( \left[ \begin{array}{c} \mu_{-j} \\ \mu_j \\
\end{array} \right], \left[ \begin{array}{cc} V(X_{-j}) & \text{cov}(X_{-j}, X_j) \\
\text{cov}(X_j, X_{-j}) & V(X_j) \\
\end{array} \right] \right). \]

By Equation (A1), the conditional distribution of \( X_j \) is

\[ X_j | X_{-j} \sim N(m_j, \nu_j), \]

where

\[ m_j = \mu_j + \text{cov}(X_j, X_{-j}) [V(X_{-j})]^{-1} (X_{-j} - \mu_{-j}), \]

\[ \nu_j = V(X_j) - \text{cov}(X_j, X_{-j}) [V(X_{-j})]^{-1} \text{cov}(X_{-j}, X_j). \]

Step 1: Find MLEs of the GP parameters \( \hat{\psi} \) using the method described in Section 3.4.1.
Step 2: Draw \( f'(X^\Delta)^{(b)} \) from Equation (11): for \( j = 1, \ldots, m \), draw a sample from

\[
\hat{f} \sim N(\mu, \nu) \text{ until } f'(X^\Delta)^{(b)} > 0,
\]

where \( X^\Delta_j \) is \( X^\Delta \) excluding \( x_j^\Delta \), \( f'(X^\Delta_j)^{(b)} = [f'(x_1^\Delta)^{(b)}, \ldots, f'(x_{j-1}^\Delta)^{(b)}, f'(x_j^\Delta)^{(b)}(b), \ldots, f'(x_{m}^\Delta)^{(b)}] \), and the parameters of the univariate normal distribution are

\[
\mu^{(b)} = m(x_j^\Delta) + \Omega(x_j^\Delta, X^\Delta)\Omega^{-1}(X^\Delta, X^\Delta) \times (f'(X^\Delta_j)^{(b)} - m(X^\Delta_j)),
\]

\[
\nu_j = \Omega(x_j^\Delta, x_j^\Delta) - \Omega(x_j^\Delta, X^\Delta)\Omega^{-1}(X^\Delta, X^\Delta)\Omega(X^\Delta_j, x_j^\Delta),
\]

where \( m(x_j^\Delta) \) is the \( j \)th element of \( m(X^\Delta) \) in Equation (11), \( m(X^\Delta_j) \) is \( m(X^\Delta) \) excluding the \( j \)th element, \( \Omega(x_j^\Delta, x_j^\Delta) \) is the \((j, j)\)th element of \( \Omega(X^\Delta) \) in Equation (10), \( \Omega(x_j^\Delta, X^\Delta_j) \) is the \( j \)th row of \( \Omega(X^\Delta) \) excluding the entry from the \( j \)th column, \( \Omega(X^\Delta, X^\Delta_j) \) is \( \Omega(X^\Delta) \) excluding the \( j \)th row and \( j \)th column, and \( \Omega(X^\Delta_j, x_j^\Delta) \) is the \( j \)th column of \( \Omega(X^\Delta) \) excluding the entry from the \( j \)th row.

Step 3: Given \( f'(X^\Delta)^{(b)} \), draw \( f(X^*)^{(b)} \) from Equation (12).

Repeat Steps 2 and 3 to obtain a stream of posterior samples \( \{f(X^*)^{(b)} : b = 1, 2, \ldots \} \).

**Section 3.3: Prediction with bound constraint**

The sampling involves drawing from a truncated multivariate normal distribution (Equation (15)). This will be done following the method in Step 2 of Case II.

Step 1: Find MLEs of the GP parameters \( \hat{\psi} \) using the method described in Section 3.4.1.

Step 2: Draw \( f(X^*)^{(b)} \) from Equation (15) following Step 2 in Case II, except that the generated samples are screened by the bound constraints \( f(x_i^*) \in U_1, \ldots, f(x_n^*) \in U_n \).

Repeat Step 2 to obtain a stream of posterior samples \( \{f(X^*)^{(b)} : b = 1, 2, \ldots \} \).