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Analysis of Irregularly Spaced Time Series: A Gaussian Process Approach

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Abstract

Conventional time series analysis methods often assume evenly spaced observations, which may not always reflect real-world data collection constraints. Motivated by a real-world example, this study highlights Gaussian processes as a potent tool for analyzing irregularly sampled time series data.

Using a simulated blood pressure dataset designed to mimic real-world dynamics, including cyclic, autoregressive, and long-term trend components, we evaluate Gaussian process regression's performance in estimating blood pressure values from one week of irregularly spaced measurements. We assess the accuracy of credible interval estimation for clinically relevant target measures through repeated simulations, comparing it with baseline methods, such as spline and linear regression, accompanied by bootstrapped confidence intervals. Our investigation extends to the impact of varying data density and sampling patterns, specifically comparing uniform and seasonal sampling, where data density fluctuates with the circadian cycle.

Results consistently demonstrate Gaussian process regression's superior performance across all target measures, data densities, and sampling patterns. While linear regression, featuring a linear trend and sinusoidal component, serves as a viable baseline under low-data scenarios, it exhibits notable estimation bias due to its inherent constraints, and thus does not improve with more data. In contrast, spline regression offers flexibility but falters with seasonal sampling due to its lack of prior function knowledge. Gaussian process regression strikes a balance between flexibility and encoding prior beliefs about the true blood pressure function, yielding accurate results even with sparse, seasonally sampled data. Notably, it explicitly models the autoregressive component, yielding more precise credible intervals compared to the bootstrapped confidence intervals of the baseline methods.

In summary, this study shows the potential of Gaussian processes as a robust tool for the analysis of irregularly sampled time series data, as exemplified by its application to blood pressure estimation.

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Notation

General Statements

Prediction refers to estimation of the expected time series value at some time x^*, with x^* being within the time range of available observations.

Forcasting refers to estimation of the expected time series value at some time x^*, with x^* being after the last available observations.

Vectors are column vectors unless stated otherwise.

Blood Pressure or BP always refers to the systolic blood pressure.

Abbreviation

GP: Gaussian process.

BP: (Systolic) Blood pressure.

TTR: Time in target range

CI: Refers to both confidence and credible interval

OLS: Ordinary Least Squares.

iid: Independent and identically distributed.

Symbols

$\mathcal{N}(\mu, \sigma^2)$: Normal distribution with mean μ and standard deviation σ

$X_1 \dots X_n$ iid $\sim F$: $X_1 \dots X_n$ are iid with distribution F

$|M|$: determinant of matrix M

$\mathbf{E}[X]$: Expectation of X

$\mathrm{Cov}(X, Y)$: Covariance between X and Y

$\mathrm{Var}(X)$: Variance of X

Chapter 1

Introduction

1.1 Motivation and Thesis Objective

This thesis aims at presenting Gaussian process regression as a powerful tool for modeling time series based on irregularly spaced observations.

The motivation for this research stems from a pressing real-world problem in the field of medicine, which will serve as a recurring example throughout this thesis. The problem revolves around estimating critical time series properties, from a dataset consisting of irregularly spaced blood pressure (BP) measurements. High BP is a well-established risk factor for cardiovascular disease, and summarizing an individual's BP levels typically involves calculating the average BP value over available measurements within a specified time range. A novel monitoring device has been developed by the company Aktiia. The device collects continuous BP estimates by converting photoplethysmography (PPG) signals into BP measurements. The sampling frequency of this system can vary widely, typically yielding around 1.5 BP measurements per hour. However, factors such as PPG signal quality and external conditions can influence this frequency, resulting in irregularly spaced measurements. Obtaining accurate estimates of true BP values at unobserved time points is essential for improving cardiovascular risk assessment and developing valuable metrics.

Standard time series analysis methods traditionally assume discrete equispaced time intervals. Introductory textbooks on time series analysis either neglect the irregularly spaced case entirely or dedicate only a limited section to continuous time models or state-space models with missing observations (Brockwell and Davis, Brockwell and Davis, Cryer and Chan, Chatfield).

Therefore, the primary objective of this thesis is to address the challenges posed by irregularly sampled time series data and demonstrate why conventional time series methods fail to deal with it. Additionally, we will elucidate why Gaussian processes are a suitable approach for modeling time series with irregularly spaced observations, using the BP time series example.

1.2 Problem Statement

To begin modeling BP measurements, we introduce the time series process $Y(x)$, which combines the true BP process $f(x)$ with independent and identically distributed (iid) Gaussian measurement noise ϵ:

$$Y(x) = f(x) + \epsilon \qquad \epsilon \sim \mathcal{N}(0, \sigma_n^2)$$

Both time series, $f(x)$ and $Y(x)$, are described as random functions. While the former is completely unobserved we have unequally spaced observations from the latter, i.e. $(Y_{t_i} : i \in \{1, 2, \dots n\})$. These observations represent Aktiia's user data.

The goal of this research is to learn about the underlying true BP process $f(x)$ based on one week of irregularly spaced observations. Instead of using real data, data will be simulated by generating the true BP process $f(x)$ and adding measurement noise ϵ. This approach offers the advantage of complete knowledge about $f(x)$, enabling us to quantify the accuracy of its reconstruction from data. However, it also introduces the challenge of simulating a time series and observations that closely mimic reality. The time series characteristics to mimic are desribed in the next subsection 1.2.1.

Instead of solely focusing on predicting $f(x)$, this thesis emphasizes a set of target measures deemed most relevant for assessing cardiovascular risk. These target measures are detailed in subsection 1.2.2.

In addition to point estimates, this research considers the construction of confidence intervals (CIs) around these estimates. Notably, the width of the CI intervals around the mean function varies over time, depending on factors such as the availability of data in the vicinity of a given time point.

For simplicity, this study exclusively deals with systolic blood pressure and does not consider diastolic measurements. All references to "blood pressure" or "BP" pertain to systolic blood pressure.

1.2.1 Characteristics of the Blood Pressure Time Series

Based on the Aktiia user data, several properties of **the BP measurements,** $(Y_{t_i} : i \in \{1, 2, \dots n\})$, have been identified:

i.) The measurements are irregularly spaced, meaning that the time between consecutive measurements varies.

ii.) Observations are not uniformly sampled across time; instead, their density follows a circadian cycle, resulting in seasonal sampling.

iii.) The sampling frequency ranges from 0.5 to 4 measurements per hour.

iv.) The difference between average daytime and nighttime BP measurements falls within the range of 0 to 20 mmHg, with an average difference of 10 mmHg.

v.) The mean BP across all users is 120 mmHg.

vi.) The within-subject one-week sample variance spans from 16 to 144 mmHg^2, with an average of 49 mmHg^2.

The true BP time series process, $f(x)$, cannot be directly observed. However, in this thesis, it is assumed to be a combination of the following components:

- A seasonal component representing the circadian cycle, as BP tends to be higher during the day than at night.
- An autoregressive component, reflecting the dependence of the output variable on its previous values.
- A long-term trend.

The magnitude of the measurement noise, denoted as ϵ, remains unknown. Nevertheless, Aktiia measurements have undergone validation against a reference method. The measured variance of the differences between Aktiia measurements and this reference is 62 mmHg^2. Consequently, we can express:

$$\begin{aligned}\text{Var}(BP_{Ref} - BP_{Aktiia}) &= 62 \text{ mmHg}^2 = \text{Var}(\epsilon_{Ref} - \epsilon_{Aktiia}) \\ &= \text{Var}(\epsilon_{Ref}) + \text{Var}(\epsilon_{Aktiia}) - 2\,\text{Cov}(\epsilon_{Ref}, \epsilon_{Aktiia})\end{aligned}$$

Assuming that the noise variance of the reference method, $\text{Var}(\epsilon_{Ref})$, equals that of the Aktiia measurements, $\text{Var}(\epsilon_{Aktiia})$, and that $\text{Cov}(\epsilon_{Ref}, \epsilon_{Aktiia}) = 0$, we would obtain a noise variance for the Aktiia measurements of 31 mmHg^2.

1.2.2 Target Measures

The primary focus of this research lies on a set of target measures crucial for estimating an individual's cardiovascular risk. These measures include:

The mean BP calculated over different time windows, such as one-hour, one-day, and one-week mean BP. The mean BP is a pivotal and frequently reported metric. Presently, it is computed based on the available measurements within the corresponding time range.

Time in Target Range (TTR) evaluates the duration during which BP values fall within a specified target range relative to the total time. It is currently determined by dividing the number of BP measurements within the range of 90 to 125 mmHg ("target range") by the total number of BP measurements available within one week.

It is noteworthy that the estimation of these target measures does not depend on forecasting future BP values but solely relies on predicting BP values within the one-week range of available data. Consequently, this thesis concentrates on reconstructing BP values between the first and last time point in the dataset.

1.3 Thesis Outline

This thesis is structured into two main sections: a theoretical exploration and an applied investigation.

1.3.1 Theoretical Section

The theoretical section starts with **Chapter 2**, where key concepts and definitions pertaining to time series are introduced. Subsequently, in **Chapter 3**, we delve into linear

regression techniques and their limitations for modeling time series from unequally spaced data. **Chapter 4** then presents Gaussian process regression and why it might be suited for time series regression of unequally spaced data.

1.3.2 Applied Section

The applied section of this thesis initiates with **Chapter 5**, where we detail the simulation study designed to evaluate the effectiveness of GP regression in predicting BP values from irregularly sampled data.

The outcomes of this simulation study are presented in **Chapter 6**, and their implications are summarized in **Chapter 7**.

Chapter 2

Characteristics of Time Series

2.1 Time Series Definition

A potentially unevenly spaced **time series** is a sequence of observation time and value pairs (t_i, x_i) with strictly increasing observation times. Let $\mathbb{T}$ be a set of observation time points; then the sequence of random variables $(X_t : t \in \mathbb{T})$ or simply (X_t) is a **time series process** with observation times $t \in \mathbb{T}$. More specifically:

- $(X_t : t \in \{1, 2, \ldots, n\})$ refers to a discrete and equispaced time series of length n.
- $(X_{t_i} : i \in \{1, 2, \ldots, n\})$ refers to an irregularly spaced time series of length n with observations at time points $t_1 < t_2 < \cdots < t_n$.
- $(X_t : t \in (0, T])$ refers to a continuous time series.

When $\mathbb{T}$ has finite length, we will often use a random column vector $\mathbf{X}$ to refer to the time series process (X_t). Sometimes a time series model will be expressed as a random function $f : \mathbb{T} \to \mathbb{R}$ instead of a collection of random variables. Throughout the thesis, the term time series is used both to refer to the data (x_t) and the process (X_t) from which it is generated.

2.2 Moments of a Time Series

A time series process (X_t) is usually characterized by its first and second moments.

Definition 2.2.0.1. *(Brockwell and Davis) The **mean function** of a time series (X_t) is:*

$$\mu_X(t) = \mathbf{E}[X_t]$$

*The **covariance function** of a time series (X_t) is:*

$$\gamma_X(r, s) = \mathrm{Cov}(X_r, X_s) = \mathbf{E}[(X_r - \mu_X(r))(X_s - \mu_X(s))]$$

2.3 Stationarity

Given that one has only one observation x_t per time point t, a necessary condition to statistically learn from a time series is stationarity.

Definition 2.3.0.1. *(Brockwell and Davis) A time series (X_t) is strictly stationary if and only if the distribution of $(X_{t_1}, \ldots, X_{t_n})$ is identical to the distribution of $(X_{t_{1+h}}, \ldots, X_{t_{n+h}})$ for all $n \in \mathbb{N}^+$ and shifts $h \in \mathbb{Z}$:*

Definition 2.3.0.2. *(Brockwell and Davis) A time series (X_t) is weakly stationary if*

$$\mu_X(t) \text{ is independent of } t,$$

and

$$\gamma_X(t+h, t) \text{ is independent of } t \text{ for each } h.$$

Whenever the term stationary is used, it is referring to weak stationarity.

2.4 Special Cases of Time Series Processes

Example 2.4.0.1. If (X_t) is a **white noise** process, then $X_t \sim WN(0, \sigma^2)$, that is $X_t \sim F$ iid for some distribution F with mean 0 and varaince σ^2. A special case is Gaussian White noise where $W_t \sim \mathcal{N}(0, \sigma^2)$ and $F = \Phi$

Example 2.4.0.2. An equispaced time series process $(X_t : t \in \{1, 2, \ldots\})$ is called an **autoregressive process** of order p or AR(p) if:

$$X_t = \phi_1 X_{t-1} + \cdots + \phi_p X_{t-p} + W_t$$

where $\phi_p \neq 0$ and (W_t) is a white noise process. The variable W_t is called the innovation at time t and is independent of all X_k, $k < t$.

Example 2.4.0.3. An equispaced time series process $(X_t : t \in \{1, 2, \ldots\})$ is called a **moving average process** of order q or MA(q) if:

$$X_t = W_t + \theta_1 W_{t-1} + \ldots \theta_q W_{t-q}$$

where $\theta_q \neq 0$ and (W_t) is a white noise process. The variable W_t is called the innovation at time t and is independent of all X_k, $k < t$.

Example 2.4.0.4. An equispaced time series process $(X_t : t \in \{1, 2, \ldots\})$ is called an **autoregressive moving average process** of autoregressive order p and moving average order q or ARMA(p, q) if:

$$X_t = \phi_1 X_{t-1} + \cdots + \phi_p X_{t-p} + \theta_1 W_{t-1} + \ldots \theta_q W_{t-q} + W_t$$

where $\phi_p \neq 0, \theta_q \neq 0$ and (W_t) is a white noise process. The variable W_t is called the innovation at time t and is independent of all X_k, $k < t$.

Chapter 3

Time Series Decomposition and Linear Regression

As most time series, the mean function of the BP time series is not constant in time and hence it is not stationary. One can try to decompose the time series $Y(t)$ into a deterministic component, the mean function $\mu(t)$ and a zero mean stationary process $R(t)$. This can be expressed in the form of a regression problem:

$$Y(t) = \mu(t) + R(t)$$

The decomposition allows to extract a stationary component $R(t)$, for which we can find a probabilistic model using the theory of such stationary time series processes. The idea is to then use this model in combination with an estimate of $\mu(t)$ to obtain a probability distribution of Y^* at some time t^*. Hence time series decomposition comes for free in regression analysis and we start with estimation of the deterministic component $\mu(t)$ which might be an arbitrary function of t.

3.1 Linear Regression with Uncorrelated Errors

Based on the knowledge we have about the system we might restrict ourselves to a family of functions for $\mu(t)$. An obvious choice for the BP time series is the family of functions featuring a linear trend with an additive seasonal component. If the seasonal component is represented by a cosine of the form $\alpha\cos(2\pi ft-\phi)$ with phase shift ϕ and known frequency f, we get the following model for the BP time series $Y(t)$:

$$Y(t) = \beta_0 + \beta_1 t + \beta_2\cos(2\pi ft) + \beta_3\sin(2\pi ft) + R(t),$$

where based on the trigonometric angle sum identities we know that $\beta_2 = \alpha\cos(\phi)$ and $\beta_3 = \alpha\sin(\phi)$.

If we assume BP observations at potentially unequally spaced time points $t_1, t_2 \ldots t_n$ and $t_1 < t_2 < \ldots t_n$, we can write in matrix notation:

$$\mathbf{Y} = X\beta + \mathbf{R}$$

Where $\mathbf{Y} = [Y_{t_1}, \dots Y_{t_n}]^\top$ is the observed time series, $X = [x_{t_1}, \dots x_{t_n}]^\top \in \mathbb{R}^{n \times 4}$ is the design matrix with i-th row, written as a column vector $x_{t_i} = [1, t_i, \cos(2\pi f t_i), \sin(2\pi f t_i)]^\top$ and $\mathbf{R} = [R_{t_1}, \dots R_{t_n}]^\top$ the zero-mean stationary time series, which we will call errors.

We can use ordinary least squares to find unbiased and asymptotically normal estimates $\hat{\beta}_{OLS} = (X^\top X)^{-1} X^\top Y$ for the regression coefficients β, without the requirement of regularly spaced data points or uncorrelated errors $R_{t_1}, \dots, R_{t_n}$ (White). In the case of uncorrelated errors with constant variance σ^2 we have $Var(\mathbf{R}) = \sigma^2 I_n$ and an unbiased and consistent estimator for $\Psi = Var(\hat{\beta}_{OLS})$ is given by:

$$\hat{\Psi} = \hat{\sigma}^2 (X^\top X)^{-1}$$

$$\text{where } \hat{\sigma}^2 = \frac{1}{n-p} \sum_{i=1}^{n} (y_{t_i} - x_{t_i}^\top \hat{\beta}_{OLS}) \text{ and } p = 4 \text{ in our example}$$

Since $\mathbf{R}$ is a time series, the assumption of uncorrelated errors is usually violated and the covariance matrix $\hat{\Psi}$ is thus no longer unbiased (Brockwell and Davis).

3.2 Linear Regression with Correlated Errors

The argument presented in this section is based on the textbook of Brockwell and Davis.

If the covariance matrix of the errors $Var(\mathbf{R}) = \Sigma$ is known, we can use generalized least squares to obtain a unbiased, consistent and efficient coefficient estimate:

$$\hat{\beta}_{GLS} = (X^\top \Sigma^{-1} X)^{-1} X^\top \Sigma^{-1} Y$$

with unbiased and consistent covariance matrix estimate:

$$Var(\hat{\beta}_{GLS}) = (X^\top \Sigma^{-1} X)^{-1}$$

If Σ is unknown one can exploit the knowledge we have about the stationary time series process $\mathbf{R}$ to estimate it. The following subsections will present two approaches to estimate Σ, β and its covariance matrix. Both methods assume an ARMA(p,q) process for $\mathbf{R}$ and equispaced time points, hence $\mathbf{R} = (R_t : t \in \{1, 2, \dots n\})$ and:

$$\Phi(B) R_t = \Theta(B) W_t, \text{where } W_t \sim WN(0, \sigma_w^2)$$

3.2.1 Maximum-Likelihood Estimation

If we additionally assume $W_t \sim N(0, \sigma_w^2)$, we can simultaneously estimate the regression coefficients and Σ by maximizing the Gaussian likelihood:

$$L(\beta, \phi, \theta, \sigma_w^2) = (2\pi)^{-\frac{n}{2}} |\Sigma_n|^{-\frac{1}{2}} \exp(-\frac{1}{2} (\mathbf{Y} - X\beta)^\top \Sigma_n^{-1} (\mathbf{Y} - X\beta))$$

Where the covariance matrix $\Sigma_n(\theta, \phi, \sigma_w^2)$ is parametrized by the coefficients θ, ϕ, σ_w^2, which define the ARMA process assumed for $(R_t : t \in \{1, 2, \dots n\})$. Assuming an ARMA(2,3) process we can implement this approach in R using the nlme library (Box, Jenkins, and Reinsel) :

```
library(nlme)
cs <- corARMA(from = ~t, p=2, q=3)
fit.gls <- gls(y ~ t + cos(2 * pi * f * t) + sin(2 * pi * f * t), corr=cs)
```

3.2.2 Sandwich Estimation

The second approach is to fit an OLS regression first and correct the estimated covariance matrix of the regression coefficients Ψ with a sandwich estimator. In the presence of autocorrelation one usually estimates $\Phi = \frac{1}{n} X^\top \Sigma X$, the covariance matrix of the scores or estimating functions $V_i(\beta) = x_{t_i}(y_{t_i} - x_{t_i}^\top \beta)$, which can then be used to derive Ψ:

$$\Psi = Var(\hat{\beta}_{OLS}) = (X^\top X)^{-1} X^\top \Sigma X (X^\top X)^{-1} = (\frac{1}{n} X^\top X)^{-1} \frac{1}{n} \Phi (\frac{1}{n} X^\top X)^{-1} \quad (3.2.2.1)$$

The general form of the estimators for Φ is:

$$\hat{\Phi} = \frac{1}{n} \sum_{i,j=1}^{n} w_{|i-j|} \hat{V}_i \hat{V}_j^\top \quad (3.2.2.2)$$

where $w = [w_0, \dots w_{n-1}]^\top$ is a weight vector and $\hat{V}_i = V_i(\hat{\beta}_{OLS})$.

Plugging $\hat{\Phi}$ into the equation 3.2.2.1 one obtains the heteroskedasticity and autocorrelation consistent (HAC) covariance estimate $\hat{\Psi}_{HAC}$.

Newey and West, Andrews and others have suggested different approaches for calculating the weights w. They all yield decreasing weights with increasing lag $l = |i - j|$. The R sandwich package implements some of these methods to estimate $\hat{\Psi}_{HAC}$. An introduction to the sandwich package and how it can be used for inference is described by Zeileis.

3.2.3 Extension to Irregularly Spaced Time Series

Although literature and "ready to use" implementations only exist for the equispaced case, both of the approaches described above could probably be extended to the case of irregularly spaced time series. For the Maximum-Likelihood approach the parametrization of the covariance matrix Σ_n as described in 3.2.1 would need to be adapted, such that the covariance of the errors at different time points depends on the actual time difference rather than the lag. Similarly for the sandwich estimator, the weights in 3.2.2.2 should depend on the time difference rather than on the lag.

3.2.4 Confidence Intervals for the Mean Function

The objective, as described in the introduction, is not only to estimate the mean function $\mu(t)$ of the time BP time series but also to find confidence intervals for it. The model for the BP time series described in 3.1 has the following mean function:

$$\mu(t) = x_t^\top \beta$$
$$\text{with } x_t = [1, t, \cos(2\pi f t), \sin(2\pi f t)]^\top$$

Hence, we may also write $\mu(x_t)$ and its $1-\alpha$ confidence interval is:

$$x_t^\top \hat{\beta} \pm q t_{n-p}(1-\frac{\alpha}{2})\sqrt{x_t^\top \Psi x_t}$$

where $\Psi = Var(\hat{\beta})$ is the covariance matrix of the estimated regression coefficients and $qt_{n-p}(1-\frac{\alpha}{2})$ denotes the $1-\frac{\alpha}{2}$ quantile of the student's t-distribution of $n-p$ degrees of freedom.

As the CI for $\mu(t)$ is based on the variance of the estimated global model parameters Ψ, it cannot adapt to the local observation density. Even if we were able to derive realistic confidence interval for the mean function of the irregularly spaced time series, the uncertainty due to the lack of data in the proximity of a time point can still not be reflected.

Chapter 4

Gaussian Process Regression

The objective of regression is generally to establish a mapping between the input variable x and its corresponding output $f(x)$. In order to solve such a problem one usually needs some additional constraints on $f(x)$. In chapter 3 we restricted ourselves to the class of linear functions. However, an alternative approach is to assign prior probabilities to all possible functions, giving higher probabilities to those considered more plausible. In this Bayesian framework, inference revolves around the posterior distribution of these functions, given some potentially noisy observations of $f(x)$.

This chapter begins by providing a formal definition of a Gaussian Process and subsequently explores its application in solving regression problems. The arguments presented in this chapter are based on the textbook of Rasmussen and Williams.

4.1 Gaussian Process Definition

A Gaussian process (GP) can be viewed as a gaussian distribution over functions or as an infinite set of random variables representing the values of the function $f(x)$ at location x. The Gaussian process is thus a generalization of the Gaussian distribution and a formal definition is given by Rasmussen and Williams :

Definition 4.1.0.1 (Gaussian Process)**.** *A Gaussian process is a collection of random variables, any finite number of which have a joint Gaussian distribution.*

As a (multivariate) Gaussian distribution is defined by its mean and covariance matrix, a GP is uniquely identified by its mean $m(x)$ and covariance (kernel) function $k(x, x')$.

We write

$$f(x) \sim GP(m(x), k(x, x'))$$

with

$$m(x) = \mathbf{E}\left[f(x)\right]$$
$$k(x, x') = \mathbf{E}\left[(f(x) - m(x))(f(x') - m(x'))\right]$$

If we assume X to be the index set or set of possible inputs of f, then there is a random variable $F_x := f(x)$ such that for a set $A \subset X$ with $A = x_1, \ldots x_n$ it holds that:

$$F_A = [F_{x_1}, \ldots, F_{x_n}] \sim \mathcal{N}(\mu_A,\, K_{AA})$$

for

$$K_{AA} = \begin{bmatrix} k(x_1, x_1) & k(x_1, x_2) & \ldots & k(x_1, x_n) \\ \vdots & & \vdots & \vdots \\ k(x_n, x_1) & k(x_n, x_1) & \ldots & k(x_n, x_n) \end{bmatrix} \text{ and } \mu_A = \begin{bmatrix} m(x_1) \\ \vdots \\ m(x_n) \end{bmatrix} \tag{4.1.0.1}$$

The finite marginals $F_{x_1}, \ldots, F_{x_n}$ of the GP thus have a multivariate gaussian distribution. In our running example we might consider X to be the time interval $T_0 = [0, T]$ however it could be higher dimensional.

Note that a GP with finite index set and hence with joint gaussian distribution is just a specific case of GP. If we assume an ARMA process with gaussian innovations for the blood pressure time series, one can view the time series as a collection of multivariate normally distributed random variables and thus as a GP.

If we consider the linear regression case from chapter 3 and assume a prior distribution on β, i.e. $\beta \sim N(0, I)$ then the predictive distribution over $\mu = X\beta$ is Gaussian:

$$\mu \sim \mathcal{N}(0, XX^\top)$$

This is equivalent to a GP with mean function $m(x) = 0$ and kernel function $k(x, x') = x^\top x'$. This special case of gaussian process regression with this specific kernel function is known as Bayesian linear regression and will be presented in the next section.

4.2 Bayesian Linear Regression

In the context of Bayesian regression, the objective is to estimate the posterior distribution of $f^* := f(x^*)$, at some input x^*, based on potentially noisy observations of $f(x)$. This is made possible by employing a prior distribution over the function $f(x)$. As shown in section 4.1, a GP is essentially assuming a Gaussian distribution over functions. This section however still stays in the domain of parametric models, in which case we assume a distribution over the parameters of the function $f(x)$, rather than over the function itself. Consequently, in Bayesian linear regression, a distribution over the regression coefficients β is assumed.

Recall the linear regression model from chapter 3. However, we are assuming a more general setting, where the data generating process does not need to be a time series process. The function is denoted with $f(x)$ instead of $\mu(t)$ and Y_i is again a noisy observation of $f(x_i)$, where the additive error R_i does not necessarily need to be from a time series process $(R_t : t \in \{t_1, t_2, \ldots t_n\})$. We obtain the following data generating model:

$$f(x_i) = x_i^\top \beta, \qquad Y_i = f(x_i) + R_i, \qquad (i = 1, \ldots n)$$

with $x_i \in \mathbb{R}^p$ being again the input vector and $\beta \in \mathbb{R}^p$ is the vector with the regression coefficients.

In matrix from:

$$\mathbf{Y} = X\beta + \mathbf{R}$$

Where $\mathbf{Y} = [Y_1, \dots Y_n]^\top$ is the observed data, $X = [x_1, \dots x_n]^\top \in \mathbb{R}^{n \times p}$ is the design matrix. We assume again gaussian but potentially correlated errors $\mathbf{R} = [R_1, \dots R_n]^\top$:

$$\mathbf{R} \sim \mathcal{N}(0, \Sigma_r)$$

If $\mathbf{R}$ is an ARMA process, then every element of the time series R_i is itself a sum of innovations. Therefore, $\mathbf{R}$ is gaussian as long as it has gaussian innovations.

The likelihood, i.e. the probability of the observations $\mathbf{Y}$ given X and β is then:

$$p(\mathbf{Y}|X, \beta) = \frac{1}{(2\pi)^{n/2}\sqrt{\det(\Sigma_r)}} \exp(-\frac{1}{2}(y - X\beta)^\top \Sigma_r^{-1}(y - X\beta)) = \mathcal{N}(X\beta, \Sigma_r)$$

Until now the regression model is exactly the same as in chapter 3. The Bayesian approach is different in that we additionally assume a prior distribution over the regression coefficients β, based on what we believe are likely values for the coefficients. To stay in the realm of gaussian processes the prior has to be Gaussian and we choose:

$$p(\beta) = \mathcal{N}(0, \Sigma_p)$$

Note how the function $f(x_i) = x_i^\top \beta$ is now no longer deterministic but a random function.

Given our observations $\mathbf{Y}$ we can use Bayes' theorem to calculate the posterior distribution over β:

$$p(\beta|\mathbf{Y}, X) = \frac{p(\mathbf{Y}, \beta|X)}{p(\mathbf{Y}|X)} = \frac{p(\mathbf{Y}|X, \beta)p(\beta)}{p(\mathbf{Y}|X)}$$

One approach is to just plug in the expressions for $p(\mathbf{Y}|X, \beta)$ and $p(\beta|\mathbf{Y}, X)$ from above, with the marginal likelihood:

$$p(\mathbf{Y}|X) = \int p(\mathbf{Y}|X, \beta)p(\beta)d\beta = \mathcal{N}(0, X\Sigma_p X^\top + \Sigma_r) \tag{4.2.0.1}$$

The term marginal likelihood arises from the marginalization over the parameter values β.

Or it can be helpful to combine the coefficients and the observations into a single random vector with multivariate normal distribution:

$$\begin{bmatrix} \mathbf{Y} \\ \beta \end{bmatrix} = \begin{bmatrix} X \\ I_p \end{bmatrix} \beta + \begin{bmatrix} I_n \\ 0 \end{bmatrix} \mathbf{R} \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ \vdots \\ \vdots \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \left[\begin{array}{c:c} X\Sigma_p X^\top + \Sigma_r & X\Sigma_p \\ \hdashline \Sigma_p X^\top & \Sigma_p \end{array}\right] \right) = p(\mathbf{Y}, \beta|X) \tag{4.2.0.2}$$

with $\Sigma_p X^\top + \Sigma_r \in \mathbb{R}^{n\times n}$ and $\Sigma_p X^\top \in \mathbb{R}^{p\times n}$.

To find now the posterior distribution $p(\beta|\mathbf{Y}, X)$ one can use the rules for deriving conditional distributions for multivariate Gaussian's presented in theorem 4.2.0.1.

Theorem 4.2.0.1. *(von Mises)*

Let $A \sim \mathcal{N}(\mu_A, \Sigma_{AA})$ and $B \sim \mathcal{N}(\mu_B, \Sigma_{BB})$ be Gaussian random vectors with the following joint distribution:

$$p(A, B) = \mathcal{N}\left(\begin{bmatrix}\mu_A\\ \mu_B\end{bmatrix}, \begin{bmatrix}\Sigma_{AA} & \Sigma_{AB}\\ \Sigma_{BA} & \Sigma_{BB}\end{bmatrix}\right)$$

Then the conditional distribution $p(\mathbf{B}|\mathbf{A} = a)$ is also normally distributed with mean $\bar{\mu}$ and covariance $\bar{\Sigma}$ of the following form:

$$\bar{\Sigma} = \Sigma_{BB} - \Sigma_{BA}\Sigma_{AA}^{-1}\Sigma_{AB} \qquad \bar{\mu} = \mu_B + \Sigma_{BA}\Sigma_{AA}^{-1}(a - \mu_A)$$

Using theorem 4.2.0.1 the posterior distribution over β is then given by:

$$\begin{aligned} p(\beta|\mathbf{Y} = y, X) &\sim \mathcal{N}(\bar{\mu}, \bar{\Sigma}),\\ \bar{\Sigma} &= \Sigma_p - \Sigma_p X^\top (X\Sigma_p X^\top + \Sigma_r)^{-1} X\Sigma_p,\\ \bar{\mu} &= \mu_\beta + \Sigma_p X^\top (X\Sigma_p X^\top + \Sigma_r)^{-1} y \end{aligned}$$

The expression for the posterior mean and covariance matrix can be further simplified using Woodbury matrix identity and we obtain:

$$\bar{\Sigma} = (X^\top \Sigma_r^{-1} X + \Sigma_p^{-1})^{-1} \qquad \bar{\mu} = \bar{\Sigma} X^\top \Sigma_r^{-1} y \tag{4.2.0.3}$$

Since $f(x) = x^\top \beta$, one can use the posterior mean and covariance matrix from 4.2.0.3 to obtain the predictive distribution of $f^* := f(x^*)$ at x^* given our observations:

$$p(f^*|\mathbf{Y}, X, x^*) = \mathcal{N}({x^*}^\top \bar{\mu}, {x^*}^\top \bar{\Sigma} x^*) \tag{4.2.0.4}$$

One can also use the rules for conditioning to directly derive $f^*|\mathbf{Y}, X, x^*$. Similar to before we can write the joint distribution $p(\mathbf{Y}, f^*|X, x^*)$:

$$\begin{bmatrix}\mathbf{Y}\\ f^*\end{bmatrix} = \begin{bmatrix}X\\ x^*\end{bmatrix}\beta + \begin{bmatrix}I_n\\ 0\end{bmatrix}\mathbf{R} \sim \mathcal{N}\left(\begin{bmatrix}0\\ \vdots\\ \vdots\\ 0\\ 0\end{bmatrix}, \left[\begin{array}{c|c} X\Sigma_p X^\top + \Sigma_r & X\Sigma_p x^*\\ \hline {x^*}^\top \Sigma_p X^\top & \Sigma_p \end{array}\right]\right) = p(\mathbf{Y}, f^*|X, x^*) \tag{4.2.0.5}$$

The expression in 4.2.0.4 can then be derived using theorem 4.2.0.1 on conditioning of multivariate Gaussian's.

The next section will extend the Bayesian approach to non-parametric models and illustrate how Bayesian linear regression is just a special case of GP regression.

4.3 Bayesian Linear Regression as Gaussian Process Regression

The linear model discussed so far, with a cyclic component represented by a cosine and a linear trend component, might be an evident first guess. However, it is unlikely that the BP values are exactly following this pattern. Instead of reducing the function space to this specific class of linear functions, we may use our domain knowledge to tell which functions of the infinite space of all functions are more likely to have generated our data. As these functions are not characterized with explicit sets of parameters, this approach belongs to the branch of non-parametric modelling. By abandoning the parameters β, Gaussian process regression directly aims for the predictive distribution of $f^* := f(x^*)$ at an input x^* given our observations.

Starting with the Bayesian linear regression example from last section and transforming it into a GP regression problem, we recall that the distribution of $F_X = [f(x_1) \dots f(x_n)]^\top$ with given $X = [x_1 \dots x_n]^\top$ is:

$$F_X \sim \mathcal{N}(0, X\Sigma_p X^\top)$$

Alternatively this can be written as a distribution over the function $f(x)$:

$$f(x) \sim GP(0, k(x, x'))$$

where $k(x, x')$ needs to be chosen such that for an input X we obtain $K_{XX} = X\Sigma_p X^\top$. Given $\Sigma_p = \sigma_p I$, we would choose $k(x, x') = \sigma_p x^\top x'$, with the input pairs x and x' only entering as a dot product.

Combining f^* and $\mathbf{Y}$ into a single random vector we can use the theorem 4.2.0.1 to arrive at the same posterior predictive distribution $p(f^*|\mathbf{Y}, X, x^*)$ as presented in 4.2.0.4. The joint distribution of f^* and $\mathbf{Y}$ can be expressed as follows:

$$\begin{bmatrix} \mathbf{Y} \\ f^* \end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} K_{XX} + \Sigma_r & K_{Xx^*} \\ K_{x^*X} & K_{x^*x^*} \end{bmatrix} \right) = p(\mathbf{Y}, f^*|X, x^*) \tag{4.3.0.1}$$

where:

$$K_{XX} = \begin{bmatrix} k(x_1, x_1) & k(x_1, x_2) & \dots & k(x_1, x_n) \\ \vdots & & \vdots & \vdots \\ k(x_n, x_1) & k(x_n, x_1) & \dots & k(x_n, x_n) \end{bmatrix},$$

$$K_{Xx^*} = K_{x^*X}^\top = \begin{bmatrix} k(x_1, x^*) \\ \vdots \\ k(x_n, x^*) \end{bmatrix} \text{ and } K_{x^*x^*} = k(x^*, x^*)$$

4.3.1 Time Series Gaussian Process Regression

Unlike in chapter 3, $f(x)$ is no longer assumed to be a deterministic and parametric function. This way, GP regression allows us to treat $\mathbf{R}$ not simply as an error term but an actual part of our signal which we can predict. If $\mathbf{R}$ is not independent noise but for example a time series, where the elements of $\mathbf{R}$ are correlated, we want to leverage the information we have about an unobserved time point given our observations. Hence, we are not interested in the posterior distribution of f^* only, but also of $Y^* := Y(x^*) = f(x^*) + R(x^*)$.

Recall the expression for the marginal likelihood $p(\mathbf{Y}|X)$ from 4.2.0.1:

$$\mathbf{Y}|X \sim \mathcal{N}(0, X\Sigma_p X^\top + \Sigma_r)$$

Alternatively, this can be expressed as a distribution over the function $Y(x)$:

$$Y(x) \sim GP(0, k(x, x'))$$

The kernel function $k(x, x')$ needs to be chosen such that for an index set X we obtain $K_{XX} = X\Sigma_p X^\top + \Sigma_r$. One can then follow again the same procedure as before and combine Y^* and $\mathbf{Y}$ into a single random vector:

$$\begin{bmatrix} \mathbf{Y} \\ Y^* \end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} K_{XX} & K_{Xx^*} \\ K_{x^*X} & K_{x^*x^*} \end{bmatrix} \right) = p(\mathbf{Y}, Y^*|X, x^*) \tag{4.3.1.1}$$

The predictive distribution $p(Y^*|\mathbf{Y}, X, x^*)$ is then again derived by conditioning.

One could also assume additional idd measurement noise on the time series $f(x) + R(x)$. We then have for the observed time series $Y(x)$:

$$Y(x_i) = f(x_i) + R(x_i) + \epsilon_i \qquad \epsilon_1 \dots \epsilon_n \text{ iid} \sim \mathcal{N}(0, \sigma_n^2)$$

To be inline with the literature on Gaussian process regression, we will from now on consider our goal to find some function $f(x)$, which is a combination of the mean function, until now denoted by $f(x)$, and the stationary time series $R(x)$. The observed time series $Y(x)$ will thus be equivalent to $f(x)$ up to some additive independent noise term ϵ. We can write:

$$Y(x_i) = f(x_i) + \epsilon_i \qquad \epsilon_1 \dots \epsilon_n \text{ iid} \sim \mathcal{N}(0, \sigma_n^2)$$

Assuming the same linear model as before, we have for $F_X = [f(x_1), \dots f(x_n)]^\top$:

$$F_X = X\beta + \mathbf{R}, \text{ with } \beta \sim \mathcal{N}(0, \Sigma_p) \text{ and } \mathbf{R} \sim \mathcal{N}(0, \Sigma_r)$$

Analogously we can write:

$$f(x) \sim GP(0, k(x, x')),$$

with $k(x, x')$ such that for an input $X = [x_1 \dots x_n]^\top$ we obtain $K_{XX} = X\Sigma_p X^\top + \Sigma_r$.

The joint distribution of $\mathbf{Y}$ and $f^* := f(x^*)$ is given by:

$$\begin{bmatrix} \mathbf{Y} \\ f^* \end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} K_{XX} + \sigma_n^2 I & K_{Xx^*} \\ K_{x^*X} & K_{x^*x^*} \end{bmatrix} \right) = p(\mathbf{Y}, f^* | X, x^*) \tag{4.3.1.2}$$

The posterior (or predictive) distribution over f^* can then again be derived by conditioning:

$$p(f^*|\mathbf{Y}, X) = \mathcal{N}(K_{x^*X}(K_{XX} + \sigma_n^2 I)^{-1}\mathbf{Y}, K_{x^*x^*} - K_{x^*X}(K_{XX} + \sigma_n^2 I)^{-1}K_{Xx^*}) \tag{4.3.1.3}$$

If we are interested in predicting $Y(X)$, i.e. the iid gaussian noise term ϵ should be included in the prediction. We choose $k(x, x')$ such that $K_{XX} = X\Sigma_p X^\top + \Sigma_r + \sigma_n^2 I$. The predictive distribution over $Y^* := Y(x^*)$ is then simply:

$$p(Y^*|\mathbf{Y}, X) = \mathcal{N}(K_{x^*X}K_{XX}^{-1}\mathbf{Y}, K_{x^*x^*} - K_{x^*X}K_{XX}^{-1}K_{Xx^*}) \tag{4.3.1.4}$$

Also note how until now we have still assumed Σ_r, the covariance matrix of $\mathbf{R}$, to be known. However, deriving Σ_r for an ARMA process with irregularly spaced samples is not straight forward, as has already been shown in chapter 3. Section 4.5 will illustrate how choosing a specific kernel function solves this problem.

4.4 Mean Function

A Gaussian process is defined by its mean function, $\mu(x)$, and covariance function, $k(x, x')$. The mean function can be subtracted from the data without affecting the covariance. In Gaussian process regression, this means the predictive variance remains independent of the mean function. Consider $Y(x) = f(x) + \epsilon$, with $f(x) = m(x) + R(x)$. Where, $m(x)$ is a deterministic mean function, $R(X)$ is a time series process and ϵ is Gaussian iid noise with variance σ_n^2. The noise term is independent of the time series process $R(x)$.

This setup allows us to model $f(x)$ using a Gaussian Process:

$$f(x) \sim GP(m(x), k(x, x'))$$

Conditioning leads to the predictive distribution for $f^* := f(x^*)$:

$$\begin{gathered} p(f^*|\mathbf{Y} = y, X, x^*) = N(\bar{\mu}, \bar{\Sigma}), \\ \bar{\mu} = m(x^*) + K_{x^*X}(K_{XX} + \sigma_n^2 I)^{-1}(y - m(X)), \\ \bar{\Sigma} = K_{x^*x^*} - K_{x^*X}(K_{XX} + \sigma_n^2 I)^{-1}K(X, x^*) \end{gathered}$$

The predictive variance $\bar{\Sigma}$ remains unaffected by $m(x)$.

Alternatively, fitting a GP to $f(x) - m(x) = R(x)$ gives:

$$R(x) = f(x) - m(x) \sim GP(0, k(x, x'))$$

The predictive distribution over $R^* := R(x^*)$ given $\mathbf{Z} := \mathbf{Y} - m(X)$ is:

$$p(R^*|\mathbf{Z} = z, X, x^*) = N(\bar{\mu}_{R^*}, \bar{\Sigma}),$$
$$\bar{\mu}_{R^*} = K_{x^*X}(K_{XX} + \sigma^n I)^{-1} z,$$

The Predictive distribution over f^* is recovered by adding $m(x^*)$ to $\bar{\mu}_{R^*}$. The predictive variance $\bar{\Sigma}$ remains unchanged, unaffected by observations or $m(x)$.

Most frameworks for GP regression assume a zero mean prior. Therefore, when you have prior knowledge about $m(x)$, it's advisable to subtract it before fitting a GP. It is also common practice to subtract the empirical mean from your data, before fitting a GP.

For further insights, Rasmussen and Williams elaborates on this topic in his book, particularly on page 27.

4.5 Kernel Functions

The Gaussian Process is defined by its mean and covariance functions. Assuming a zero-mean Gaussian process, defining a prior distribution over $f(x)$ or $Y(x)$ involves selecting a kernel function only. The kernel is evaluated at inputs $X = [x_1, \ldots, x_n]^\top$ to establish the predictive distribution of f^* or y^*.

Kernel choice depends on assumptions about correlation in your output for input pairs x and x'. For modeling the BP time series, three relevant stationary covariance functions are considered and presented in this section. Following from stationarity, these functions depend on $\tau = x - x'$ only. We discussed covariance functions and stationarity for time series in Sections 2.2 and 2.3, respectively.

The following subsections draw upon the doctoral thesis of Duvenaud and the book of Rasmussen and Williams, which provide comprehensive coverage of covariance functions for Gaussian Processes.

4.5.1 Squared Exponential Kernel

The squared exponential kernel is also known as radial basis function (RBF) kernel or Gaussian kernel and has the form:

$$k(\tau) = \exp(-\frac{\tau^2}{2l^2})$$

Here, l is the length scale, and $\tau = x - x'$. The length scale governs the rate of function change, as shown in Figure 4.1. The RBF kernel generates infinitely differentiable, smooth outputs, regardless of the length scale.

4.5.2 Matérn Class of Kernels

The Matérn covariance function is expressed as:

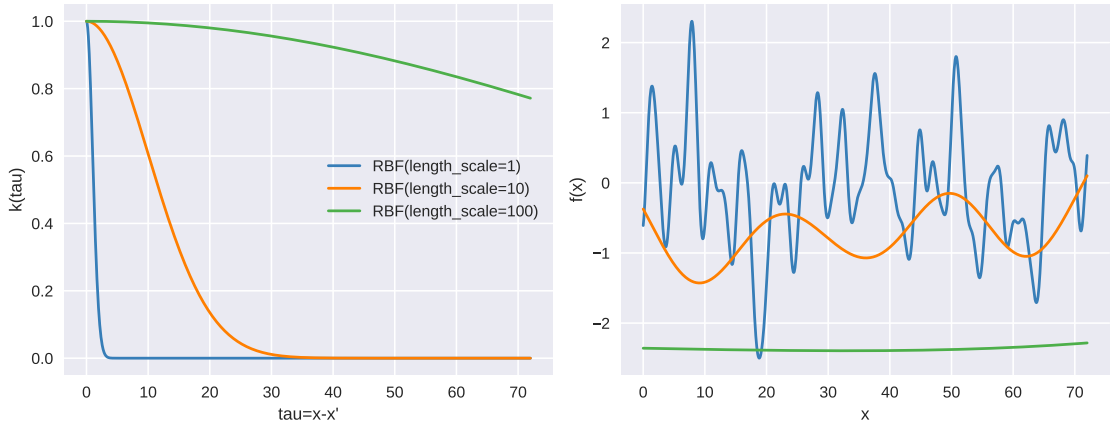


Figure 4.1: RBF Kernel function for different length scale (left panel) and a sample generated by such a GP (right panel)

$$k_\nu(\tau) = \frac{2^{1-\nu}}{\Gamma(\nu)} \left(\frac{\sqrt{2\nu}\tau}{l} \right)^\nu K_\nu \left(\frac{\sqrt{2\nu}\tau}{l} \right)$$

Here, ν and l are positive parameters, and K_ν is a modified Bessel function. Figure 4.2 illustrates the Matérn covariance function and corresponding sample paths for various ν values.

For $\nu = r + 1/2, r \in \mathbb{N}$, the Matérn covariance function simplifies to:

$$k_{\nu=r+1/2}(\tau) = \exp\left(-\frac{\sqrt{2r+1}\tau}{l} \right) \frac{r!}{(2p)!} \sum_{i=0}^{r} \frac{(r+i)!}{i!(r-i)!} \left(\frac{2\sqrt{2r+1}\tau}{l} \right)^{r-i} \tag{4.5.2.1}$$

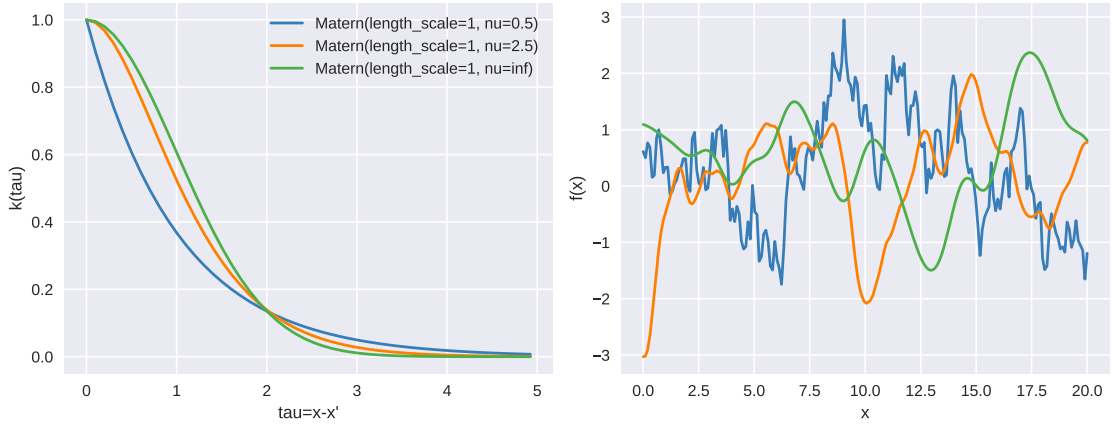


Figure 4.2: Matérn kernel function for different ν (left panel) and a sample generated by the corresponding GP (right panel)

Setting $\nu = 1/2$ with input domain $X \subset \mathbb{R}$ results in a continuous-time AR(1) process, also known as the Ornstein-Uhlenbeck process. With $\nu = 1/2$, i.e., $r = 0$, the Matérn covariance function becomes:

$$k(\tau) = \exp\left(-\frac{\tau}{l}\right) \tag{4.5.2.2}$$

More generally, for $\nu = p - 1/2$ and $X \subset \mathbb{R}$, the Matérn kernel matches the covariance function of a specific case of a continuous AR(p) process. For a deeper understanding of this topic, please refer to chapter 4 of the book by Rasmussen and Williams.

4.5.3 Periodic Kernel

The periodic kernel allows modeling functions with repeating patterns and is defined as:

$$k(x, x') = \sigma^2 \exp\left(-\frac{2\sin^2(\pi|x - x'|/p)}{l^2}\right)$$

Here, p represents the period, and l is the length scale. Figure 4.3 illustrates the impact of different length scales.

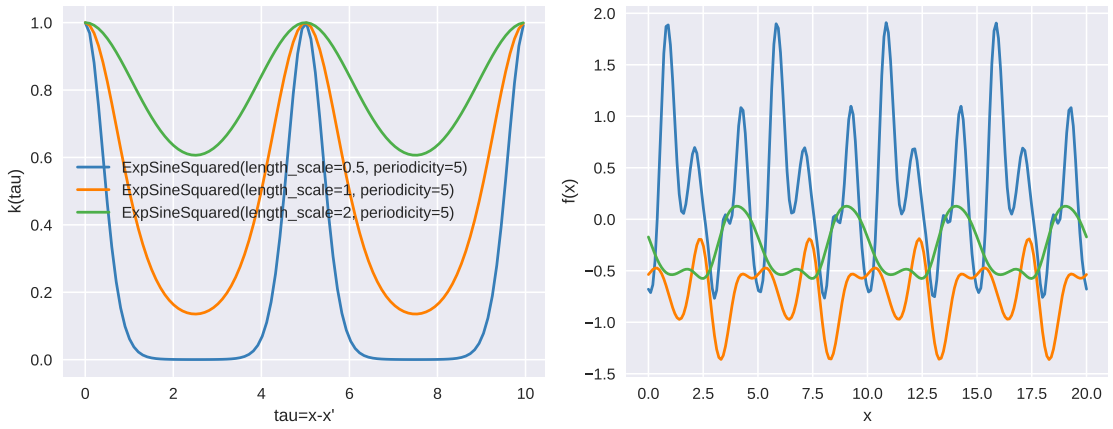


Figure 4.3: Periodic kernel function for different length scales (left panel) and a sample generated by the corresponding GP (right panel)

Throughout this thesis, we will also refer to the periodic kernel as the ExpSineSquared kernel.

4.5.4 Additive Kernels and Decomposition of Predictive Mean

Additivity of the kernel implies additivity of the predictive mean. For instance if we choose $Y(x) \sim GP(0, k(x, x'))$ with $k(x, x') = k_1(x, x') + k_2(x, x')$, then the predictive (posterior) mean $\bar{\mu}(x^*)$ is given by:

$$\begin{aligned}\bar{\mu}(x^*) &= (K_{1,x^*X} + K_{2,x^*X})(K_{XX})^{-1}\mathbf{Y} = K_{1,x^*X}(K_{XX})^{-1}\mathbf{Y} + K_{2,x^*X})(K_{XX})^{-1}\mathbf{Y} \\ &= \bar{\mu}_1(x^*) + \bar{\mu}_2(x^*)\end{aligned}$$

where:

$$K_{1,x^*X} = \begin{bmatrix} k_1(x_1, x^*) & \dots & k_1(x_n, x^*) \end{bmatrix},$$
$$K_{2,x^*X} = \begin{bmatrix} k_2(x_1, x^*) & \dots & k_2(x_n, x^*) \end{bmatrix},$$

and

$$K_{XX} = \begin{bmatrix} k(x_1, x_1) & \dots & k(x_1, x_n) \\ \vdots & & \vdots \\ k(x_n, x_1) & \dots & k(x_n, x_n) \end{bmatrix}$$

This decomposition allows us to study the contribution of the different (additive) kernel components on the predictive mean function.

4.6 Performance Assessment

Inference, in the case of Gaussian process regression, revolves around the posterior (predictive) distribution of the response variable. To evaluate how effectively the predictive distribution explains the observed values $\mathbf{y}^*$, it is common practice to calculate the probability of these values based on the predictive distribution. Equation 4.3.1.4 presents an expression for the predictive distribution of $\mathbf{Y}^* := [Y(x_1^*), \dots, Y(x_k^*)]^\top$ at arbitrary inputs $X^* = [x_1^*, \dots, x_k^*]$. Expanding the expression from 4.3.1.4 we obtain:

$$\log p(\mathbf{Y}^* = \mathbf{y}^* | \mathbf{Y}, X) = -\frac{k}{2} \log 2\pi - \frac{1}{2} \log |\bar{\Sigma}| - \frac{1}{2} (\mathbf{y}^* - \bar{\mu})^\top \bar{\Sigma}^{-1} (\mathbf{y}^* - \bar{\mu}) \tag{4.6.0.1}$$

where $\bar{\Sigma} = K_{X^*X^*} - K_{X^*X} K_{XX}^{-1} K_{XX^*}$ and $\bar{\mu} = K_{X^*X} K_{XX}^{-1} \mathbf{Y}$.

The higher the log probability, the better the fit to the data. In contrast to other performance metrics it accounts for the complete predictive distribution rather than just a point estimate. For instance, when employing the sum of squared errors between the true values y^* and the predictive mean $\bar{\mu}$, the predictive covariance matrix $\bar{\Sigma}$ is completely ignored.

4.7 Model Selection

Model selection in Gaussian process regression involves identifying the optimal covariance function along with the optimal hyperparameters. Two common approaches for model selection are cross-validation, using a performance-based loss function as discussed in Section 4.6, and Bayesian model selection, which will be explored in the subsequent subsections. The concepts and ideas discussed in this section are primarily derived from Chapter 5 of the textbook from Rasmussen and Williams.

4.7.1 Bayesian Model Selection

Bayesian model selection aims to find the most probable model given the available data using a hierarchical specification of the model. In a parametric model setting, the lowest level consists of the parameters β, followed by the hyperparameters θ, which control the parameter distribution. The highest level encompasses the set of possible model structures M_i.

The posterior distribution over the parameters β is determined using Bayes' rule:

$$p(\beta|\mathbf{Y}, X, \theta, M_i) = \frac{p(\mathbf{Y}|X, \beta, M_i)p(\beta|\theta, M_i)}{p(\mathbf{Y}|X, \theta, M_i)}$$

Here, $p(\mathbf{Y}|X, \beta, M_i)$ represents the likelihood, $p(\beta|\theta, M_i)$ denotes the prior, and $p(\mathbf{Y}|X, \theta, M_i)$ represents the marginal likelihood.

However, in the non-parametric setting of Gaussian processes, the parameter β does not exist and is replaced by the function f itself. Consequently, at the lowest level, the distribution over the function f is modeled using a Gaussian process. Similarly to the parametric setting, the posterior distribution over the function values $f^* = f(x^*)$ at some arbitrary input x^* is given by:

$$p(f^*|\mathbf{Y}, X, \theta, M_i) = \frac{p(\mathbf{Y}|f^*, M_i)p(f^*|\theta, M_i)}{p(\mathbf{Y}|X, \theta, M_i)}$$

This is equivalent to the expression in 4.3.1.3 for the posterior distribution over the function values f^* when assuming a Gaussian process prior $f \sim GP(0, k(x, x'))$. However, in the equation above, $k(x, x')$ is expressed through θ and M_i.

By assuming a prior distribution over the hyperparameters θ, a similar expression can be obtained for the posterior distribution over the hyperparameters:

$$p(\theta|\mathbf{Y}, X, M_i) = \frac{p(\mathbf{Y}|X, M_i, \theta)p(\theta|M_i)}{p(\mathbf{Y}|X, M_i)}$$

Maximizing $p(\theta|\mathbf{Y}, X, M_i)$ yields the optimal hyperparameters. However, when non-Gaussian priors are assumed for θ, evaluating $p(\theta|\mathbf{Y}, X, M_i)$ can be challenging. In such cases, it is common to maximize the marginal likelihood $p(\mathbf{Y}|X, \theta, M_i)$ with respect to the hyperparameters θ. This approach is equivalent to assuming uniform distributions over the hyperparameters. The next subsection will provide more details on how to calculate and maximize the marginal likelihood for Gaussian process regression.

Note that the scheme mentioned above can be extended to maximize the posterior over the model structures M_i in order to determine the optimal model structure. In Gaussian process regression, this corresponds to finding the optimal kernel function type. However, instead of directly evaluating the posterior, it is often achieved through simultaneous optimization of the marginal likelihood with respect to the model structure M_i and its hyperparameters θ. By jointly optimizing these components, we can effectively identify the most suitable kernel function for the given problem.

Marginal Likelihood

In the context of Bayesian linear regression, the marginal likelihood expression was previously introduced in subsection 4.2, assuming a prior distribution of $p(\beta) = \mathcal{N}(0, \Sigma_p)$ and a likelihood function of $p(\mathbf{Y}|X, \beta) = \mathcal{N}(X\beta, \Sigma_r)$. The following expression for the marginal likelihood is obtained by marginalizing over β:

$$p(\mathbf{Y}|X) = \int p(\mathbf{Y}|X, \beta)p(\beta)d\beta = \mathcal{N}(0, X\Sigma_p X^\top + \Sigma_r) \tag{4.7.1.1}$$

Furthermore, as discussed in section 4.3, the marginal likelihood can also be represented as a distribution over the function $Y(x)$:

$$Y(x) \sim GP(0, k(x, x'))$$

Here, the kernel function $k(x, x')$ is chosen such that for an index set X, we obtain $K_{XX} = X\Sigma_p X^\top + \Sigma_r$.

By the definition of a Gaussian process, $\mathbf{Y}|X$ follows a multivariate normal distribution with a covariance matrix of $K_{XX}(\theta)$, which is a function of the hyperparameters θ. The log marginal likelihood is hence given by:

$$\log p(\mathbf{Y}|X, \theta) = -\frac{1}{2}\mathbf{Y}^\top K_{XX}^{-1}(\theta)\mathbf{Y} - \frac{1}{2}\log|K_{XX}(\theta)| - \frac{n}{2}\log 2\pi \tag{4.7.1.2}$$

Since the marginal likelihood already incorporates a trade-off between model fit and model complexity, it is a suitable candidate for solving the model selection problem. The first term, $-\frac{1}{2}\mathbf{Y}^\top K_{XX}^{-1}(\theta)\mathbf{Y}$, represents a measure of the data fit. The second term, $\frac{1}{2}\log|K_{XX}(\theta)|$, penalizes more complex models. The last term $\frac{n}{2}\log 2\pi$ serves as a normalization constant.

Chapter 5

Methods

The last chapter introduced Gaussian process regression to establish a mapping between a time point x and its corresponding BP value. Since Gaussian Processes are capable of modeling time series in continuous time and hence deal with irregularly spaced data, they seem to be a good candidate for modeling a time series from which we only have irregularly sampled noisy measurements.

This chapter outlines the methodology for evaluating the performance of Gaussian process regression and baseline methods for estimating blood pressure values from noisy measurements. It also discusses the analysis of adversarial factors that may affect estimation accuracy.

5.1 Problem Statement

Recall the problem statement from section 1.2. First, we assumed the following model for the BP measurements $Y(x)$ at a time point x:

$$Y(x) = f(x) + \epsilon \qquad\qquad \epsilon \sim \mathcal{N}(0, \sigma_n^2)$$

where $f(x)$ denotes the true BP process and ϵ is iid measurement noise, independent from $f(x)$.

The goal is to estimate the true BP values $f(x)$ at some input time X, based on noisy observations of $f(x)$ at some training time points X_{train}. For the sections of this chapter, we define:

- $X := \{x_1, \ldots, x_n\}$: An index set spanning the one-week time range of interest, with 10 BP values per hour. It defines the time points at which we want to predict BP values and hence represents the regression input.
- $X_{train} \subset X$: The training indexes.
- $G_X := (g(x) : x \in X)$ for some function $g(x)$. Specifically:

  $F_X := (f(x) : x \in X)$: The true BP values at inputs X.

$Y_X = (Y(x) : x \in X)$: The noisy BP measurements at inputs X, which constitute the response variable in the context of regression.

$Y_{X_{\text{train}}} := (Y(x) : x \in X_{\text{train}})$: The noisy measurements at training indexes.

- $(X_{train}, Y_{X_{train}})$: The training data used for estimating F_X
- $K_{XX'} := \begin{bmatrix} k(x_1, x'_1) & \dots & k(x_1, x'_m) \\ \vdots & & \vdots \\ k(x_n, x'_1) & \dots & k(x_n, x'_m) \end{bmatrix}$,for some kernel function, $k(x, x')$

  and some inputs $X = (x_1, \dots x_n)$ and $X' = (x'_1, \dots x'_m)$.

Additionally, when referring to the estimated values, $\hat{F}_X$ is used instead of F_X.

5.2 Overview

To assess the suitability of GPs for this problem, the following tasks have been defined:

- Simulate F_X and the training data (X_{train}, $Y_{X_{train}}$) (section 5.4)
- Employ Gaussian process regression to obtain $\hat{F}_X$ from the training data (section 5.5)
- Derive target measures from $\hat{F}_X$, including 95% credible intervals (section 5.3)
- Evaluate performance using:
  - CiCoverage: Equals one if the true target measure value extracted from F_X was covered by the credible interval, zero otherwise.
  - CiWidth: The width of the credible interval

These steps are repeated $S = 100$ times, and the final performance is assessed by averaging CiCoverage and CiWidth. Pseudocode 1 provides a more detailed illustration of this process.

To contextualize the performance of GP regression, it is compared to the performance of baseline methods (section 5.6). Additionally, the impact of adversarial factors on estimation accuracy is discussed in section 5.7.

5.3 Target Measures

In subsection 1.2.2, the mean BP over different time windows and TTR has been defined as the measures of interest. These measures are extracted from F_X to obtain the true target measure values and from $\hat{F}_X$ to obtain the estimated target measures.

The **one-week mean BP**, $\bar{F}_X$, was calculated as the mean of all values in F_X:

$$\bar{F}_X = \frac{1}{n} \sum_{x \in X} f(x)$$

The **one-hour and one-day BP means**, $\bar{F}_{X_1} \dots \bar{F}_{X_W}$, were calculated by taking the mean value of $f(x)$ evaluated at the different time windows $X_1 \dots X_W \subset X$. For the first

one-hour or one-day window X_1, this is:

$$\bar{F}_{X_1} = \frac{1}{n_1} \sum_{x \in X_1} f(x),$$

with n_1 being the number of elements in X_1

To obtain a single measure, in each simulation iteration s, a time window was chosen uniformly at random from $X_1 \dots X_W$. The estimation performance was assessed for this time window only, and the mean performance over all S simulations was reported.

TTR was calculated by dividing the number of BP values in F_X within the target range by the total number of values in F_X:

$$\frac{1}{n} \sum_{x \in X} \mathbb{1}\{\ 90 < f(x) < 125\}$$

5.4 Blood Pressure Time Series Simulation

For simulating the blood pressure time series, the goal is to match the properties described in section 1.2. Simulation starts by generating the true BP time series process, $f(x)$. This process is then sampled at the desired time points X to obtain F_X. Finally, noise is added to obtain Y_X.

The true BP process $f(x)$ is modeled by a Gaussian process (true GP) since GPs are flexible enough to represent the properties specified for $f(x)$ in section 1.2.1.

5.4.1 Mean function

A reasonable assumption for the mean function is to keep it constant and equal to the global mean BP value of 120 mmHg. We have:

$$f(x) \sim GP(120, k(x, x'))$$

From section 4.4, we know that this is the same as writing:

$$f(x) - 120 \sim GP(0, k(x, x'))$$

For simplicity, we are going to completely ignore this constant mean function throughout the rest of the thesis and model the true BP process $f(x)$ with the following GP:

$$f(x) \sim GP(0, k(x, x'))$$

where we write $f(x)$, although we actually mean $f(x) - 120$.

5.4.2 Kernel function

The chosen kernel function to match the properties from section 1.2.1 is:

$$k(x, x') = 2.24^2 * \text{Matérn}(l = 3, \nu = 0.5) + 14^2 * \text{Periodic}(l = 3, p = 24) + 2.24^2 * \text{RBF}(l = 50)$$

where l denotes the length scale, and p denotes the periodicity of the corresponding kernel function in hours. The formal definition of the Matérn, Periodic, and RBF kernel functions and their parameters is provided in section 4.5.

Each of these kernels models one of the components described in 1.2.1:

- The Matérn kernel with $\nu = 0.5$ models the AR(1) component
- The Periodic kernel models the circadian cycle
- The RBF kernel models a long-term trend

The kernel function is illustrated in figure 5.1, and some samples drawn from this GP are shown in Figure 5.2.

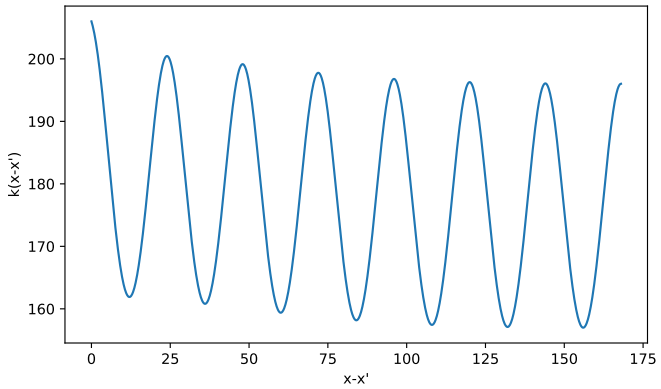


Figure 5.1: The True Kernel Function $k(x, x')$

5.4.3 Simulation of the BP Measurements

The BP measurements time series process $Y(x)$ is obtained by adding iid measurement noise $\epsilon \sim \mathcal{N}(0, \sigma_n^2)$ to $f(x)$. The measurement noise variance σ_n^2 is set to 31 mmHg^2, as explained in subsection 1.2.1. The measurement indexes X_{train} are then chosen from X, yielding the training data, $Y_{X_{train}}$. The different downsampling patterns used to produce the training data are described in section 5.7.

Appendix A.2 additionally presents the distributions of some simulated BP measurement properties.

5.5 Gaussian Process Regression

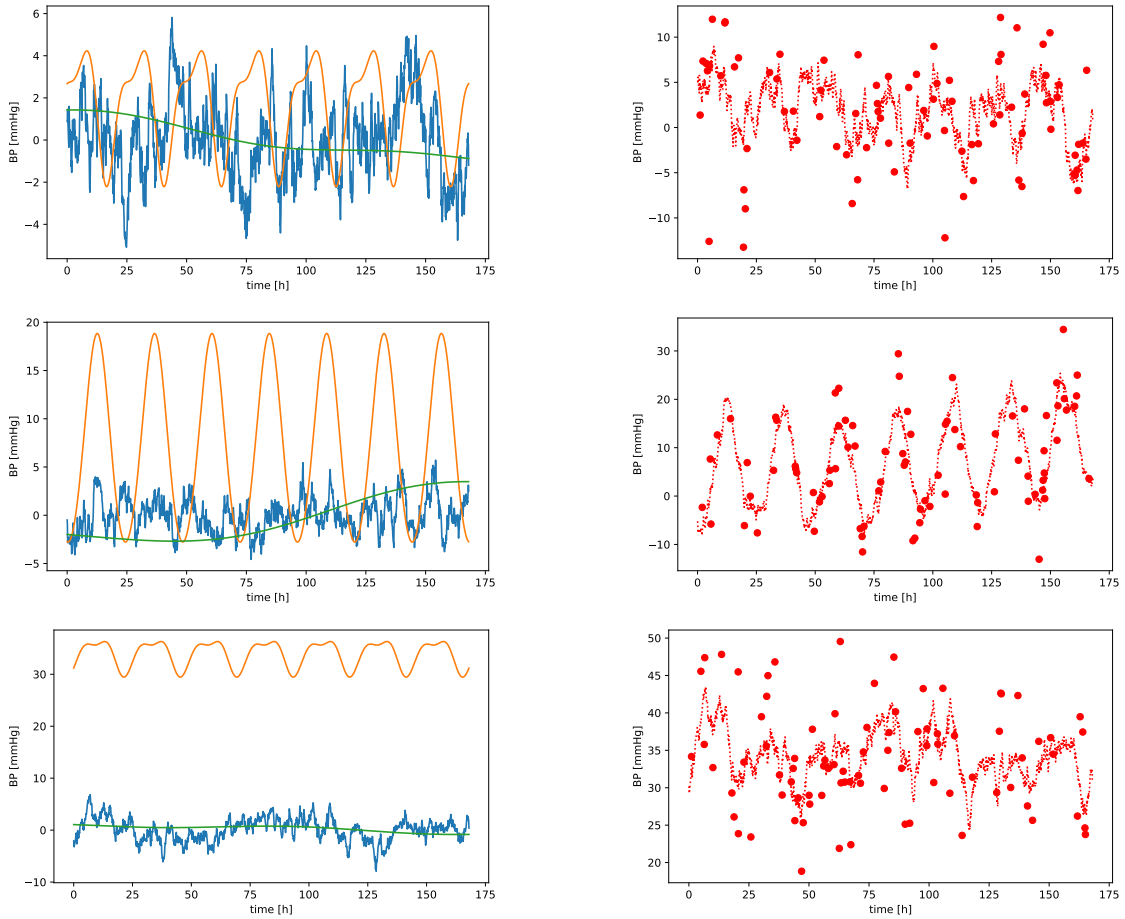
A Gaussian process regression was fitted to $Y_{X_{\text{train}}}$ to estimate F_X. The kernel function used has the same form as the one used for simulation but with variable hyperparameters:

$$k(x, x') = \sigma_M^2 \cdot \text{Matérn}(l, \nu = 0.5) + \sigma_P^2 \cdot \text{Periodic}(l, p = 24) + \sigma_R^2 \cdot \text{RBF}(l)$$

The hyperparameters, σ_M^2, σ_P^2, σ_R^2, and l, were found by maximizing the marginal likelihood, as described in subsection 4.7.1, yielding the optimal kernel $\hat{k}(x, x')$. Optimization has been performed using the "L-BFGS-B" algorithm from Python's "scipy.optimize.minimize" module, which belongs to the family of quasi-Newton methods.

To evaluate the performance of GP regression for a specific target measure, the following steps were repeated $S = 100$ times:

- Simulated data was obtained by sampling from the true GP



(a) The sample F_X shown to the right, decomposed in to the contribution of the Periodic kernel (orange), Matérn kernel (blue), RBF kernel (green).

(b) Each figure shows one sample F_X drawn from the true GP (red dashed line) with 87 irregularly spaced noisy observations (red dots)

Figure 5.2: Three samples (right side) drawn from the true GP and the decomposition of theses samples (left side)

- $\hat{k}(x, x')$ was otained by fitting a GP regression to the simulated data
- The predictive distribution over F_X was obtained from $\hat{k}(x, x')$
- Target measure estimates, along with equal-tailed credible intervals, were calculated by sampling from the predictive distribution.

CI coverage was computed by determining the number of times the true target measure fell within the credible interval, divided by the total number of simulations S. CI width was calculated by averaging the width of the CIs across all S simulations. This process is summarized in Algorithm 1.

5.6 Baseline Methods

Some other methods were fitted to $Y_{X_{train}}$ as a reference, to which the GP performance was compared to. The chosen baseline methods presented in this section are: linear

Algorithm 1 Simulation and Evaluation Flow

Caluclate avergage CiCoverage and CiWdith over S simulations by repeated generation of syntetic data and fitting of a GP regression. Target measure extimates and equal-tailed credible intervals were extracted from the predictive distribution obtained in every simulation iteration s.

Inputs:

X	▷ Regression input
K_{XX}	▷ True kernel function evaluated at the input X
S	▷ Number of simulations
K	▷ Number of draws from the predictive distribution to estimate CIs
α	▷ Significance level to calculate $1-\alpha$ CIs
σ_n^2	▷ Measurement noise variance
TargetMeasure	▷ Function to extract target measure from F_X or $\hat{F}_X$

Output:

CiCoverage	▷ Credible interval coverage
CiWidth	▷ Credible interval width

Initialize: CiCoverageList = [ ], CiWidthList = [ ],
for $s = 0 \dots S$ **do**
  F_X = sample from $\mathcal{N}(0, K_{XX})$ ▷ Sample from the true GP
  $X_{train} \subset X$ ▷ Choose training indexes
  $Y_{X_{train}} = F_{X_{train}} + \epsilon$, $\epsilon \sim \mathcal{N}(0, \sigma_n^2)$
  $\hat{k}(x, x') = \text{GP.fit}(X_{train}, Y_{X_{train}})$ ▷ Find the optimal kernel
  $\hat{F}_X = \hat{K}_{XX_{train}}(\hat{K}_{X_{train}X_{train}} + \sigma_n^2 I)^{-1} Y_{train}$ ▷ predictive mean
  $\hat{\Sigma}_{F_X} = \hat{K}_{XX} - \hat{K}_{XX_{train}}(\hat{K}_{X_{train}X_{train}} + \sigma_n^2 I)^{-1}\hat{K}_{X_{train}X}$ ▷ predictive covariance
  Initialize: $\hat{M} = [\,]$
  for $k = 0 \dots K$ **do**
    $\hat{F}_{X,k}$ = sample from $\mathcal{N}(\hat{F}_X, \hat{\Sigma}_{F_X})$ ▷ Sample from predictive distribution
    $\hat{M}$.append(TargetMeasure($\hat{F}_{X,k}$)) ▷ Extract target measure
  end for
  m = TargetMeasure(F_X) ▷ Extract true target measure
  $\hat{m}$ =mean($\hat{M}$)
  $ci = (\text{quantile}_{\alpha/2}(\hat{M}), \text{quantile}_{1-\alpha/2}(\hat{M}))$ ▷ Equal-tailed credible interval
  CiCoverageList.append($ci\,[0] \leq m \leq ci\,[1]$)
  CiWidthList.append($ci\,[1] - ci\,[0]$)
end for
CiCoverage = mean(CiCoverageList)
CiWidth = mean(CiWidthList)

regression, spline regression, overall mean, and naive TTR. All methods, but naive TTR, estimate the target measure through the estimation of F_X. The calculation of the target measure and confidence interval is described in Algorithm 2. The procedure is equivalent to GP regression, except that one does not sample from the posterior distribution but uses bootstrap samples instead.

Algorithm 2 Target Measure Estimation with Bootstrap CI

Inputs:

X ▷ The regression input
F_X ▷ True BP values at inputs X
$X_{train}, Y_{X_{train}}$ ▷ The training data
σ_n^2 ▷ Measurement noise variance
RegressionMethod ▷ The baseline method
TargetMeasure ▷ Function to extract target measure from F_X or $\hat{F}_X$

Output:

CiCoverage ▷ Credible interval coverage
CiWidth ▷ Credible interval width

Initialize: $\hat{M} = [\,]$
for $k = 0 \ldots K$ **do** ▷ K bootstrap iterations
  $X^* =$ sample with replacement from X_{train}
  $\hat{F}_{X,k} = \text{RegressionMethod.fit}(X^*, Y_{X^*}).\text{predict}(X)$
  $\hat{M}.\text{append}(\text{TargetMeasure}(\hat{F}_{X,k}))$ ▷ Extract target measure
end for
$m = \text{TargetMeasure}(F_X)$ ▷ Extract true target measure
$\hat{m} = \text{mean}(\hat{M})$
$ci = ((2\hat{m} - \text{quantile}_{1-\alpha/2}(\hat{M}), (2\hat{m} - \text{quantile}_{\alpha/2}(\hat{M})))$ ▷ Confidence interval
$\text{CiCoverage} = (ci\,[0] \leq m \leq ci\,[1])$
$\text{CiWidth} = (ci\,[1] - ci\,[0])$

5.6.1 Linear Regression

The model used has already been presented in section 3.1 and it features a linear trend and seasonal component:

$$Y(x) = \beta_0 + \beta_1 x + \beta_2 \cos(2\pi f x) + \beta_3 \sin(2\pi f x) + R(t),$$

where f, the frequency, is known and equals $1/\text{period} = 1/24$.

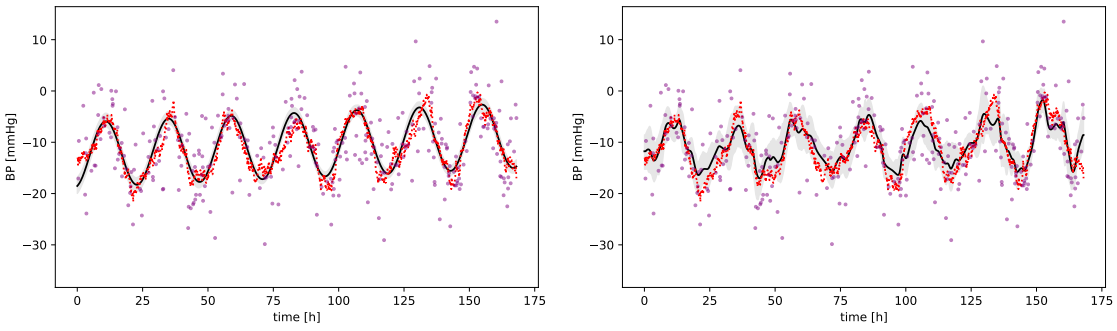
The seasonal component has variable phase shift and amplitude. Ordinary least square regression has been fit to the training data $(X_{train}, Y_{X_{train}})$ to obtain the regression coefficients and thus $\hat{F}_X$.

5.6.2 Spline Regression

The scikit-learn Python package has been used to generate regression splines for predicting F_X. First, X_{train} and X were transformed to cubic B-splines using the "sklearn.preprocessing.SplineTransformer" class. Knots have been placed uniformly along the quantiles of X_{train}. The number of knots was chosen to be equal to the number of training data points but not more than a 100. Ridge regression is then fit to the transformed training input $X\text{trans}_{train}$ and the response $Y_{X_{train}}$. The regularization parameter α determines the smoothness of the resulting function, and the optimal number has been identified through 10-fold cross-validation. The code section 5.3 provides more implementation details, and figure 5.4b shows an example of $\hat{F}_X$ estimated from training data using regression splines.

```python
import numpy as np
from sklearn.preprocessing import SplineTransformer
from sklearn.linear_model import Ridge

def fit_and_predict_spline_regression(
                X_train: np.ndarray,Y_X_train: np.ndarray, X: np.ndarray,
                alpha: float) -> np.ndarray:
    """
    Parameters
    ----------
    X_train, Y_X_train: The training data
    X: The time indexes at which to generate predictions
    alpha: The regularization parameter used for ridge regression

    Returns
    ---------
    F_X_hat: The BP value predictions at inputs X
    """
    # Number of splin knots
    n_knots = min(len(np.unique(x_train)), 100)
    spline = SplineTransformer(degree=3, n_knots=n_knots,
                               extrapolation="constant",
                               knots="quantile")
    # Compute knot positions of splines.
    spline.fit(X_train)
    # Transform to B-splines
    Xtrans_train = spline.transform(X_train)
    Xtrans = spline.transform(X)

    # Fit ridge regression
    lm = Ridge(alpha=alpha).fit(Xtrans_train, Y_X_train)

    # Predict BP values at inputs X
    F_X_hat = lm.predict(Xtrans)
    return F_X_hat
```

Figure 5.3: Spline Regression Estimation of F_X



(a) Linear Regression

(b) Spline Regression

Figure 5.4: Linear regression and spline regression used to estimate some example of true BP values F_X. The estimated BP values $\hat{F}_X$ (black line), the true BP values (red dashed line) and the training data (purple dots). The gray area shows the bootstrap CI.

5.6.3 Overall Mean

This method sets $\hat{F}_X$ to the mean of all measurements $Y_{X_{train}}$ everywhere.

5.6.4 Naive TTR

This method directly estimates the target measures from the noisy measurements $Y_{X_{train}}$, without estimating F_X first. The one-hour, one-day, and one-week means were calculated by taking the mean of the available measurements within the time period. If no measurements are available within that period, the mean overall measurements were used.

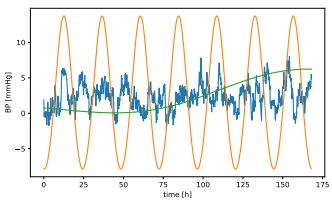
For calculating TTR, the number of measurements within the range over the total number of available data points.

5.7 Adversarial Analysis

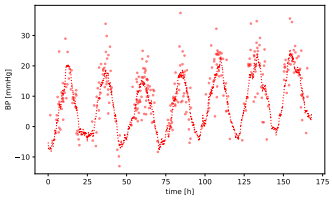
This section explores the influence of the sampling pattern on the accuracy of target measure estimates. As discussed in Section 1.2.1, data density was expected to vary within the Aktiia population, and measurements were not uniformly sampled. Instead, data density followed a circadian cycle, referred to as "seasonal sampling."

To create varying levels of data density, downsampling was applied to the dataset X to obtain X_{train}. Different downsampling factors were investigated, including 20, 10, 5, and 2.5. A downsampling factor of 20 indicated that X_{train} contained only 5% of the original data in X, which initially had 10 time points per hour. Consequently, a downsampling factor of 20 or a data fraction of 0.05 implied that measurements were, on average, taken every other hour.

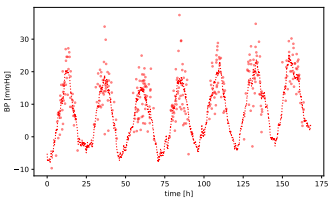
Seasonal sampling was implemented by extracting the true seasonal component from the original BP samples. The values of these seasonal components shifted to contain only positive values and scale to sum up to one, served as probability weights when selecting data for X_{train} from X. A more extreme seasonal sampling pattern has been produced by using the squared values of the seasonal component as probability weights. The decomposed seasonal component and the resulting seasonal sampling are illustrated in Figure 5.5.



(a) Decomposed $f(x)$



(b) $f(x)$ and measurments from seasonal sampling.



(c) $f(x)$ and measurments from extreme seasonal sampling.

Figure 5.5: Panel (b) and (c) show the sample $f(x)$ (red dashed line) drawn from the true GP with measurments generated by seasonal and extreme sampling (red dots). Panel (a) shows $f(x)$ decomposed into its components. The probability weights used for downsamplin X are calculated from the values of the periodic component (orange)

5.8 Computational Frameworks

All code has been written in Python. For Gaussian process simulation and regression, for fitting the spline regression and linear regression, the Pyton package scikit-learn has been used.

Chapter 6

Results and Analysis

This chapter presents the performance of GP regression in estimating various measures based on a simulation study. The estimation performance of GP regression is compared with that of baseline methods. The performance is reported for different downsampling factors, where a downsampling factor of 2 implies that the training data contains half of the samples from the original signal F_X, which has 10 samples per hour. Additionally, results for both uniform and seasonal sampling are presented.

6.1 Target Measures

In this section, we evaluate the effectiveness of GP regression ("gp") in estimating specific target measures. These target measures include the one-week mean, one-day mean, one-hour mean, and time in the target range (TTR). We compare the estimation performance of GP regression with that of several baseline methods, including linear regression ("linear"), spline regression ("spline"), overall mean ("overall_mean"), and naive TTR ("naive_ttr").

6.1.1 One-Week Mean

Figure 6.1 illustrates the performance of different methods in estimating the one-week mean under different sampling patterns. Subfigure 6.1a and 6.1b display the results for uniform and seasonal sampling, respectively. Within each subfigure, the panels represent decreasing downsampling factors from left to right.

Performance is presented in terms of confidence or credible interval (CI) width and CI coverage. CI width represents the width of the estimated 95% CI for the one-week mean BP value, measured in mmHg. CI coverage indicates the number of times the true one-week BP values were covered by the estimated CI over 100 simulations.

Ideally, a method should achieve 95% CI coverage with a very low CI width, positioning itself in the upper-left corner of the plot. Achieving 95% coverage is considered more critical than having a low width. Based on this 100 simulation runs, the confidence intervals of the CI coverage values have been calculated. Whenever these confidence intervals of the CI coverage spans across 95% coverage, the method is deemed adequate.

It is important to note that all plots have the same range of CI coverage values on the y-axis, but the x-axis range of CI width values varies. As expected, CI width values increase with larger downsampling factors and with seasonal sampling.

For the one-week mean the overall mean is equivalent to the naive TTR estimate. Therefore, naive TTR is omitted from this analysis. All methods perform adequately with uniform sampling. While linear and spline regression seem to produce the smaller confidence intervals for the largest downsampling factor than GP regression, the three methods have similar width as more data gets available.

In the presence of seasonal sampling, the overall mean obviously does not provide good estimates. GP regression generally comes closest to the target coverage, but for high downsampling factors, linear regression remains competitive and provides even smaller CI widths. However, the more data available the more linear regression seems to diverge from the true BP values. This effects are more pronounced in the face of extreme seasonal sampling. Spline regression does not cope well with seasonal sampling it has very low CI coverage with smallest CIs across the board.

In conclusion, both linear and GP regression produce the best one-week mean estimates. Linear regression is preferable for very high downsampling factors, while GP regression is recommended for downsampling factors below 5, corresponding to an average of 2 or more measurements per hour.

6.1.2 One-Day and One-Hour Mean

Figures 6.2 and 6.3 illustrate the performance of different methods in estimating the one-day and one-hour mean, respectively, based on various downsampling patterns.

GP regression consistently produces the best estimates for both the one-hour and one-day mean across all sampling patterns. Its superiority becomes more pronounced with increased data availability and an increasing amount of seasonal sampling.

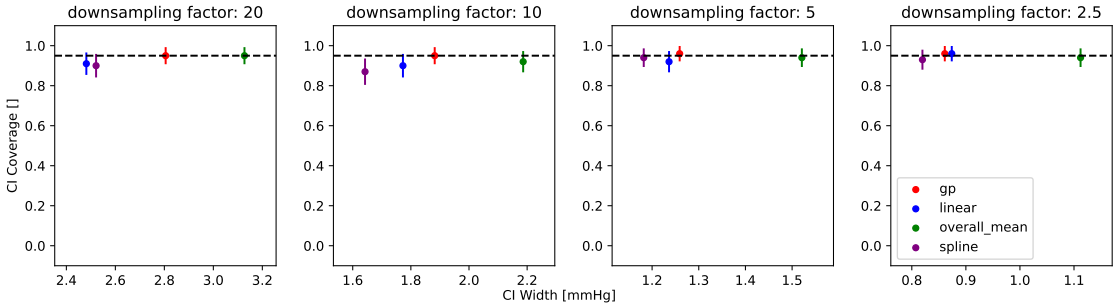
Spline regression produces close to adequate results when there is uniform sampling and high data availability. However, spline regression struggle with seasonal sampling especially as the averaging window decreases to one hour. However, as more data is added, spline regression does not only reduce CI width but also comes closer to the target coverage, whereas linear regression does generally produce worse CI coverage with more data available.

In the case of uniform sampling, the one-day mean is adequately approximated by the naive TTR method.

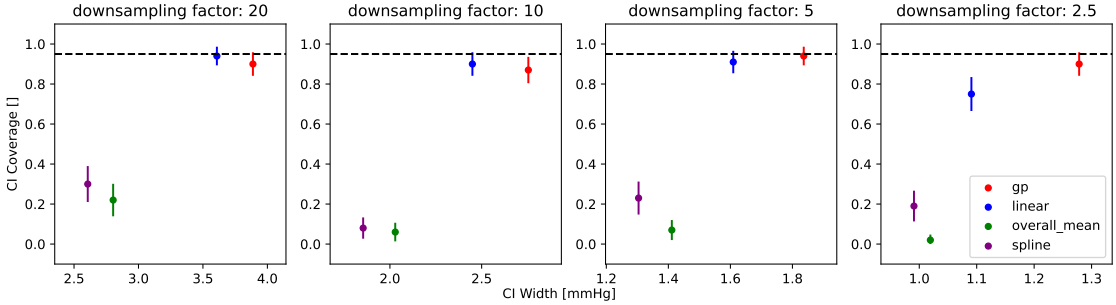
In conclusion, GP regression is the only method, that can produce adequate CIs for the expected one-day and one-hour mean BP.

6.1.3 Time in Target Range

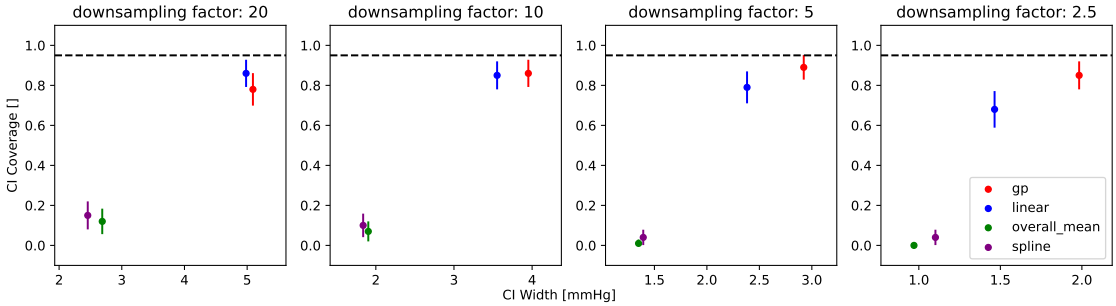
Figure 6.4 displays the performance of different methods in estimating TTR based on various downsampling patterns. Among these methods, GP regression stands out as the only one consistently achieving adequate CI coverage for most of the downsampling patterns. While spline regression comes close to the CI coverage target under uniform sampling and large downsampling factors it struggles again with seasonal sampling. Linear regression on the other hand does achieve a CI coverage of about 70% regardless of the sampling pattern, again demonstrating how it is less data dependent. The approach currently used by Aktiia for estimating TTR (”naive_ttr”) performs poorly. This is because it does not estimate TTR through the estimation of $f(x)$ but directly operates on the noisy measurements $Y(x)$. As a result, it generally underestimates TTR.



(a) One-Week Mean - Uniform Downsampling



(b) One-Week Mean - Seasonal Downsampling



(c) One-Week Mean - Extreme Seasonal Downsampling

Figure 6.1: Performance comparison of various methods for estimating the one-week mean across different downsampling patterns. The dashed horizontal line indicates the target CI coverage of 95%.

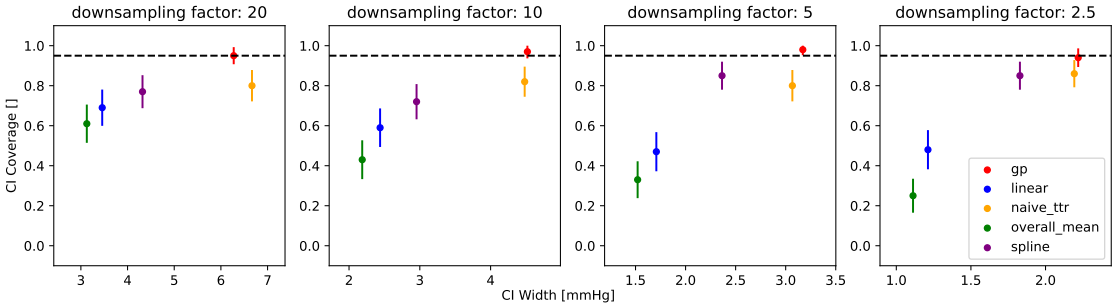
6.2 Examples

This section presents illustrative examples to support the observations made in the preceding section.

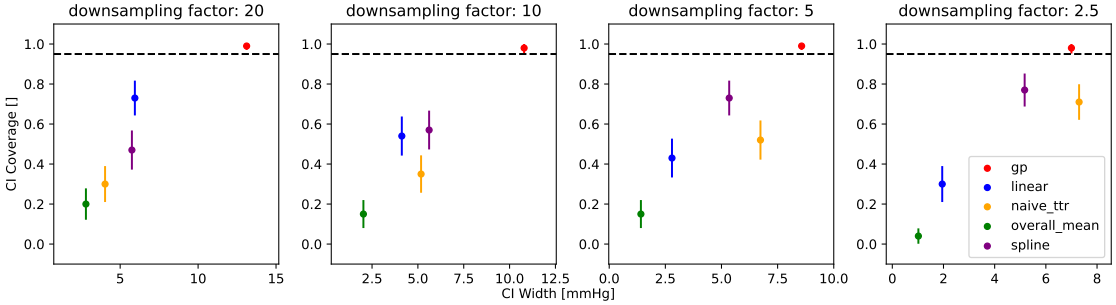
6.2.1 Impact of Downsampling Factor

Figure 6.5 provides an example of how various methods perform as more data is incorporated. In this context:

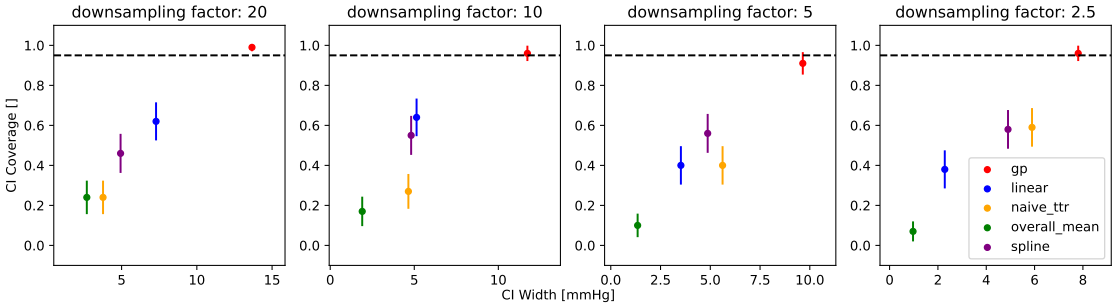
- Linear regression demonstrates the ability to produce accurate estimates even at high downsampling factors. However, the linear model can only fit a very constrained set of function and hence does not exhibit substantial improvement as more data is



(a) One-Day Mean Performance - Uniform Downsampling



(b) One-Day Mean Performance - Seasonal Downsampling



(c) One-Day Mean Performance - Extreme Seasonal Downsampling

Figure 6.2: Performance comparison of various methods for estimating the one-day mean across different downsampling patterns. The dashed horizontal line indicates the target CI coverage of 95%.

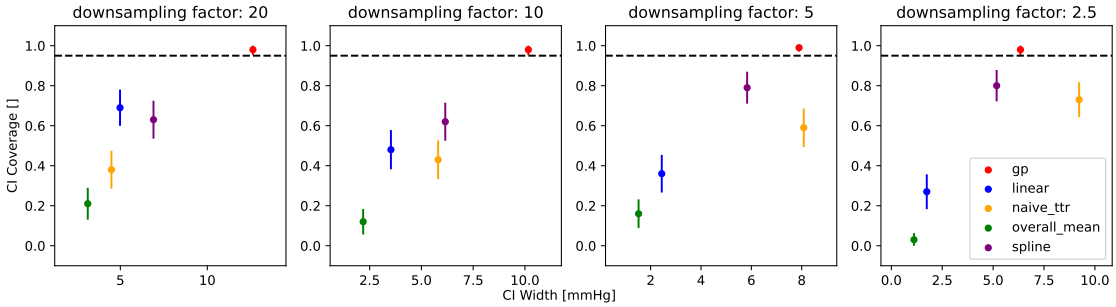
included.

- Conversely, GP and spline regression displays notable improvements with an increasing amount of data.
- Spline regression struggles to capture the cyclic component under low data density however produces very similar results to GP regression at high data density.

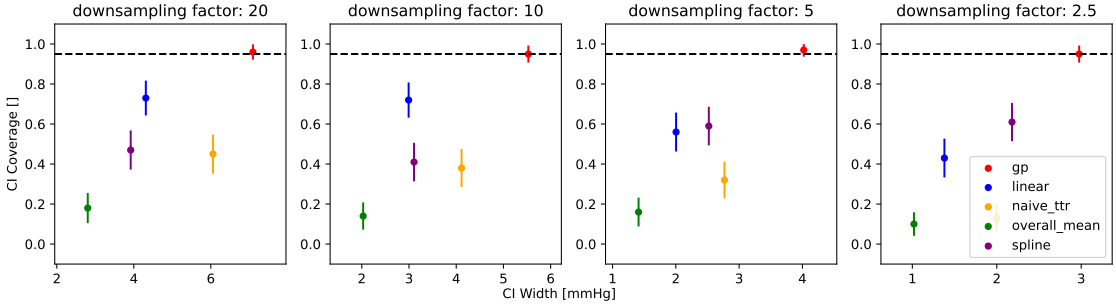
6.2.2 Seasonal Samping and Downsampling Factor

Figure 6.6 illustrates the influence of different downsampling factors in the presence of extreme seasonal sampling on the estimated BP values and CIs. In this context:

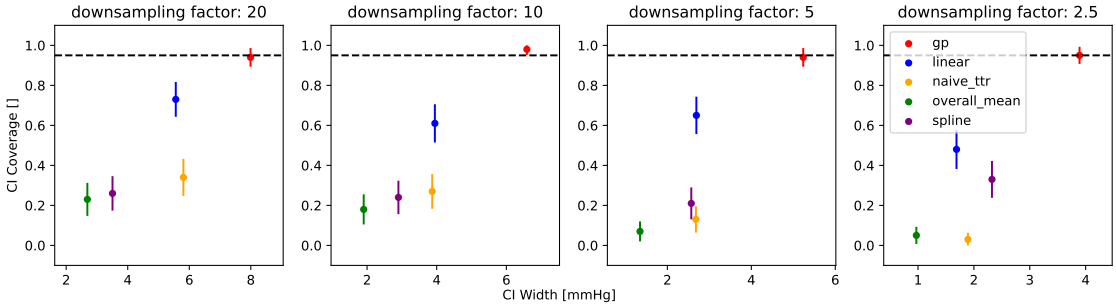
- Linear regression once again demonstrates its ability to produce reasonably accurate



(a) One-Hour Mean Performance - Uniform Downsampling



(b) One-Hour Mean Performance - Seasonal Downsampling



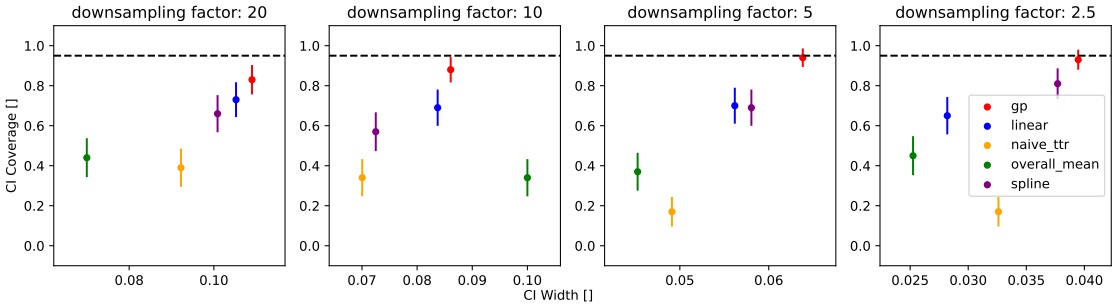
(c) One-Hour Mean Performance - Extreme Seasonal Downsampling

Figure 6.3: Performance comparison of various methods for estimating the one-hour mean across different downsampling patterns. The dashed horizontal line indicates the target CI coverage of 95%.

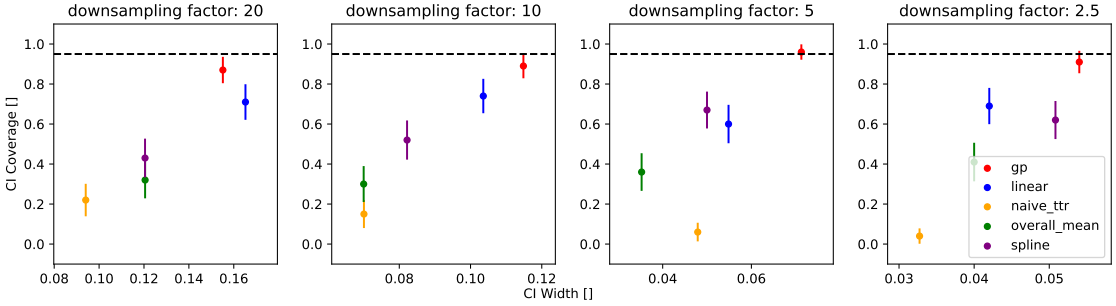
results when only limited data is available. However, as more data is added, the BP estimates do not improve, while the CIs get narrower leading to worse CI coverage.

- Spline regression, on the other hand, does not prioritize fitting a cyclic pattern, leading to highly inaccurate predictions in the valleys, where there is fewer data. Predictions improve, albeit primarily in the peaks, as more data is added.
- GP regression consistently yields accurate BP values for high and low downsampling factors. With the addition of more data at the peaks, it effectively reduces local uncertainty. However, uncertainty remains high in the valleys where data is sparse.

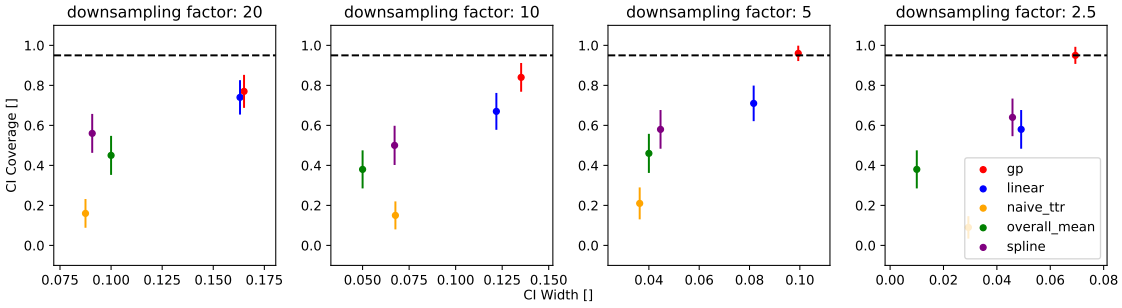
The second example in Figure 6.7 illustrates how linear regression predictions deteriorate with an increasing amount of data. Both GP and spline regression encounter difficulties in accurately estimating BP values in the valleys, and as more data is introduced, their



(a) TTR Performance - Uniform Downsampling



(b) TTR Performance - Seasonal Downsampling



(c) TTR Performance - Extreme Seasonal Downsampling

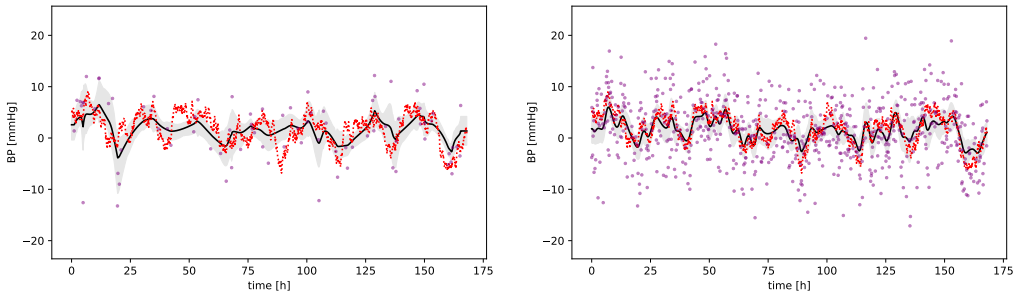
Figure 6.4: Performance comparison of various methods for estimating TTR across different downsampling patterns. The dashed horizontal line indicates the target CI coverage of 95%.

improvements are primarily observed in the peaks. Notably, at a downsampling factor of 2.5, GP regression produces estimates that closely align with those of spline regression. However, the confidence intervals generated by GP regression better capture the local uncertainty in the valleys of the function, where data is scarce.

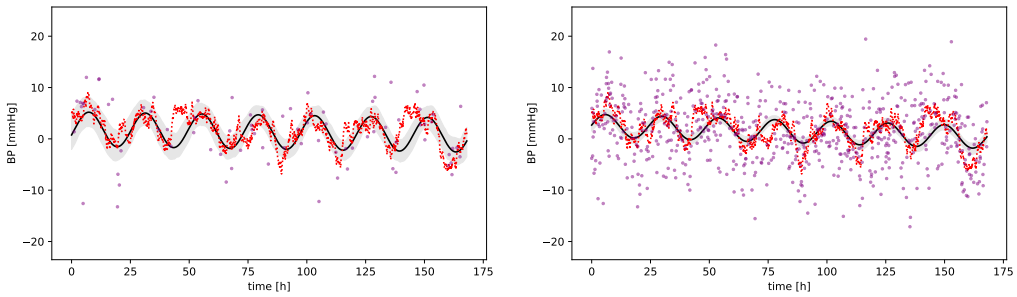
6.2.3 Dominant Cyclic Component vs. Dominant AR Component

Figure 6.8 presents a comparison of predictions under two scenarios: when the AR component dominates and when the cyclic component takes precedence. In this context:

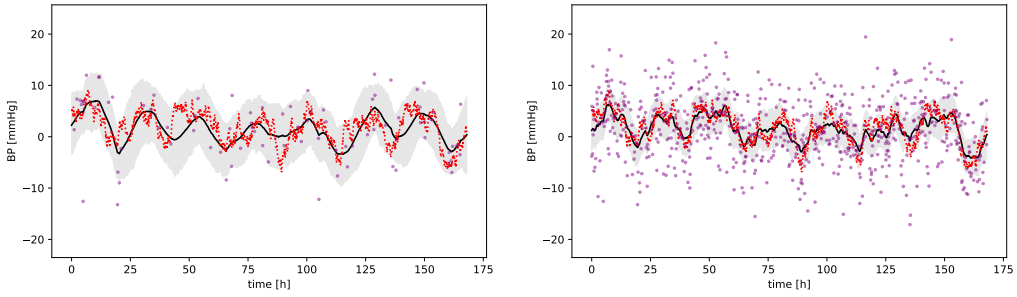
- When the cyclic component is predominant, all methods perform well and provide accurate predictions also for a large downsampling factor of 10. Spline and GP regression provide larger CIs, resulting in superior CI coverage.



(a) Spline Regression

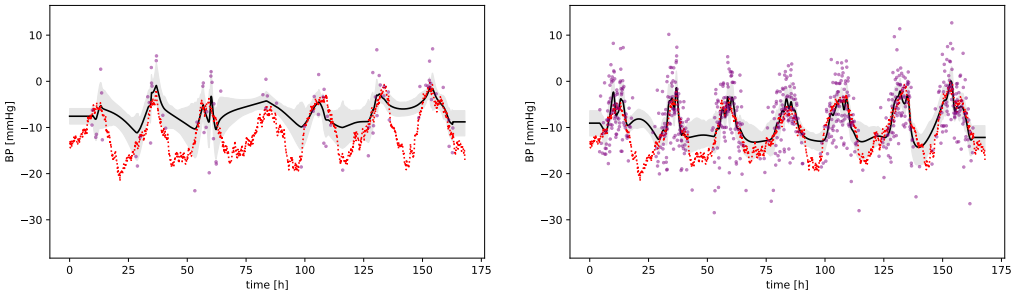


(b) Linear regression

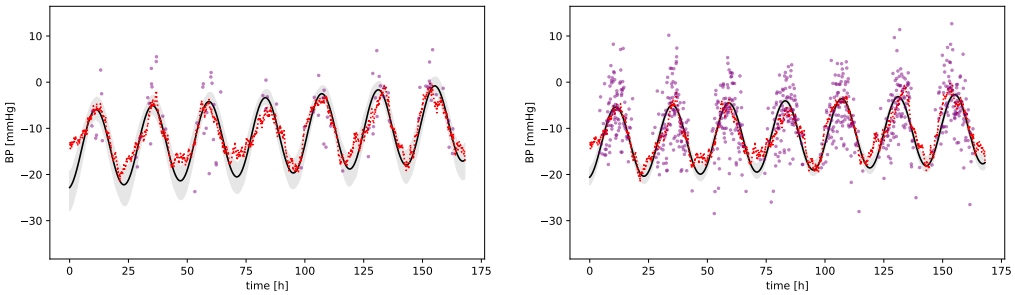


(c) GP regression

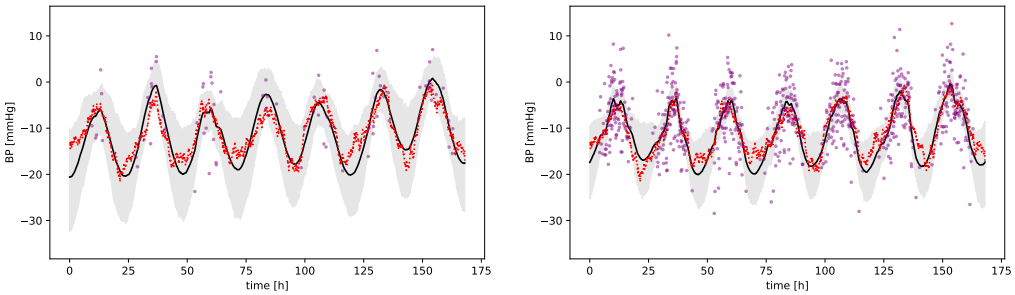
Figure 6.5: Impact of Downsampling Factor: Estimated BP values $\hat{f}(x)$ (black) and corresponding confidence intervals (gray area) based on measurements (purple dots) using various methods. Measurments have been obtained using a downsampling factor of 20 (left panels) and 2.5 (right panels). The true BP values, $f(x)$, (red dotted line) are the same in all shown scenarios.



(a) Spline Regression

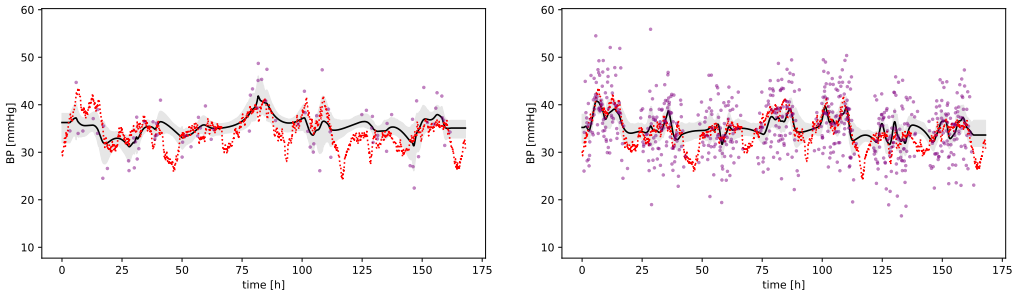


(b) Linear regression

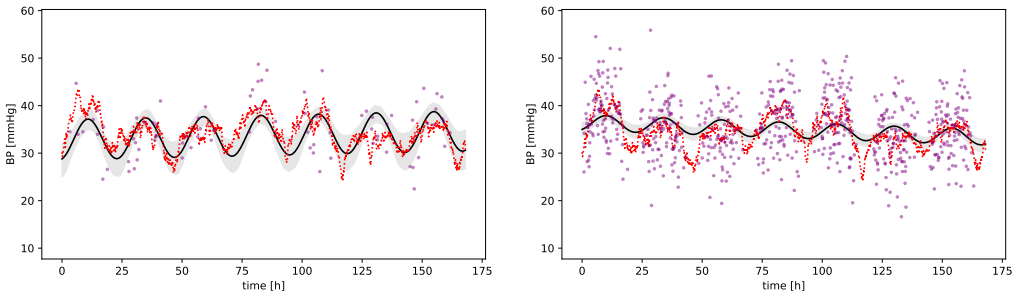


(c) GP regression

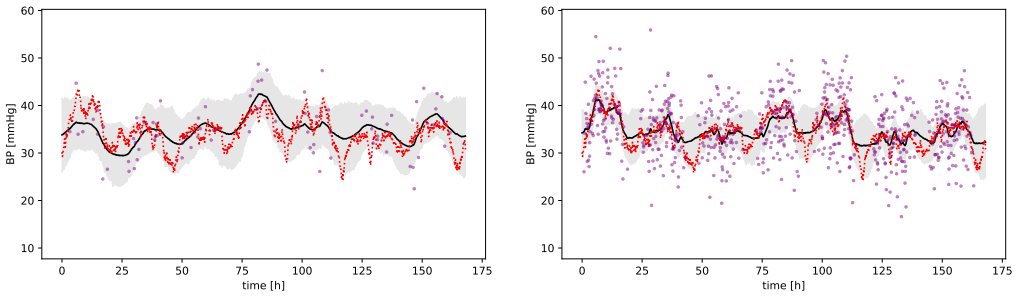
Figure 6.6: Seasonal Samping and Downsampling Factor Example 1: Estimated BP values $\hat{f}(x)$ (black) and corresponding confidence intervals (gray area) based on measurements (purple dots) using various methods. The measurements were obtained through extreme seasonal sampling with downsampling factors of 20 (left panels) and 2.5 (right panels). The true BP values, $f(x)$, are represented by the red dotted line.



(a) Spline Regression



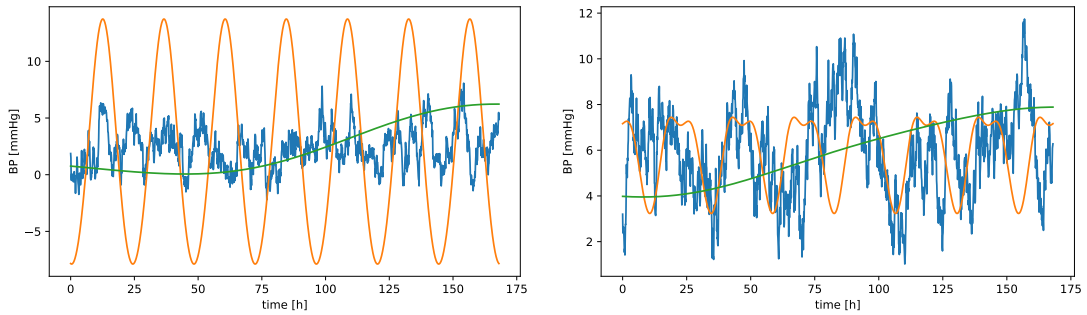
(b) Linear regression



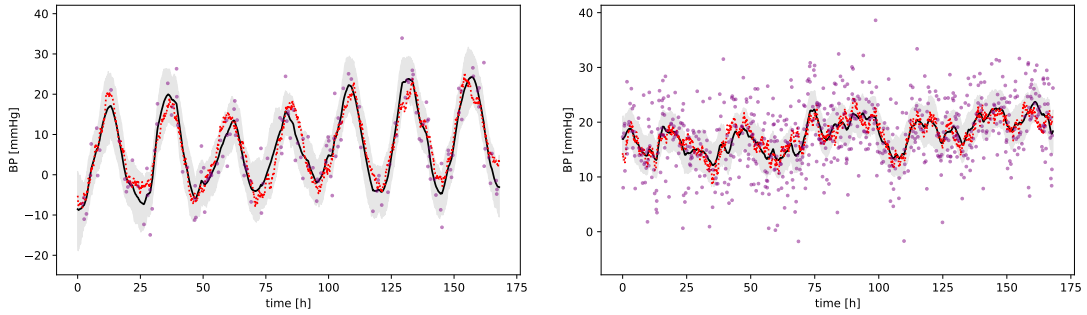
(c) GP regression

Figure 6.7: Seasonal Samping and Downsampling Factor Example 2: Estimated BP values $\hat{f}(x)$ (black) and corresponding confidence intervals (gray area) based on measurements (purple dots) using various methods. The measurements were obtained through extreme seasonal sampling with downsampling factors of 20 (left panels) and 2.5 (right panels). The true BP values, $f(x)$, are represented by the red dotted line.

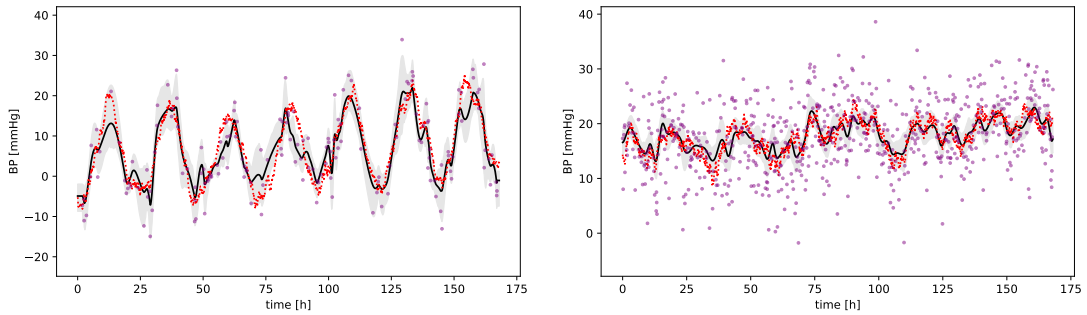
- However, when the AR component is predominant:
  - Only spline and GP regression are capable of providing reliable local BP value estimates, provided there is a sufficient amount of data. However, in situations with limited data availability, GP regression tends to overemphasize the influence of the AR component while underestimating the contribution from the cyclic component. This behavior is depicted in sub-figure 6.9c. Due to the flexibility of the kernels used, they may occasionally capture features originating from another kernel.
  - In contrast, linear regression is constrained to predict a perfect sinusoid with a linear trend. Consequently, it struggles to effectively fit the AR component, even when data availability is high (downsampling factor of 2.5), resulting in inaccurate predictions. Furthermore, it tends to underestimate uncertainty in such cases.



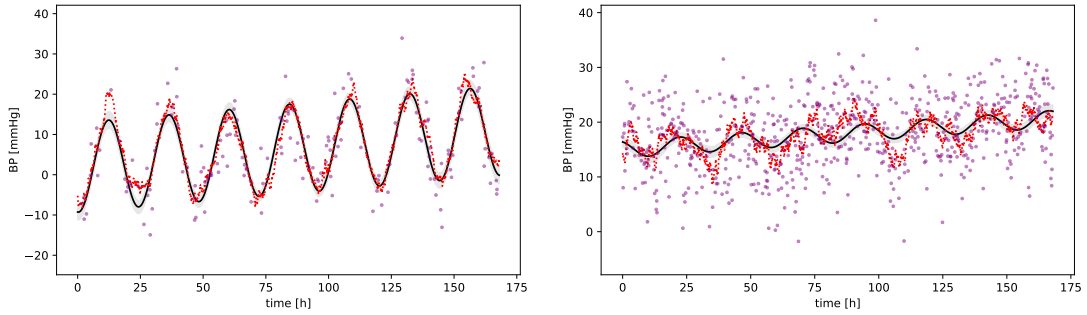
(a) Decompositon of $f(x)$: The cyclic component is shown in orange, the AR component in blue.



(b) GP regression

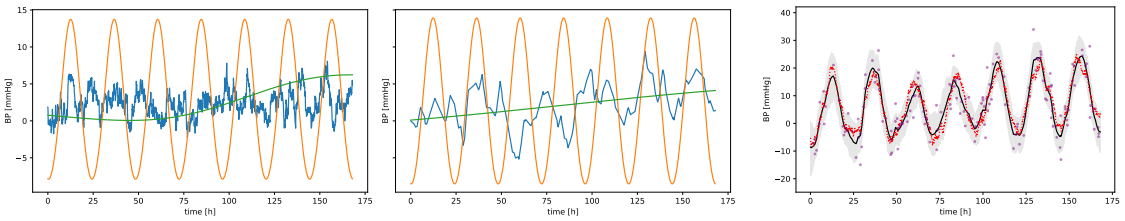


(c) Spline Regression

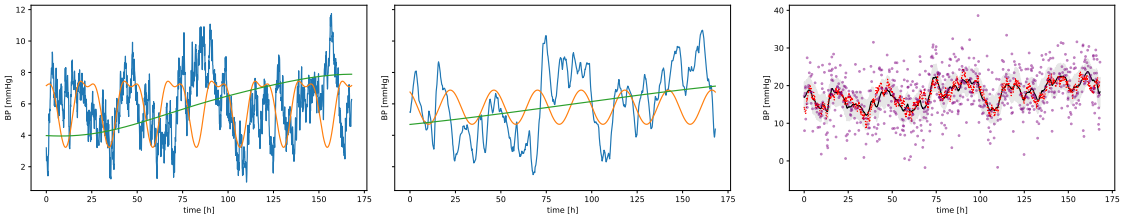


(d) Linear regression

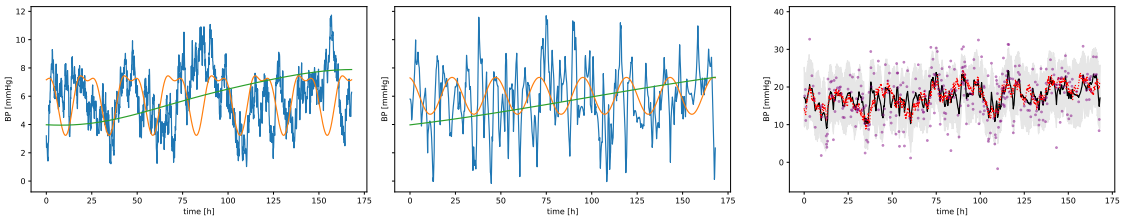
Figure 6.8: Dominant Cyclic Component vs. Dominant AR Component: Estimated BP values $\hat{f}(x)$ (black) and corresponding confidence intervals (gray area) based on measurements (purple dots) using various methods. The measurements were uniformly sampled with a downsampling factor of 5. The true BP values, $f(x)$, are depicted by the red dotted line. The right panels show BP value predictions under a prominent AR component and with a dwonsampling factor of 2.5, while the left panels display predictions under a prominent cyclic component and with a downsampling factor of 10.



(a) Dominant Cyclic Component - Downsampling Factor of 10



(b) Dominant AR Component - Downsampling Factor of 2.5



(c) Dominant AR Component - Downsampling Factor of 5

Figure 6.9: The left panels display the decomposition of the true BP values $f(x)$. The middle panels illustrate the decomposition of the estimated BP values $\hat{f}(x)$. The cyclic component is represented in orange, the AR component in blue, and the long-term trend in green. When the cyclic component is dominant, fewer data points are required to obtain accurate BP estimates compared to when the AR component is dominant. In the case of a dominant AR component, GP regression tends to underestimate the contribution from the cyclic component. When using a downsampling factor of 5, GP regression also tends to overestimate the variance associated with the AR component.

Chapter 7

Discussion and Conclusion

The objective of this thesis was to demonstrate the limitations of conventional time series methods when dealing with irregularly sampled data. Furthermore, we aimed to determine whether Gaussian processes could serve as a viable approach for modeling time series with irregularly spaced observations, using the BP time series as an illustrative example.

In the theoretical section of this thesis, we elucidated that while linear regression methods for handling correlated errors do exist, readily available implementations are primarily designed for equispaced data. Consequently, we introduced GP regression as a method capable of modeling time series in continuous time.

A simulation study was subsequently conducted to investigate the suitability of GP regression for modeling the BP time series, which featured irregularly spaced observations. We assessed the performance of GP regression in estimating specific target measures and compared these results with those obtained using baseline methods. The key findings and implications are summarized in the following section.

The final section of this thesis presents the limitations of the simulation study and suggest potential directions for future research and improvement.

7.1 Comparison of GP Regression and Baseline Methods

Overall, when considering all downsampling patterns and target measures, GP regression outperforms the baseline methods. This superiority is particularly evident when calculating the mean over small time windows, such as one-hour and one-day means. This performance can be attributed to the fact that GP regression explicitly models the dependencies among BP values across different time points. Consequently, the uncertainty predictions are based on the amount of data available at time points that are highly correlated, either positively or negatively, with the time point of prediction. Since the degree of correlation depends on the proximity to the prediction point, this results in larger CI when data density is low around the prediction point.

In contrast, linear regression, while providing narrower CIs compared to GP regression, maintains adequate CI coverage for the one-week mean under large downsampling factors. However, linear regression does not exhibit significant improvement with an increase in data, and CI coverage even decreases with more data in the case of seasonal sampling. This limitation can be attributed to the inherent constraints of the linear model, which can

only capture a linear trend with a perfect sinusoidal seasonal pattern. This characteristic makes the method less reliant on the amount of data available.

Spline regression, as a non-parametric method, is more data-dependent. Thus, its performance generally improves with more data but encounters difficulties with seasonal sampling, as it does not attempt to fit a cyclic pattern. At high data densities with uniform sampling, spline regression produces estimates of expected BP values that closely resemble those of GP regression, albeit with slightly inferior CI coverage.

Although GPs fall under the category of non-parametric methods, they offer the option to express prior beliefs about the function of interest through the choice of kernel. In our case, a function with a cyclic pattern with a periodicity of 24 hours, an AR component, and a long-term trend are favored. This choice does not impose as many constraints on the predictions as linear regression does while simultaneously encoding more information about the function to be fitted compared to spline regression. These properties position GP regression as the ideal candidate for analyzing BP time series based on irregularly spaced samples.

Seasonal sampling leads to reduced performance in all cases but most pronounced in spline regression. Interestingly, when confronted with seasonal sampling, more data generally results in a reduction in CI coverage and width for linear regression. Conversely, for GP and spline regression, CI coverage typically increases with more data. However, only GP regression offers adequate local CIs that expand in size when there is less data available.

7.2 Limitations and Future Work

In the current study, GP regression is employed to estimate values generated from a GP itself. This unique approach provides GP regression with a potential advantage over baseline methods. To ensure a fairer comparison, we suggest the following:

- Investigate entirely different methods for simulating BP values. Ideally, this method would also offer greater control over the simulated samples. Currently, when generating random samples from a GP, our ability to control the shape of the produced functions is limited to the choice of the kernel function.
- Investigate the implications of employing a misspecified kernel during estimation. We have consistently used the same combination of kernel types - specifically, RBF, Matérn, and Periodic kernels - for both simulation and estimation, with only kernel hyperparameters adjusted. It would be intriguing to understand how sensitive predictive performance is to the mismatches in the kernel function.
- Investigate the influence of non-Gaussian measurement errors on predictive performance.

Additionally, expanding the scope of adversarial analysis to examine different kernel and measurement noise combinations would provide valuable insights. While some assumptions about the BP time series were based on real-world BP data, the contributions of measurement errors and the autoregressive (AR) components to real-world data remain largely uncertain. It has been demonstrated that a larger AR component in the signal makes predictions more challenging, and the same would apply if the simulated measurement noise were increased. Thus, by varying the contributions of these different components, we can gain a deeper understanding of the limits of the regression methods.

GP regression credible interval estimates were calculated based on the equal-tailed credible interval (ETI). Another commonly used credible interval is the highest posterior density interval (HDI), which yields different intervals, particularly when dealing with asymmetric distributions - a scenario that might be expected for TTR. Therefore, for the next simulation study, it is advisable to calculate both HDI and ETI to determine which one is better suited to the specific problem at hand.

The company's specific areas of interest for further exploration include:

- Simulation of a seasonal component that evolves over time. This can be achieved by multiplying the Periodic kernel, used so far for simulation, with another kernel that models this temporal evolution, such as an RBF kernel.
- Calculate day and night BP values. This task requires defining "day" and "night," a task that could be facilitated by incorporating the predicted cyclic component.
- Assess the computational complexity of the used regression methods

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Appendix A

Complementary information

Additional material. For example long mathematical derivations could be given in the appendix. Or you could include part of your code that is needed in printed form. You can add several Appendices to your thesis (as you can include several chapters in the main part of your work).

A.1 Ornstein-Uhlenbeck Process

The autocovariance function of an Ornstein-Uhlenbeck process can be derived by solving the stochastic differential equation (SDE) that defines the process.

Starting with the SDE for an OU process:

$$dX_t = \theta(\mu - X_t)dt + \sigma_w dW_t,$$

where X_t is the value of the process at time t, θ is a positive constant that determines the speed of mean reversion, μ is the long-term mean of the process, σ_w is the standard deviation of the random shocks, and W_t is a standard Wiener process or Brownian motion.

The solution to the SDE is:

$$X_t = X_0 e^{-\theta t} + \mu(1 - e^{-\theta t}) + \sigma_w e^{-\theta t} \int_0^t e^{\theta s} dW_s$$

The process is stationary if $\theta > 0$. The autocovariance function of an OU process is given by $Cov(X_t, X_{t-k}) = \frac{\sigma_w^2}{2\theta} e^{-\theta k}$, where $k \geq 0$ and $\theta > 0$.

This is the same expression as we have obtained in 4.5.2.2, where $k(0) = \sigma^2 = \frac{\sigma_w^2}{2\theta}$ and $l = 1/\theta$

To see how the Ornstein-Uhlenbeck can be considered a continuous time analogue to the discrete time AR(1) process one can use the Euler-Maryuama discretization of the process. Considering again the SDE for an OU process:

$$dX_t = \theta(\mu - X_t)dt + \sigma_w dW_t,$$

The process can be discretized at times $(k\Delta t)_{k \in \mathbb{N}_0}$:

$$X_{k+1} - X_k = \theta\mu\delta t - \theta X_k \Delta t + \sigma_w(W_{k+1} - W_k)$$

The random variables $(W_{k+1} - W_k)$ are independent and identically distributed normal random variables with expected value zero and variance Δt. Therefore, we can set $\sigma_w(W_{k+1} - W_k) = \sigma_w\sqrt{\Delta t}\epsilon$ with $\epsilon \sim \mathcal{N}(0, 1)$ to obtain the following recursion:

$$X_{k+1} = \theta\mu\Delta t - (\theta\Delta t - 1)X_k + \sigma_w\sqrt{\Delta t}\epsilon$$

The recursion for an AR(1) process is:

$$X_{k+1} = c + aX_k + b\epsilon$$

Which is identical to the expression above if $c = \theta\mu\Delta t$, $a = 1 - \theta\Delta t$ and $b = \sigma_w\sqrt{\Delta t}$

A.2 Properties of the Simulated Time Series Samples

This section presents the distribution of some crucial properties from the simulated BP time series. These histograms have been created by drawing 100 samples from the true GP.

The shown property distributions should match those from Section 1.2.1.

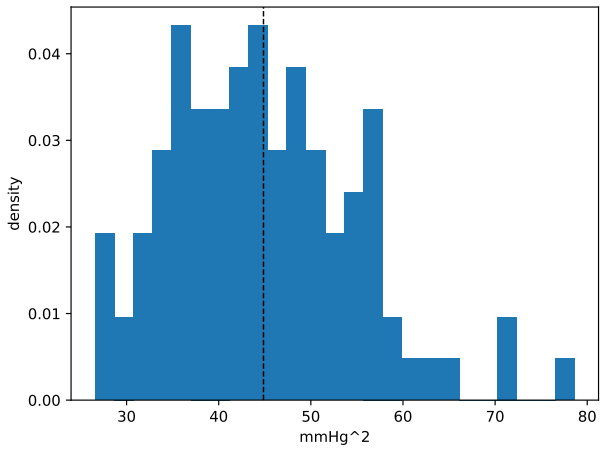

Figure A.1: Distribution of One-Week BP Variance from Simulated Measurements: The one-week variance should span from from 16 to 144 mmHg^2, with an average of 49 mmHg^2

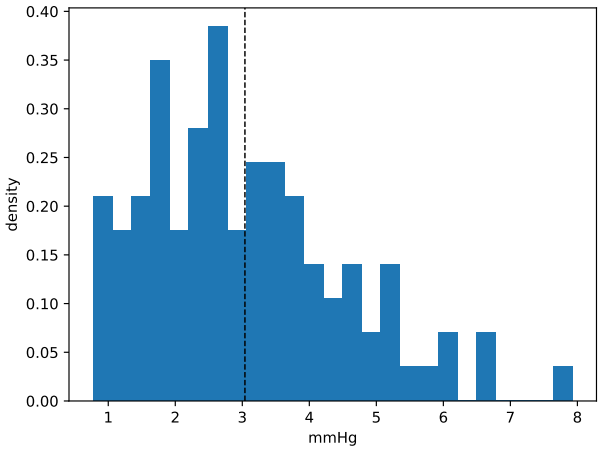

Figure A.2: Distribution of the Night Dip Magnitude from Simulated Measurements: Here the night dip magintude is defined as half of the difference between average daytime and nighttime BP measurements. Should fall within the range of 0 to 10 mmHg

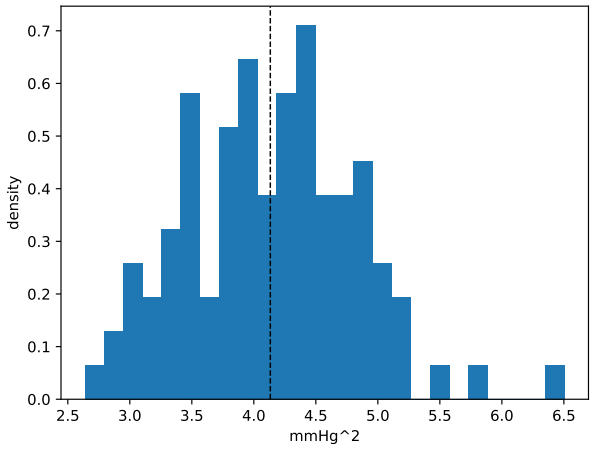

Figure A.3: Distribution of the AR Component Variance from Simulated Measurements: There exists no target values for the variance of the AR component.

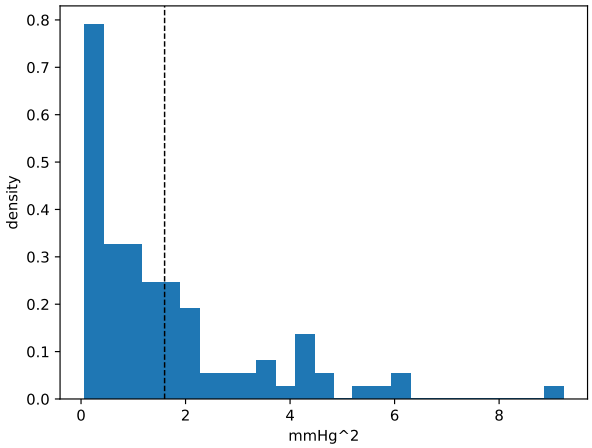

Figure A.4: Distribution of the RBF Component Variance from Simulated Measurements: There exists no target values for the variance of teh RBF components

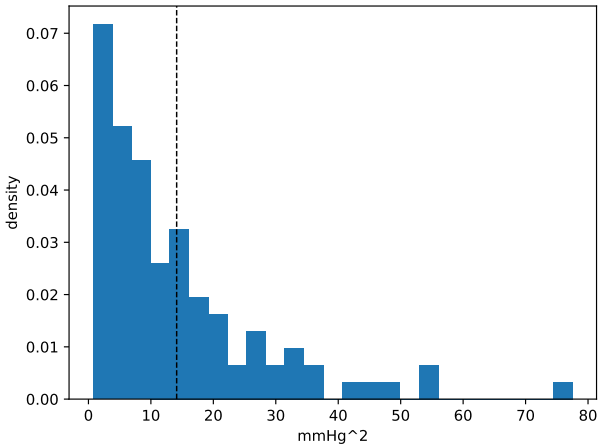

Figure A.5: Distribution of the Periodic Component Variance from Simulated Measurements: The target ranges for the variance of the periodic component are provided in the form of night dip values (see Figure A.2)

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