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Examining the Applicability of Functional Principal Component Analysis by Conditional Expectation (PACE) in Cervical Dilation Data from the Labour Progression Study

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Abstract

Functional Data Analysis (FDA) is a method for extracting information from curves or functions based on time-related processes with discrete measures. This thesis explores the methodology for constructing and analysing curves studying labour progression, specifically in data containing the cervical dilation of 7277 primiparas. Identifying the trajectory functions of cervical dilation can support the development of tools used by health personnel to identify and monitor deviations from the normal range of cervical dilation and labour duration. Successful application of FDA can also enhance the understanding of potential explanatory variables that influence the rate and temporal pattern of cervical dilation and its variation among individuals.

Data from digital vaginal exams that measure cervical dilation are complex due to sparse and irregular measurements for each participant and various forms of censoring, such as right censoring due to intrapartum cesarean section. The approach of Principal Analysis by Conditional Expectation (PACE) is explored to address these challenges. PACE is a Functional Principal Component Analysis (FPCA) algorithm that fits curves to sparse and irregular data. The trajectory functions for each participant are attempted to be recovered with corresponding estimates for the derivatives. However, PACE was unsuccessful in fitting curves to the cervical dilation data. Simulated data with known underlying distributions points to the limitations of PACE: When the data consist of multiple distributions and are sufficiently sparse, the method will produce an inaccurate estimation of mean and covariance functions. This means that PACE does not distinguish between different distributed groups; instead, it prioritises and directs the curve trajectories towards the weighted cross-sectional mean.

The implications of PACE being inappropriate for fitting cervical dilation curves include failure to capture data variability and dynamics and the inability to perform functional regression and correlation analysis. The thesis concludes that FDA, in this case, is premature and calls for further development of methods that can handle the level of sparseness, irregularity, and censoring as seen in data from digital vaginal exams.

Keywords:

Censored functional data; Cervical dilation; Complex functional data; Functional Data Analysis (FDA); Functional Principal Component Analysis (FPCA); Functional Principal Component Analysis by Conditional Expectation (PACE); Irregular functional data; Labour progression; Sparse functional data

Sammendrag (Norwegian)

Funksjonell dataanalyse (FDA) er en metode der man undersøker kurver eller funksjoner basert på tidsrelaterte prosesser med diskrete målinger. Denne masteroppgaven utforsker metodikken i studiet av fødselsprogresjon, nærmere bestemt i dilatasjonen på livmormunnen hos 7277 fødende. De underliggende kontinuerlige funksjonene til en typisk fødsel kan bidra i utviklingen av retningslinjer til helsepersonell for identifisering og monitorering av fødsler som avviker fra normalområdet til livmormunnsdilatasjon og varighet på fødsel. En vellykket anvendelse av FDA kan videre øke forståelsen av potensielle forklaringsvariabler som har en innvirkning på hastigheten og tidsmønsteret til en fødsel, og kartlegge variasjonen i disse mellom fødende.

Data fra vaginale undersøkelser som måler livmormunnsdilatasjon er komplekse på grunn av sparsomhet og uregelmessighet i antall målinger for hver deltaker. I tillegg eksisterer det ulike typer sensur, som for eksempel høyresensur når en fødsel ender i keisersnitt. Derfor utforskes funksjonell hovedkomponentanalyse via betinget forventning (PACE). PACE er en metode for funksjonell prinsipalkomponentanalyse, og kan brukes i kurvetilpasning for sparsomme og irregulære data. De underliggende kontinuerlige funksjonene for hver deltaker er forsøkt reetablert, med korresponderende estimater for de deriverte kurvebanene. PACE er imidlertid mislykket i kurvetilpasningen av livmormunnsdilatasjonsdataene. Kurvetilpasning på simulerte data med en kjent underliggende fordeling peker i retning begrensningene til metoden: Når data består av forskjellige fordelinger og er sparsomme nok, blir ikke gjennomsnitts- og kovariansfunksjonene estimert nøyaktig. Effekten er at metoden ikke identifiserer de ulikt fordelte gruppene, men vektlegger og tvinger de estimerte kurvebanene mot det vektede tverrgjennomsnittet.

Kurvetilpasning med PACE beskriver variansen og dynamikken i dataene dårlig, slik at vi ikke kan utføre funksjonell regresjon og korrelasjonsanalyse. Oppgaven etterlyser derfor en videreutvikling av metoder som kan håndtere den graden av sparsomhet som finnes i livmormunnsdilatasjonsdata fra vaginale undersøkelser.

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Rakel Thuv Kosmo, Norwegian University of Life Sciences, 15th June 2023

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Abbreviations

BMI - Body mass index

CS - Cesarean section

CTG - Cardiography

ECG - Electrocardiogram

FDA - Functional Data Analysis

FPCA - Functional Principal Component Analysis

FVE - Fraction of Variance Explained

ICS - Intrapartum cesarean section

NIC - Newborn intensive care

PACE - Functional Principal Component Analysis by Conditional Expectation

PROM - Prelabour rupture of membranes

STAN - Electrocardiogram ST segment analysis

SOAP - Sparse Orthonormal Approximation

VE - Digital Vaginal Exam

WHO - World Health Organization

Nomenclature

Amniotomy - Artificial rupture of the amniotic sac to induce labour

Auscultation - Measurment of fetal heart rate during active labour

Apgar - Standardized assessment of infant health, post labour

Cardiotocography - Graphic recording of the electronic monitoring of fetal heart rate and the parturient's uterine contractions

Censored data - Value of an observation is only partially known

Cephalopelvic disproportion - Mismatch between the size of the fetal head and size of the maternal pelvis

Clusters - Birth care units in Norway

Episiotomy - Surgical incision in the perineum during labour

External os - External orifice of the uterus, the opening of the uterine cervix into the vagina

Harmonics - Optimal empirical orhonormal basis functions, also known as eigenfunctions

Labour dystocia - Definition of when a labour progression is slower than what is expected to be normal

Longitudinal data - Data collected from the same subjects, over some time

Neonates - Newborns

Nullipara - Not previously given birth

Parturient - Being in labour, giving birth

Parturition - Childbirth

Primigravid - Pregnant for the first time

Primipara - Nullipara during and after labour

Progression curve - A curve showing the expected labour progression throughout the active stage of labour

Singleton pregnancy - Results in the birth of a single infant

Sparse data - Few measurements available for each subject

1 Introduction

1.1 Background

Functional data analysis (FDA) refers to statistical methods for analysing curves or functions, such as time series or growth curves. The primary objective of FDA is to extract meaningful features and patterns from functional data and to model their variability and dependencies. The initial step in FDA is estimating continuous curves based on discrete measures. While many sampling techniques produce extensive data sets with a high number of measurements for each curve, there are also many situations where the number of discrete measurements is limited.

The application of FDA to sparse data, commonly encountered in longitudinal studies, presents several challenges. Characterised by a restricted number of observations per subject, sparse data may be insufficient to accurately capture the underlying smooth trajectories. Additionally, data may be subject to significant measurement error, censoring, and mixed distributions, further complicating the analysis.

In this thesis, the application of interest is data from a digital vaginal exam (VE) that measures cervical dilation. Cervical dilation is the opening of the cervix during labour, and healthcare providers will typically measure the dilation at few and irregular times. Due to variations in the time of arrival to the birth care unit and different outcomes (i.e., vaginal delivery or intrapartum cesarean section (ICS)), censoring may also be present.

Cervical dilation data are crucial in assessing the risk of complications and initiating interventions during labour. Exaggerated or improper use of obstetric intervention during labour can cause preventable harm and increase the risk of additional interventions. Further, it increases the costs of labour care. Intervention is a broad term ranging from the change of labouring position, or increased monitoring, to urgent deliveries by ICS. While these interventions may be a crucial part of safe labour for some, evidence suggests unnecessary use can have unfavourable consequences (Abalos et al., 2020; Dahlen et al., 2012).

The most frequent indication of ICS is labour dystocia. Dystocia refers to slow or ceasing progression in labour, but a precise diagnosis definition remains controversial (Abalos et al.,

2020). The causes can, for instance, be cephalopelvic disproportion or inefficient uterine contractions in the parturient. Because of varying research and practices, it is plausible that misdiagnoses of labour dystocia are present. The exact specification of when labour dystocia occurs will naturally impact the response regarding labour management and ICS rates (Zhang et al., 2010).

When assessing the overall labour duration and the progression patterns, measures such as the frequency and duration of contractions and descent of the fetal head are of interest. However, in clinical practice, cervical dilation is often considered the primary indicator of labour dystocia and is used to guide interventions to reduce maternal, fetal, and neonatal risks. Therefore, points of reference to cervical dilation are vital when developing tools that enable health personnel to detect true labour dystocia (Bernitz et al., 2018).

1.2 History of the Graphic Analysis of Cervical Dilation

Friedman (1955) was the first to present cervical dilation against time. After studying 100 nulliparas during the first stage of labour, he modelled a sigmoid curve stretching from the onset of labour until full dilation of the cervix, as illustrated in Figure 1. The x-axis represents time in hours, and the y-axis centimetres of dilation; Friedman instructed the responsible care provider to mark the coordinate results after each examination of cervical dilation. The documented points were then linearly interpolated by drawing a line between each measure.

During analysis, Friedman divided the progression of the first stage of labour into four phases corresponding to the typical slope of these curves:

1) The latent phase, from 0 to 2-2.5 cm
2) The acceleration period, from 2-2.5 to 3-3.5 cm
3) The steady period, from 3-3.5 to 8.5-9 cm
4) The deceleration period, from 8-8.5 to 10 cm

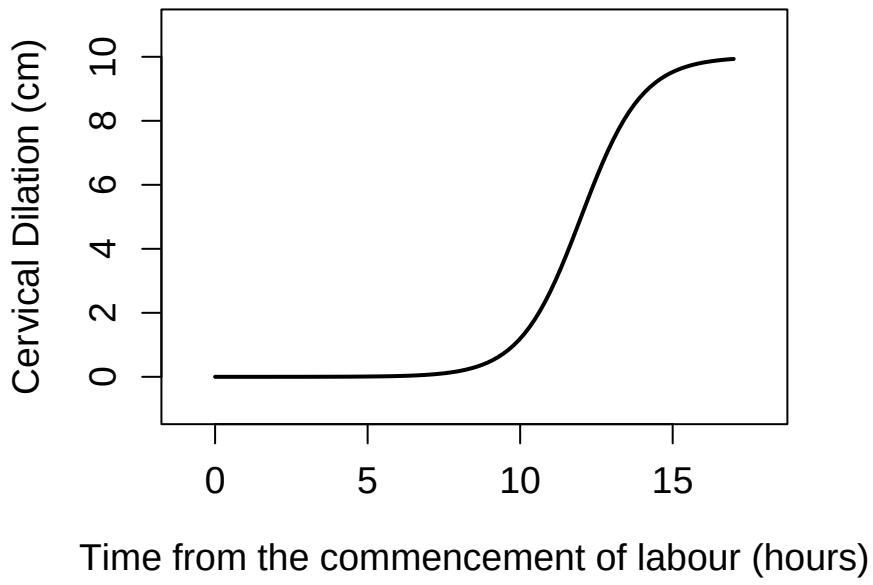

Figure 1: An adaption of Friedman's sigmoid-shaped curve describing labour progression by mapping cervical dilation against time.

In Friedman's analysis, the maximum slope was present during the third phase, or the steady period between three and nine centimetres of cervical dilation. During this phase, cervical dilation had a linear relationship with time. However, the entire curve Friedman modelled did not apply to the practical assessment of labour progression because it begins at the onset of labour, including the latent phase. The onset of labour is difficult to define because it might not be recognisable due to mild or irregular contractions. Parturients usually arrive at the birth care unit at different stages of labour, and it is common to have some cervical dilation present at the time of the first assessment. These issues prevent an accurate measurement position along the x-axis since the axis represents the time since the onset of labour.

In the early seventies, obstetricians Philpott & Castle (1972) developed a guideline based on Friedman's work. Addressing the problem of defining the onset of labour, Philpott & Castle (1972) used the arrival time to the birth care unit as the starting point. The guideline included "alert" and "action" lines intended to detect anomalies and trigger caution and

subsequent action when labour ceased progressing. After studying 100 labours, the mean rate of cervical dilation in the slowest ten per cent of labour progressions formed the alert line. This alert line followed a perfectly linear pattern, with an incline of one centimetre per hour, consistent with Friedman's concept of a steady period. The parallel action line was then arbitrarily drawn four hours to the right of the alert line. Figure 2 depicts the proposal. However, compared with previous practice on 624 nulliparas in Rhodesia (now Zimbabwe), the results indicated that the alert line managed to separate efficient from inefficient labours. Moreover, the placement of the action line prompted both a reduction in the use of oxytocic simulation and a lowered ICS rate.

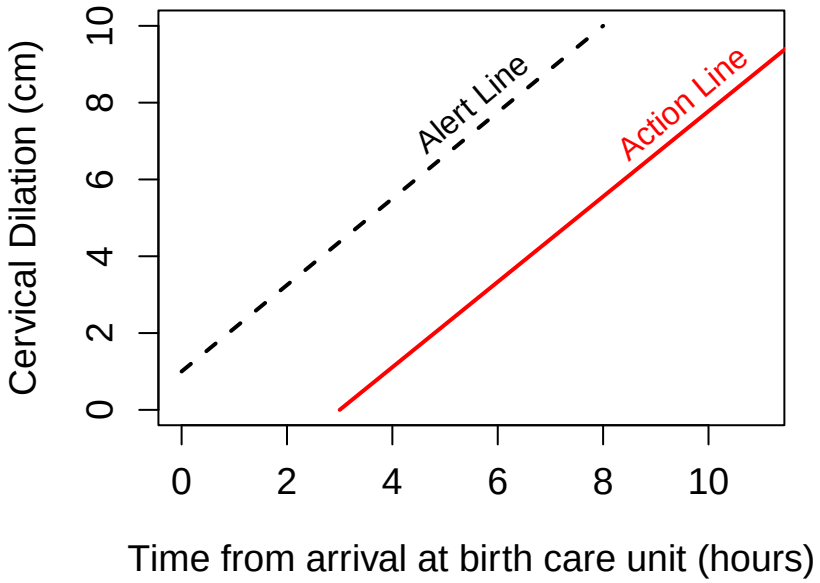

Figure 2: An adaption of Philpott and Castle's proposed alert- and action lines. The lines are based on Friedman's steady period and constitute the basis for WHO's partograph for assessing labour progression.

In 1994, the World Health Organization (WHO) presented a partograph with guidelines for assessing labour progression (World Health Organization, 1994). The WHO partograph is an accessible tool for monitoring labour, used worldwide for the early detection of complications. It is a composite of several measurements, but among these is a cervical dilation chart for

assessment of potential labour arrest. The WHO cervical dilation chart consists of the same alert and action line as proposed by Philpott & Castle (1972) as reference thresholds, with the following definition of the different phases in the first stage of labour:

1) The latent phase, from 0 to 3 cm
2) The active phase, from 4 to 10 cm

The Friedman curve has had a profound impact on labour assessment and is considered a significant contribution to the field of obstetrics. Although the acceleration and deceleration periods are now disregarded, the concept of a steady period where the cervix dilates as a linear growth process still influences obstetric practices today (Abalos et al., 2020). Philpott & Castle (1972)'s initial objective was to provide a simple tool to guide health personnel in rural or isolated settings, but the proposed thresholds have become valuable for labour units worldwide through the WHO partograph and its cervical dilation chart. The partograph has been the subject of extensive multicentre testing with resulting verification of effect. Whether this effect has reached its optimum is still a subject of exploration.

There is a standing question on designing a partograph with optimal guidelines for assessing labour progression (Mathai, 2009). Considering the substantial changes in labour management during the last fifty years and the increase of the parturient's body mass index (BMI) and age raises the question of whether the WHO partograph for assessing labour progression can be improved. It is primarily designed for use in nulliparous low-risk labours and excludes a fair proportion of labours. Additionally, cervical dilatation over time as an isolated factor may not be optimal when defining labour dystocia. Other variables, such as frequency and duration of contractions, cervical effacement, fetal station, and medication, may need some consideration in the analysis before establishing a particular guideline (Abalos et al., 2020).

1.3 Present Proposals for Assessing Labour Progression

In 2010, Zhang et al. published a study of labour in a larger contemporary cohort, where they presented a hyperbolic labour progression curve and a proposal for a new guideline for labour assessment. The hyperbolic curve has significant disparities compared to the

WHO partograph. Zhang et al. (2010) found that cervical dilation develops more slowly, mainly before reaching 6 cm. Moreover, they found that the increase in dilation accelerates as labour advances, more similar to an exponential growth curve rather than a linear one. They suggest some ICSs are initiated too early, based on the current definition of prolonged labour, and that by following the new proposed guideline, we allow more time during early active labour before diagnosing dystocia.

In the Labour Progression Study (LaPS), Bernitz et al. (2018) compared the two guidelines, Zhang's and WHO's, for assessing labour progression at fourteen Norwegian obstetrics units, which constituted random clusters, by investigating the respective prevalence of ICSs in 7277 nulliparas. The initial hypothesis was that Zhang's "more dynamic" approach would lead to fewer ICSs. However, the results suggested no difference between the groups. The overall ICS frequency was lowered, but only significantly in the group subject to the WHO partograph. The causes can be manifold, but an imminent proposition is that the increased focus on following a specific guideline reduced the use of ICS. These results accentuate the importance of clear guidance and proper instructions in assessing labour dystocia.

In 2020, the WHO presented the Labour Care Guide (LCG) to support the implementation of its 2018 updated recommendations on intrapartum care (World Health Organization, 2018, 2020). In the assessment of cervical dilation, the LCG discards the action line. Instead of the linear alert line, they suggest an alert is triggered when a certain lag time dependent on the current cervical dilation is exceeded without progress. The lag times are defined by:

- 5 cm: $\geq$ 6 hours
- 6 cm: $\geq$ 5 hours
- 7 cm: $\geq$ 3 hours
- 8 cm: $\geq$ 2.5 hours
- 9 cm: $\geq$ 2 hours

I.e., if the cervical dilatation remains at 5 cm for six or more hours, it will prompt an alert. The lag time is reduced as the labour progress, agreeing with the findings of Zhang et al. (2010). The LCG's recommendation for assessing labour progression is based on healthy

women with a spontaneous onset of labour.

In Norway, about 50 % of parturients have either high-risk pregnancies, are induced or have an elective cesarean section, in which the LCG may not be applicable. Adopting the LCG will also require a major change in routines and training for health personnel. Therefore, the Norwegian Society for Gynecology and Obstetrics's guideline to intrapartum care, *Veileder i fødselshjelp*, suggests awaiting the introduction of the LCG until there are more extensive studies that show a further effect on reduction in the frequency of interventions and an increase in birth experience among parturients than what is currently available (Rossen et al., 2020).

1.4 Functional Data Analysis of Labour Progression

The LaPS (Bernitz et al., 2018) recorded the measured cervical dilation of the VE's performed during each of the included labours. We can use these data to construct curves that capture the central dynamics present in the sample, enabling us to compare a given labour with a norm to produce guidelines and recommendations. Previously, this type of data has been analysed with traditional statistics, for example, by linear interpolation and estimation of the arithmetic mean. However, since the collection of measurements for each participant fixed against time can be used to describe a continuous process, a potential application is FDA.

Reducing the discrete measurements to a single smooth curve is one of the main characteristics of FDA. A smooth curve is then, as a whole, considered a single observation. FDA plays an increasingly important role in medical research because symptoms are usually interesting when followed over some time. By using derivatives, FDA enables additional insight into curve dynamics and can thus detect intricate patterns that are unavailable with more conventional approaches (J. Ramsay & Dalzell, 1991).

Moreover, using the curves for further inference in, e.g., a functional linear model enables analysis with other explanatory variables. However, traditional FDA is incompatible with the complicated nature of cervical dilation data from VE's. Performing a VE upon clinical indication means the data are irregularly and not randomly sampled. Furthermore, the

data are sparse and censored. Principal Analysis by Conditional Expectation (PACE) is a nonparametric method that aims to perform FPCA on sparse and irregular data, estimating the FPCA-scores by conditioning on the observed data to provide predictions and confidence bands for individual trajectories (Yao et al., 2005).

1.5 Aim of Study

The main purpose of the analysis is to explore how PACE perform in curve fitting for sparse and irregularly sampled data. Specifically, in tracking labour progression by analysing cervical dilation measurements obtained from VE's of participants in the LaPS dataset. We discuss the challenges and limitations of using PACE for FDA purposes and aim to determine if PACE is a suitable approach for fitting curves to cervical dilation data.

Secondary objectives include identifying and diagnosing potential problems and providing a comprehensive overview of the cervical dilation data, emphasising significant characteristics and potential implications. We also aim to highlight the unrealised potential of FDA in assessing labour progression.

2 Materials and Methods

2.1 The Labour Progression Study (LaPS)

The LaPS investigates the clinical consequences of using two guidelines for progression in the active phase of labour for primiparous women with a singleton vertex fetus and spontaneous onset of labour at 14 obstetric units in Norway. The study is a cluster-randomised trial conducted between 2014 and 2017, where the 14 units constituted clusters. The response variable was the prevalence of ICS (Bernitz et al., 2018). The data collected during the study includes 7277 participants, with 205 corresponding explanatory variables. Among these, this thesis explores the recorded cervical dilation in 4660 participants.

2.2 The Cervical Dilation Data

The dataset contains cervical dilation data for each participant. Cervical dilation is a key indicator of labour progression during the active phase of labour. It is measured by performing a digital vaginal examination of the parturient, using two fingers to estimate the diameter of the external os in integers. Cervical dilation is usually assessed at admission to determine the current phase of labour and then subsequently when required to monitor progress. This dataset has recordings at varying times for each participant, the number of measurements per participant ranging from a single point to 53 measurements, in the range of $[0, 25]$ hours.

Although the participants were examined upon admission, the first recorded time of the cervical dilation discrete measures is the first measured cervical dilation of at least 4 cm, which indicates the active phase of labour. It is a deliberate part of the study design, based on a definition of active labour, and the cervical dilation values less than 4 cm are not part of the study sample in this thesis. When a participant reaches 10 cm of cervical dilation, it marks the second stage of labour and no further digital vaginal exams. For some participants, 10 cm is never observed, usually due to ICS.

2.2.1 Methodological Implications

Random Distribution of Measurements The term "random" in a data sampling sense refers to sampling without bias. Randomness in the clinical trial context is essential because it helps ensure that the compared groups are similar in all respects except for the tested intervention. The clusters in the LaPS were assigned to different groups (treatment and control) through a random process. However, in the case of the digital vaginal exam during labour, there is a conscious decision that triggers the execution of measurement, meaning that the timing of the measurements is not randomly distributed along the course of labour or in the population. This lack of randomness restricts the generalisation of the results observed through the sampled data.

Irregular Sampling Irregularly sampled data refers to data collected at non-uniform time intervals. Irregular sampling is the case for data from a digital vaginal exam, in which some external factor determines the timing of measurements. The irregularity presents some practical implications during analysis since many standard statistical methods assume that the data is regular, i.e., measured at fixed and evenly spaced time intervals.

Censoring Censored data is data when the value of a variable is only partially known. In cases where the initial cervical dilation measurement has exceeded 4 cm, the data are left-censored because part of the active phase progression is unknown. When 10 cm is unobserved, the data is right-censored. Censored data can introduce challenges when analysing data since standard statistical methods assume a complete data set and may not be appropriate since they do not account for the uncertainty introduced by censoring.

Sparseness The LaPS cervical dilation data is also sparse. The high dimension, with 53 possible times for measurement and relatively few observations per participant, results in a large proportion of missing values. Sparse data can complicate the analysis because of reduced statistical power and violation of common statistical assumptions.

Alignment The start of the partogram marks the first measurement ≥ 4 cm of cervical dilation. The arrival of participants to the study is at varying increments in the progression of the active phase of labour, which make the data misaligned. We must align the curves along the time axis to compare our population's temporal patterns of labour progression.

The LaPS cervical dilation data consists of discrete measurements taken at different points in time. However, our interest lies in the underlying continuous dilation process during the active phase of labour. This aim points towards a functional approach, but the nature of this data requires statistical techniques that can handle irregularity, censoring and sparseness.

2.3 Other Explanatory Variables

In addition to the location of the birth care unit and the allocation of guidelines, the cervical dilation measurements and potential ICS, many other explanatory variables are included in the LaPS. These variables are important in the study of labour progression because they are known to influence either labour progression or maternal and neonatal outcomes.

The study collected maternal information such as age, height, weight, BMI, smoking status, marital status and education level. Upon admission to the birth care unit, the following data were documented: Gestational age, the reason for admission, spontaneous labour onset, prior and current contractions, and cervical dilation.

During active labour, the study also recorded the use of amniotomy, oxytocin, non-invasive stimulants, medical and non-medical pain relief, operative delivery, and the diagnosis of dystocia according to the specific guideline. Potential fetal monitoring, such as intermittent auscultation, intermittent cardiotocograph (CTG) and electrocardiogram ST segment analysis (STAN), was also noted.

In the acute phase of the postnatal period, the responsible personnel recorded presentation, neonatal scalp pH-value, scalp lactate, Apgar-score, head circumference, umbilical cord pH-value and blood base, presence of metabolic acidosis and sex. Additionally, if admission to the newborn intensive care (NIC) was administered, and any intrapartum fetal or neonatal

death during the first week. Maternal outcomes such as bleeding, labial, cervical or anal tears, episiotomy use and the presence of a continuous midwife during delivery were also included.

Initially, including a range of these maternal and neonatal variables in the analysis was considered to provide a comprehensive understanding of labour progression. However, as the project evolved, it became clear that this would not be possible. Despite this, the thesis includes a descriptive description of some of these variables to provide an overview of the study population.

2.4 Functional Data Analysis

Functional data analysis (FDA) refers to the statistical branch of fitting smooth curves to discrete measures, as described by J. O. Ramsay & Silverman (2005).

2.4.1 The Traditional Approach

Functional Data arise when we seek to model a continuous process, and the data available are discrete measures. When we join the measurement points with smoothing techniques to obtain continuous curves, the resulting set of curves is called a functional data set, and each functional data point is a curve. In our case, for a specific labour, the dilation measurements for a given participant are a discrete set of values over a continuous period but measured at discrete time points. Smoothing gives us a resulting curve which, as a whole, is functional data, i.e., the basic unit of analysis is an entire curve.

Generally, a functional dataset is n curves on a given interval $[T_1, T_2]$. For a given point of measure $y_i(t_j)$ we have that $y_i(t_j) \in \mathbb{R}$ and $t_j \in [T_1, T_2]$, where $i = 1, 2, ..., n$ and $j = 1, ..., J$.

In the hypothetical and somewhat intimidating scenario where all labours last 26 hours, and all participants have a cervical exam every half hour: $y_i(t_j)$ may be the cervical dilation of participant $i = 1, 2, ..., 7277$ at time t_j, $j = 1, 2, ..., 53$. Then the values of the curves are defined in the specific points $t_{i,j}$.

Usually, and certainly in a digital vaginal exam, some measurement error will be present. Therefore, in the estimation of the continuous curves, we apply the following model:

$$y_i(t_j) = x_i(t_j) + \varepsilon_{ij}, \tag{1}$$

where $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$ is the term that captures the error, or noise, observed at time t_j, independent of $x_i(t_j)$. Since we want to estimate the underlying continuous process, we can disregard the noise in $y_i(t_j)$ by simply approximating $x_i(t_j)$. When performing FDA, the estimated smooth curve $x_i(t_j)$ is our basic unit for participant i.

There are several ways to approximate the smooth curve $x_i(t_j)$. For example, we could fit a polynomial to the data. However, this will generally imply complicated high-order polynomials or over-smoothed curves. We can use a different, related approach to reduce complexity while preserving local fluctuations. Dividing the state space into intervals, we can approximate the behaviour of $x_i(t_j)$ using polynomials in each of these intervals. By knotting the polynomials together, we get the overall estimated curve. This approach is known as spline interpolation. The curve has a global smoothness because we ensure that the second derivative of subsequent polynomials equals the previous one in each junction. Appendix A.1 provides a more detailed technical description of curve fitting in traditional FDA.

Functional Principal Component Analysis (FPCA) is a method for finding the main patterns of variation in functional data. It is similar to the classical principal component analysis (PCA), but the resulting principal components are functions or curves instead of vectors. In the functional domain, we seek to decompose the functional data into a mean function and a series of optimal empirical orthonormal basis functions, known as the harmonic curves, because they resemble the vibration modes of a string. The harmonic curves capture the main features and patterns of temporal variation. Each participant has a coefficient score corresponding to each harmonic. This FPCA-score indicates how much a given participant's individual curve trajectory deviates from the mean curve in the direction of the harmonic. Appendix A.2 and J. O. Ramsay & Silverman (2005) give further details on

FPCA.

2.4.2 Functional Data Analysis for Sparse Longitudinal Data

Longitudinal data, such as the LaPS cervical dilation data, are often sparse, which means that only a few measurements are available for each subject, sometimes measured irregularly. We can expand Equation (1) to capture the irregularity by replacing the fixed time j with a participant-specific time index t_{ij}. Then the model we consider is:

$$y_{ij} = x_i(t_{ij}) + \varepsilon_{ij}, \tag{2}$$

where $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$, $i = 1, ..., n$ and $j = 1, ..., N_i$. N_i is the number of measurements made on the i'th participant and is considered random, consistent with sparse and irregular data. The random variables N_i are assumed to be independent and identically distributed.

Sparse and irregular data pose a challenge for FDA because the traditional methods require many regularly spaced measurements per participant. Proposed solutions for performing FDA even on this type of data include PACE.

Principal Analysis by Conditional Expectation (PACE) is an alternative method for fitting curves to functional data proposed by Yao et al. (2005). It is a nonparametric approach to estimate the harmonics for sparse longitudinal data, assuming randomly located measurements with a random number of repetitions for each subject, determined by an underlying smooth trajectory and measurement error. The method is simple to implement and allows for the prediction of individual smooth curves even when few, or only one, measurements are available for each participant. In contrast to the traditional approach to curve fitting in FDA, using basis functions to represent functional data, PACE estimates the harmonics and FPCA scores directly from the data and uses these to estimate the individual curves, $x_i(t_j)$.

The method is not, however, well-suited for data that does not have a common domain. The mean is weighted by a pooling of the data across all observations, so each observation con-

tributes to estimating the mean according to its distance from other observations. In broad terms, PACE accounts for missing data by borrowing information from nearby observations.

The smoothing is performed by fitting simpler models to localised subsets of the data by designing approximating functions that aim to capture illustrious temporal patterns. The subsets of which these functions are fitted are called the bandwidth and are a smoothing parameter: Increasing the bandwidth will lead to a smoother resulting function. For further details, see Appendix B.1 and Yao et al. (2005).

2.5 Simulating Data

Investigating methods on simulated data where the underlying distribution is known allows for testing and validation of the performance under controlled conditions. By simulating data with known properties, we can assess how well the methods can recover the underlying distribution and identify potential limitations. For example, we can vary the sample size and degree of noise, introduce irregularity, sparseness and censoring.

The first step is to simulate a complete dataset. By choosing the trajectory of the simulated data to have a sigmoidal, linear and exponential shape, we know the true underlying trajectories of the data. These curve trajectories were chosen to reference Zhang's, Friedman's and WHO's respective cervical dilation findings.

To create the exponentially shaped curves a sequence of values in a certain range was generated, and the exponential function applied. A similar approach was used to obtain the second set of values, but by applying the sigmoid function instead, defined by $\frac{1}{1+e^{-x}}$. To obtain linearly increasing values, the `rnorm()` function were used to draw a random number from the normal distribution, and then added for each iteration in the span of the domain. Normally distributed random noise is added for each collection of values to create individual differences.

The data is then restricted to the interval $[4, 10]$ using min-max normalisation to replicate the results of a VE during the active phase of labour (see Appendix C.2).

To further mimic a VE the measurements are converted to integer values, and a random

number of missing values, placed at random times, add irregularity, and uniform sparseness to the simulated data. However, the endpoints, i.e., the first and last value were not removed. Finally, a random sampling of the distribution of missing values in the selected study sample were performed, and added to the complete data.

2.6 Software

This thesis is written in Rmarkdown using RStudio version 2023.06.0 (Build 421). Data preprocessing, building and analysis were also performed in RStudio with `R` version 4.2.2 (R Core Team, 2022). The `R` source code is available at GitHub.

2.7 Ethics

Clinical data used in the thesis was collected in context of the LaPS, with ethical approval obtained by the Regional Committee for Medical and Health Research Ethics: 2013/1862/REK South-East. The data was anonymised prior to the present analysis, and can no longer be used to identify the participants. Further considerations regarding ethical and regulatory requirements is available in the LaPS protocol (Bernitz et al., 2017).

3 Results

3.1 Study Sample Characteristics

This section provides characteristics of the LaPS dataset to give an overview of the study population through frequency distributions among the participants and measures of central tendency and variability.

Table 1: Maternal characteristics in the LaPS dataset

n=7277		**n (%)**	**Mean (SD)**
Higher education		4429 (60.9)	
Marital status	*Married*	2047 (28.1)	
	Cohabitant	4831 (66.4)	
	Single	339 (4.7)	
	Other	60 (0.8)	
Age			27.7 (4.5)
BMI (kg/m2)*			23.7 (4.3)

Note:
* Pregravid

Table 2: Neonatal characteristics in the LaPS dataset

n=7277		**n (%)**	**Mean (SD)**
Sex	*Female*	3644 (50.1)	
	Male	3633 (49.9)	
Transfer to NICU*		274 (3.8)	
Gestational age (days)			281 (7.5)
Weight (g)			3523 (421)
Head circumference (cm)			35 (1.5)

Note:
* Newborn intensive care unit

The LaPS (Bernitz et al., 2018) included birth care units from all geographical health regions in Norway, with more than 500 births annually. The study population comprised 7277 women, with a median (IQR) age of 27 (6) years and BMI of 23 (35) kg/m^2. The most frequent reason for admission was contractions, see Figure 3b. Table 1 and 2 lists some of the maternal and neonatal characteristics in the sample, while Figure 3a depicts the distribution of participants among the birth care units, with a range of 1151 participants.

Table 3 contains characteristics of the labours. Most participants arrived during the latent phase of labour, with a median (IQR) cervical dilation of 3 (3) cm. The partogram base measurement refers to the first measured cervical dilation $\geq$ 4 cm, and was recorded for all participants. The fetal presentation was primarily occiput or head-first (98.9 %). The median (IQR) duration of the recorded active phase was 5 (5.5) hours; when including fetal descent and expulsion, it was 6.4 (6.5) hours.

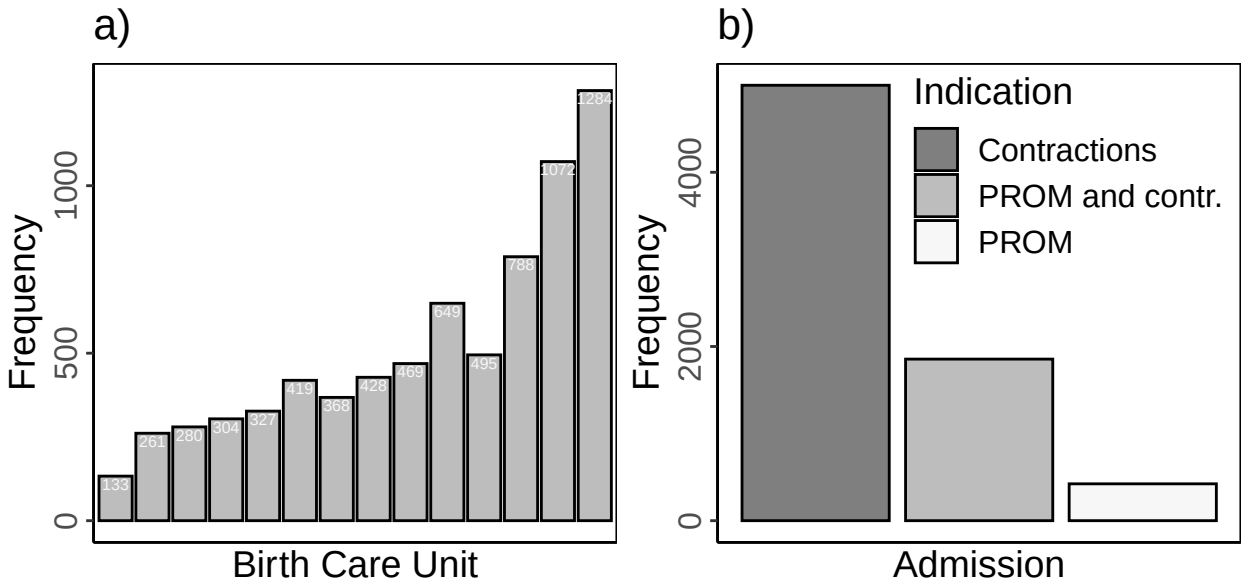

Figure 3: In the LaPS dataset. a) Frequency of labours grouped by birth care unit. b) Reason for admittance to the birth care unit (PROM: Prelabour rupture of membranes).

Table 3: Labour characteristics in the LaPS dataset

n=7277		**n (%)**	**Mean (SD)**
Guideline	*WHO*	3305 (45.4)	
	Zhang	3972 (54.6)	
Labour dystocia according to guideline		3394 (46.6)	
Fetal presentation	*Occiput anterior*	6746 (92.7)	
	Occiput posterior	449 (6.2)	
	Breech	1 (0.0)	
	Face	4 (0.1)	
	Brow	13 (0.2)	
	Forehead (Sinciput)	16 (0.2)	
	Other	48 (0.7)	
Amniotomi		2619 (36.0)	
Oxytocin		3219 (44.2)	
Medical pain relief	*EDA*	3566 (49.0)	
	Spinal	118 (1.6)	
	N20	3585 (49.0)	
	Pudendal	158 (2.2)	
	Opiates	228 (3.1)	
	Other	107 (1.4)	
Operative delivery	*CS*	467 (6.4)	
	Vacuum	1302 (18.0)	
	Forceps	118 (1.6)	
Cervical dilation (cm), admission*			4.3 (3.0)
Cervical dilation (cm), partogram base**			5.0 (1.5)
Length of active phase (hours)***			5.6 (4.0)
Length of first stage (hours)****			7.1 (4.4)

Note:

* Admission refers to the cervical dilation recorded at arrival to the birth care unit

** Partogram base refers to the first measure in the partogram

*** The active phase is defined as the period between 4 cm and 10 cm of cervical dilation

**** The first stage of labour is the active phase plus fetal descent and expulsion

3.2 Cervical Dilation Characteristics

The number of participants with a recorded cervical dilation during the active phase is 7277. Figure 4a is the number of observations at each time point, while Figure 4b shows the observations for each participant linked together by straight lines. The arithmetic mean for the observations across all participants at each time point is shown in red, also connected by straight lines. Figure 4b shows varying starting points along the y-axis, and several lengths along the x-axis, capturing the diversity in both initial cervical dilation and duration of the active phase, with a respective range of 4-10 cm and 0-24.5 hours. The mean initial cervical dilation is 5 cm, while after half an hour, it has increased to just above 8 cm. Comparing this with the frequency plot in Figure 4a, the sample size is significantly smaller after half an hour. The reduction from time 0 to 0.5 hours is just above 90 %. In Figure 4b, it is also notable that in some cases, the recording of measurements ceases before reaching 10 cm of cervical dilation and that the cervical dilation process is not strictly increasing everywhere. The VE is performed upon clinical indication and seems highly dependent on the course of labour. This is particularly evident in Figure 4b where the arithmetic mean for each time point has a local spike just above 8 cm after only 30 minutes. The parturients that had a VE at this time are few, and further along in labour. This is a tendency throughout, which suggests that the probability of having a VE increases as the labour advances toward the end of the active phase, and are thus not performed randomly across participants.

The final cervical dilation recording announce the end of the active phase of labour, either because of ICS or transition to the second stage of labour. Figure 5 shows the measured cervical dilation and the time of the last VE in participants with vaginal parturition (5a) and ICS (5b). Comparing the y-axis of the two plots, it's evident that the relative frequency of ICS is low. The variance in active phase duration is also more pronounced compared with the participants with vaginal parturition, which are decidedly left-skewed in Figure 5a, with a median (IQR) of 9.5 (6) hours for ICS versus 4.5 (6) hours for vaginal parturition. The proportion of right-censoring is much higher for participants with ICS, because the final observation is below 10 cm, as illustrated by the multicolored bars in Figure 5b.

Some of the participants with a vaginal parturition have an active phase duration which can

be characterized as prolonged. Looking at Figure 5a: 75 % of the participants concluded the active phase within 8 hours, and the average duration was 5.3 hours. However, many of these participants have a left-censored active phase progression. E.g., if the first observation is 9 cm, and the second observation is 10 cm after one hour, the length of the active phase is recorded as 1 hour. The value of the initial measurement will, of course, affect the average time in the active phase. Only considering the participants where the boundary values (4 and 10 cm) of the active phase are available, i.e., the uncensored cases (n=3279), the median (IQR) length is 6.5 (6) hours, and the average is 7 hours. The slight discrepancy between the median and mean suggests a left skew, consistent with Figure 5a. Further, the long tail and sparse distribution in Figure 5a indicate a high variability and low frequency of participants with an active phase duration exceeding 7 hours.

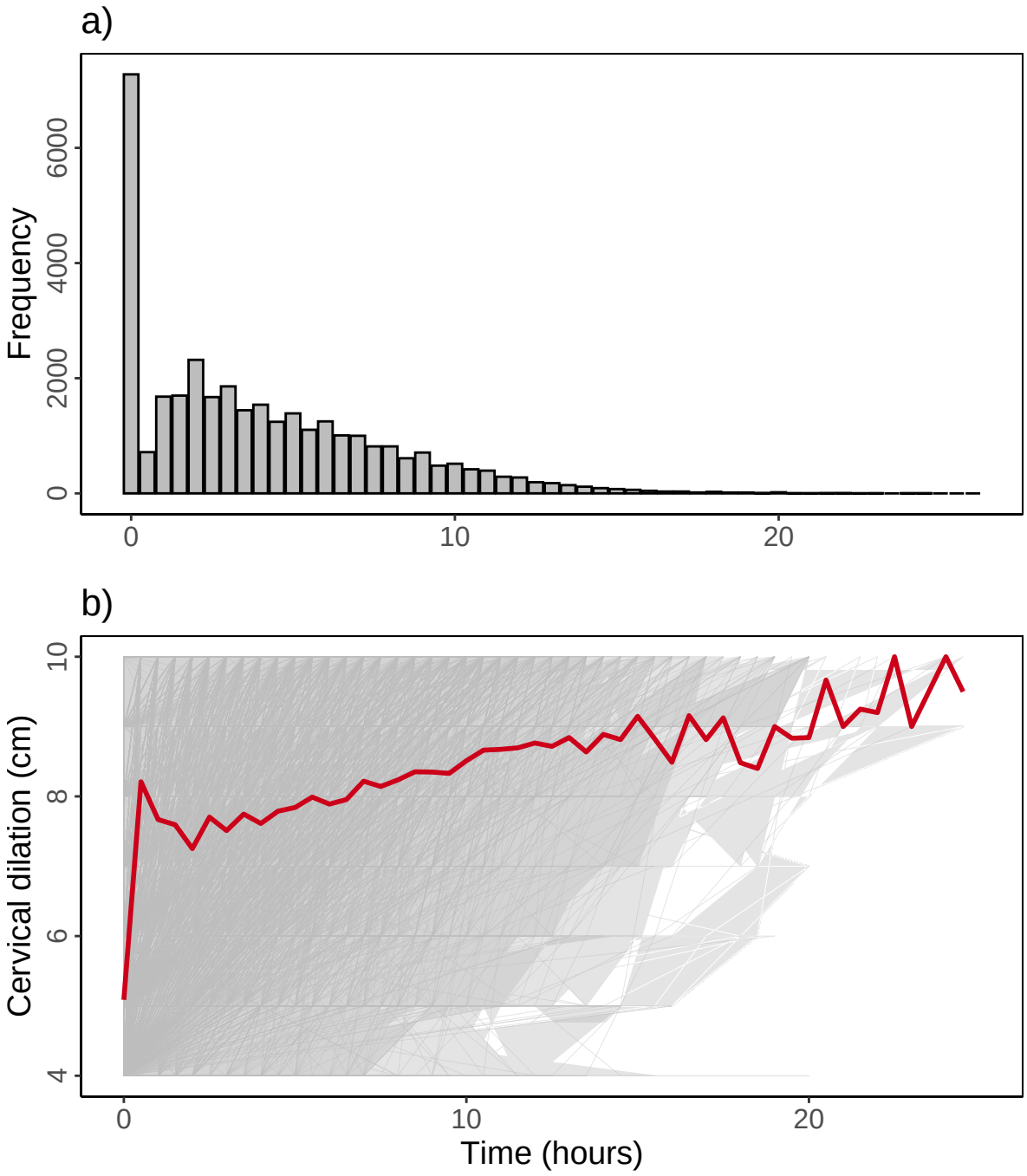

Figure 4: From the LaPS cervical dilation measurements. a) Number of measurements at each time point. b) Observed cervical dilation with linear interpolation of the observations for each participant, with the arithmetic mean for each time point also linearly interpolated in red.

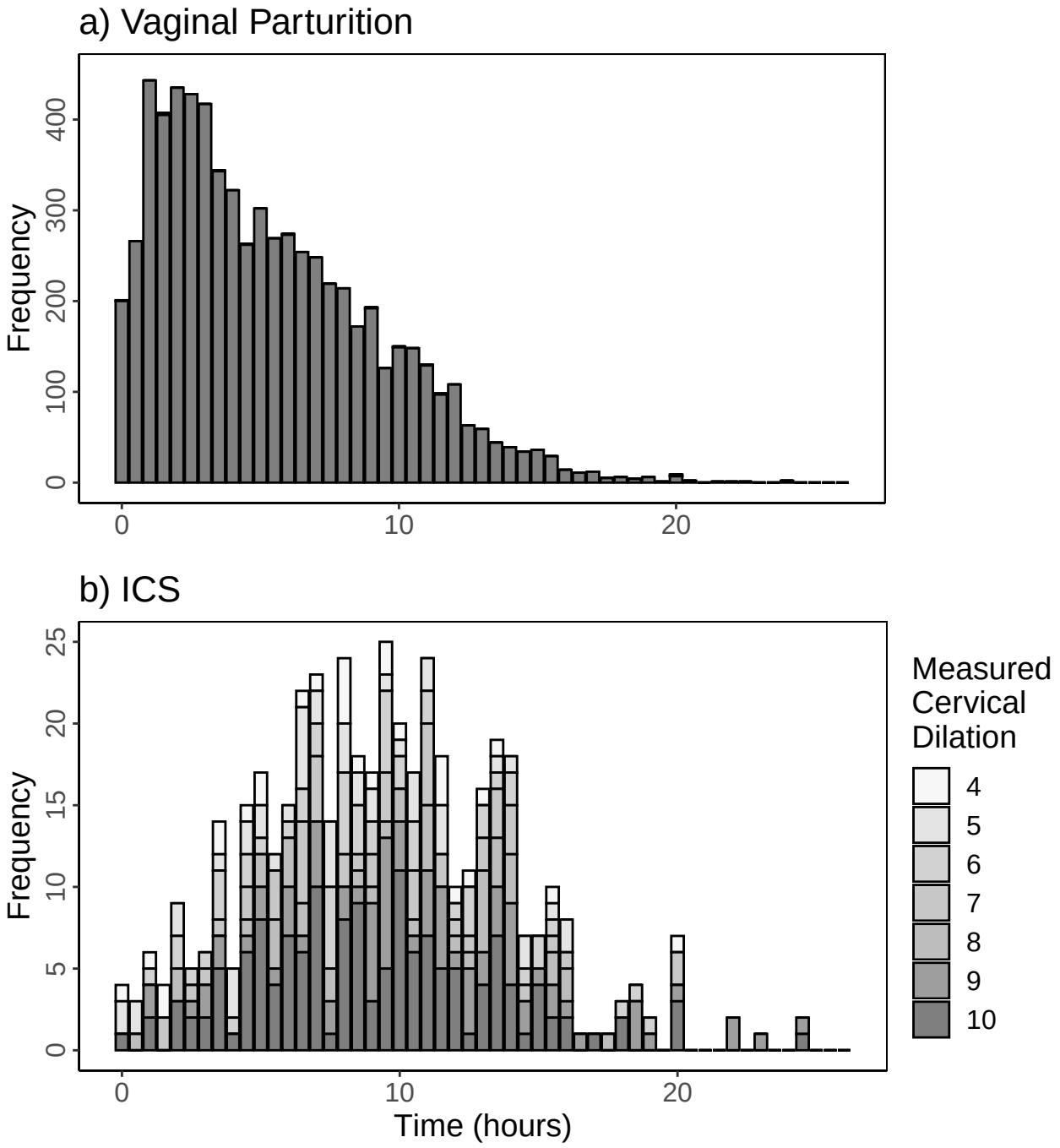

Figure 5: Time and value of final cervical dilation measurement in the LaPS dataset. a) Participants with vaginal parturition. b) Participants with ICS.

3.3 Data Exclusion and Alignement

One of the challenges in applying the PACE method for FDA is to deal with the different domains of the curves. The PACE method requires that all the curves have a common domain, and it stretches or shrinks each curve to fit this domain. Therefore, this study applies PACE to the corresponding cervical dilation measurements of 4660 participants in the LaPS dataset.

This thesis' selected study sample excludes participants who had an ICS (n=467), primarily because there was no evident common "landmark" for curve alignment. Additionally, we only considered participants who had an active phase concluded within 7 hours, corresponding to the average duration among participants with uncensored labour progression, eliminating n=1939 participants.

To ensure an accurate analysis of temporal patterns and trends, the selected study sample omits participants with only one recorded cervical dilation measurement of 10 cm after the initial VE (n=200). Furthermore, participants with recordings that did not cease after 10 cm was observed (n=11) were excluded due to possible inaccurate assessment and issues concerning alignment.

Figure 5a shows that for virtually every participant with vaginal parturition, 10 cm is the final observed measurement, making it a natural point of alignment prior to curve fitting. Considering Figure 4b, alignment is necessary since health personnel performs the VE's at various times for each participant, i.e., in different phases of active labour. We can dismiss this specific variability by considering the base time at 10 cm of cervical dilation.

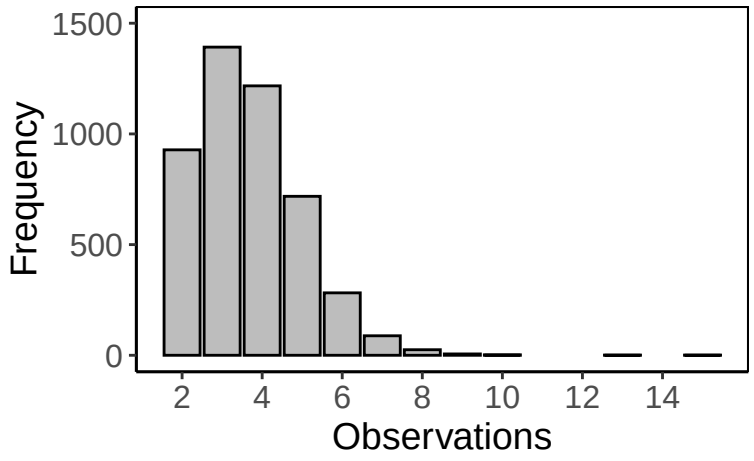

Figure 6: Number of recorded measurements in the selected study sample (n=4660).

Figure 6 gives an overview of the number of recorded measurements per participant in the selected study sample, and there are still some issues concerning sparseness. The median (IQR) is 4 (1) points of measure. Since the chosen domain is 7 hours, with a possible recording every half hour, a participant with four recorded cervical dilation measurements will have missing data at 11 points in time.

To summarise, applying PACE on the LaPS cervical dilation data severely violated method assumptions; therefore, selective filtering for facilitation of curve fitting with PACE reduces the study sample to n=4660. Figure 7 shows each participant's observations linked together by straight lines, aligned by making 10 cm the starting point in time. The plot has had a re-reversal of the x-axis to ease comparisons with previous graphical illustrations of cervical dilation during the active phase of labour. It is visible that aligning the curves excludes the variability due to time shifts. In Figure 7, the black curve is the arithmetic mean, also linearly interpolated. In contrast to the red curve in Figure 4b, this curve has similarities to existing literature descriptions.

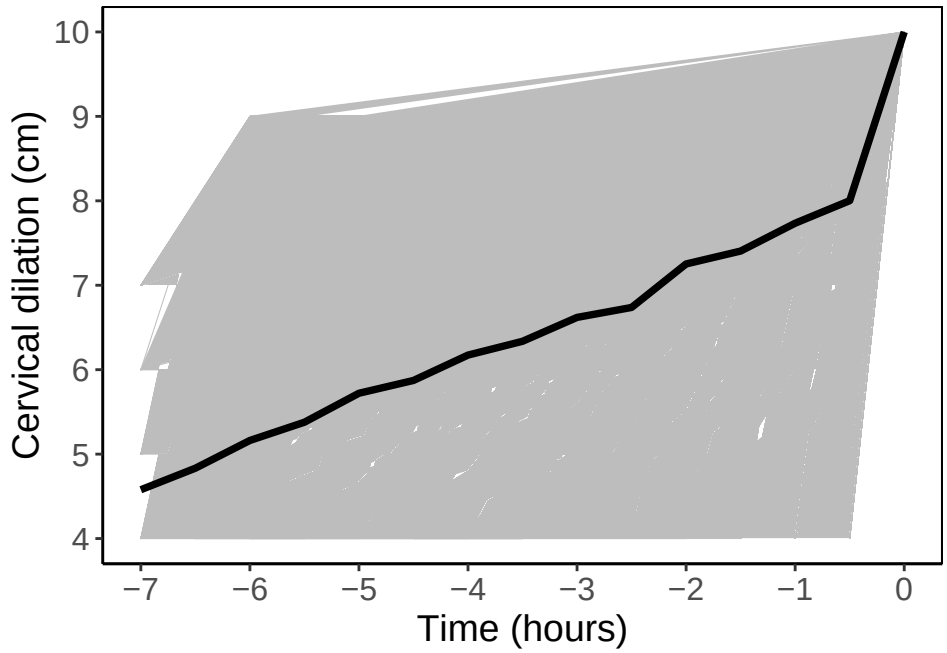

Figure 7: Observed cervical dilation data in the selected study sample (n=4660), with linear interpolation of the observations for each participant. The black curve is the arithmetic mean for each time point also linearly interpolated. The data are aligned in the endpoint at 10 cm which marks the new initial time point. In this plot the x-axis is re-reversed for intuitive purposes.

3.4 Curve Fitting Clinical Data with PACE

The curves were fitted on a selection of participants with vaginal parturition concluding the active phase within 7 hours, and having at least two points of measure (n=4660). The data was aligned by reversing the order of observations, so that 10 cm is observed at time 0. The plots presented in this section have a back-reversed x-axis similar to Figure 7. The number of harmonics, K, is chosen based on a 99 % threshold for the fraction of variance explained (FVE, see Appendix C.1).

The `FPCA()` function in the `fdapace` package is used to implement the curve fitting (Zhou et al., 2022a). The package offers various visualization and reporting tools that facilitate interpretation of the results, and several options for tuning the `FPCA()` function. For example, it is possible to specify the bandwidth, choice of smoothing kernel and -parameter.

3.4.1 Default Parameter Options

Initially, the fitting was performed using the default parameter options of the `FPCA()` function, except defining the data type as sparse. Figure 8 is the pool of estimated path trajectories in the selected sample. The collection of curves seems promising: With `fdapace` 4660 curve trajectories are effectively estimated and it provides a plausible functional data set. In Figure 8, the red, solid curve is the estimated mean curve, and the black solid curve is the linearly interpolated cross-sectional mean, also seen in Figure 7. The two solid curves are consistent with each other, but the estimated mean has a continuous smoothness. Comparing the estimated curve trajectories in Figure 8 with the observed data linearly interpolated for each participant in 7, the upper left corner and lower right corner has significant disparities.

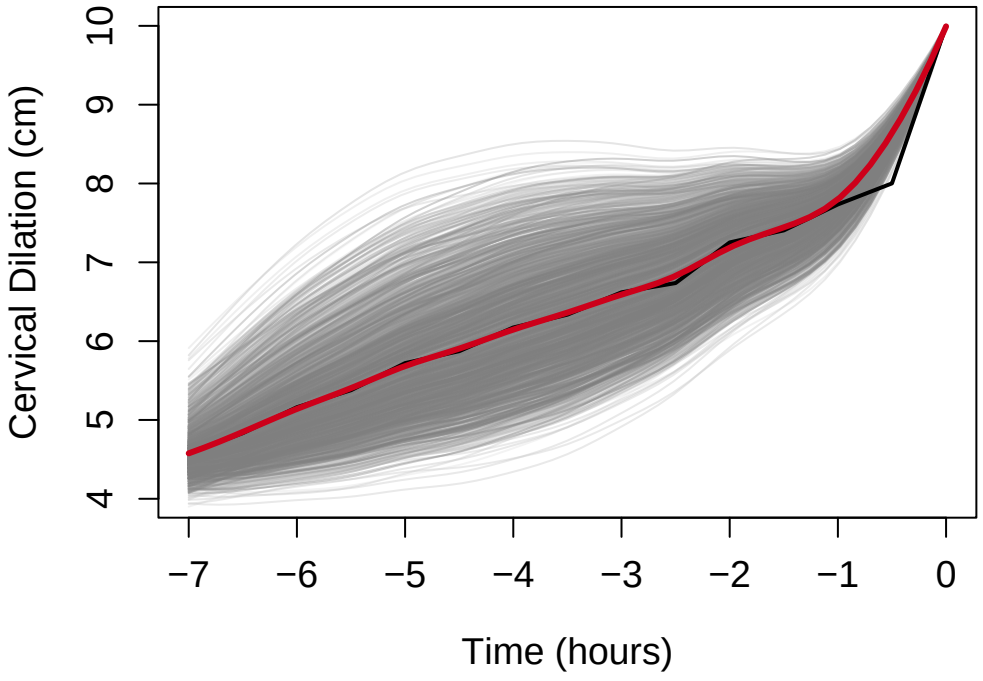

Figure 8: Estimated path trajectories of the cervical dilation with PACE's default parameter options. The red curve is the estimated mean curve, while the black curve is the arithmetic mean linearly interpolated.

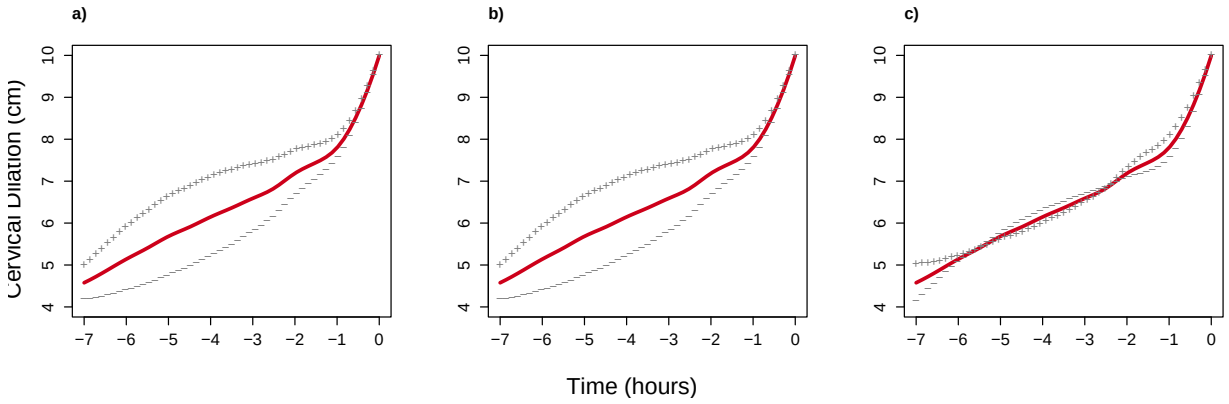

Figure 9: Results from FPCA, based on curves fitted using PACE with default options. The figures depics FPC-scores relative to the estimated mean. The solid purple line is the estimated mean curve, while the lines marked by with plus and minuses marks the shape of the trajectory when one SD of the FPC-score is added or subtracted from the mean curve. a) The first FPC with FVE: 84.2 %. b) The second FPC with FVE: 10.9 %. c) The third and final FPC with FVE: 4.9 %.

Figure 9 describes the harmonic curves estimated with FPCA in context of the estimated mean curve. The first harmonic, 9a, explains most of the total variability (84.2 %) in the data. Participants with a high score for the first harmonic tend to have a steeper progression in the early active phase, but a more flattened curve about 4 hours before the second stage, compared with those with a low score. The latter proportion, i.e. participants with a low FPC1 score, has a tendency similar to the hyperbolic curve. As seen in Figure 9a, the initial cervical dilation seems to be an important factor of the first harmonic. For the subsequent harmonics, 9b-c, interpretation is more difficult. However, also the second and third harmonic create an impression that the initial cervical dilation is of relevance.

Figure 10 contains a sample of four random participants that are chosen for further assessment of the curve fitting. The plots combine observed data and their respective estimation of curve trajectory, and it is evident that the fitting was unsuccessful. In the example in Figure 10a we have six points of measure, a fairly good selection in comparison to the general sparseness in the selected data. However, the estimated curve lies steadily below the observations. In Figure 10b and 10d the observed data has a very different dynamic than the estimated curves, which very much resembles the estimated mean. Figure 10c contain extremely sparse data, with only two points of measure, and the estimated trajectory is

reduced to the estimated mean curve, as seen in Figure 8 and 9.

Comparing the estimated curves, Figure 8, with the raw, linearly interpolated data in Figure 7, and assessing a sample of observed data points along with their respective estimation of curve trajectory 10, it is evident that the curve fitting with `FPCA()`'s default parameter options was unsuccessful. In the examples presented in Figure 10 we see that the curves are excessively smoothed towards the estimated mean function, being very similar in form, but that the observations will somewhat influence the height of the curves along the y-axis.

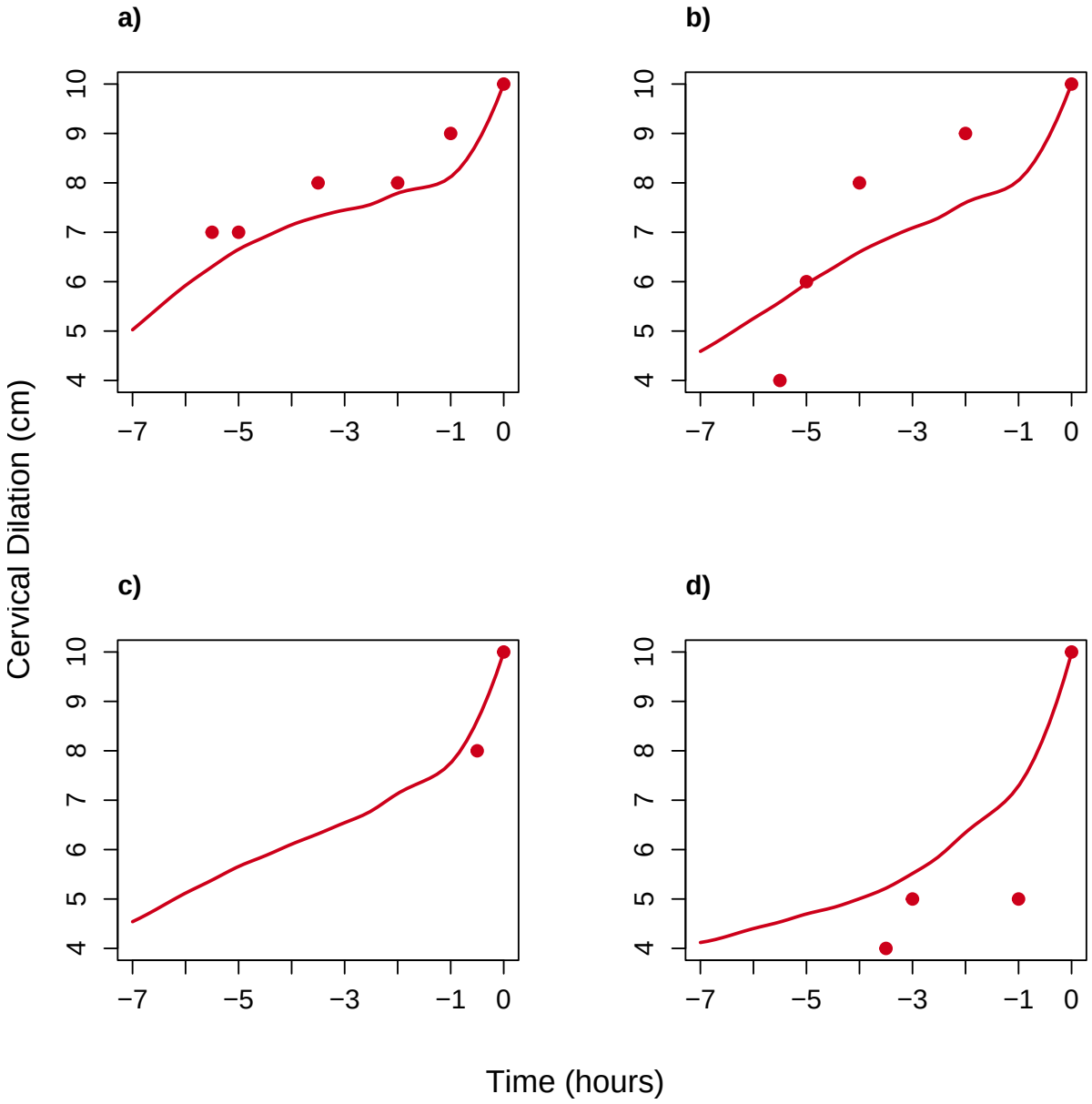

Figure 10: a-d) Estimated path trajectories of the cervical dilation in four participants fitted with PACE's default parameter options. The dots are the participants respective measurment observed at a certain time.

3.4.2 Parameter Tuning

To improve the fitted curves, parameters of the `FPCA()` function were modified. The bandwidth affects the estimation of the covariance structure, controlling the amount of smoothing, the choice of smoothing kernel will alter how the data are weighted when estimating the mean and covariance function, and the smoothing parameter, ρ, controls the amount of regularisation (Zhou et al., 2022b). The final choice of parameters in the FPCA function was obtained by visual inspection of the effect on the resulting curves, experimenting with different kernels and bandwidths to explore the effects of varying degrees of smoothing.

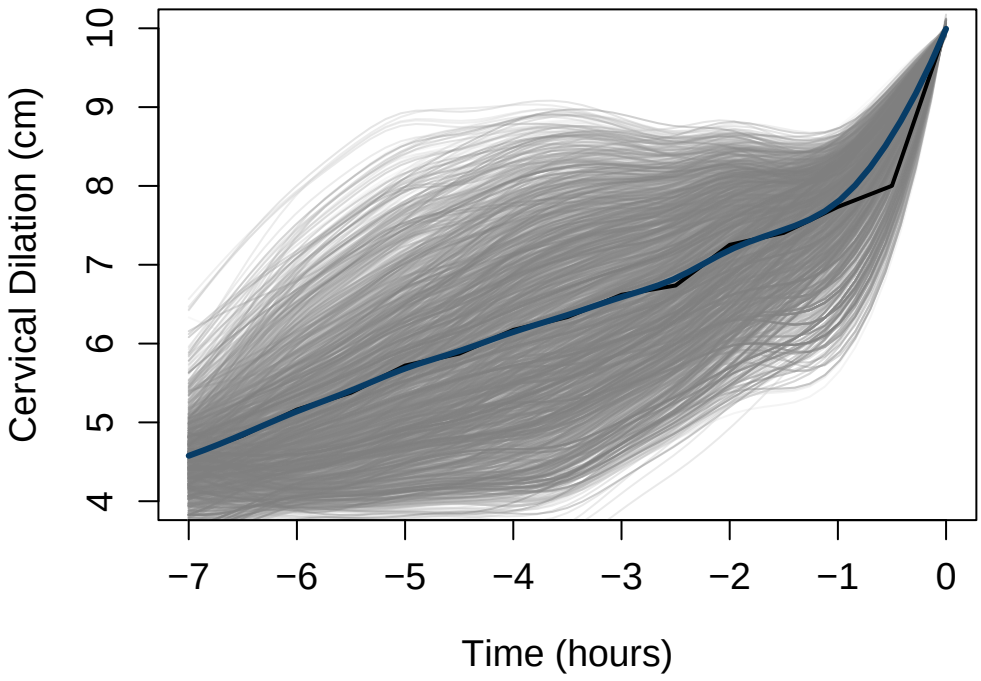

Figure 11: Estimated path trajectories of cervical dilation fitted using PACE with a ridge parameter for regularisation, and a user defined bandwidth value of 0.5 for the smoothed covariance function. The blue curve is the estimated mean curve, while the black curve is the arithmetic mean linearly interpolated.

To reduce the smoothing, the bandwidth was reduced up until the curves appeared jagged. Additionally, the regularization method for the smoothing parameter was adjusted to `ridge`. The reduced bandwidth was not possible to combine with another choice of smoothing kernel, thus the default Gaussian kernel was used. This means that data closer to the center of the domain has more impact, compared with those further away. The number of harmonics increased to $K = 4$ using the same 99 % threshold for the FVE.

Figure 11 is the collection of estimated path trajectories after parameter tuning. In contrast to the estimated curves in Figure 8, the curves in Figure 11 are subject to less smoothing and seemingly capture more variability. The upper left corner and lower right corner of the domain is also more similar the observed data linearly interpolated for each participant in Figure 7. Figure 12 illustrates the harmonic curves estimated with FPCA. The first, second and third harmonic, 12a-c, is consistent with the harmonics in 10. However, in this case we have a fourth harmonic with FVE 1.5 %. This variability might be random noise.

The examples in Figure 13 is the same four participants as depicted in 10, combining the observed data and each of the participants respective estimation of curve trajectory. The fit in 13a is quite good, but the tail of the curve is still drawn towards the estimated mean. In 13b and 13d there is a slight improvement: The estimated trajectory are more influenced by the observed data than in Figure 10b and d, but they still resemble the estimated mean. Figure 13c is reduced to the estimated mean, in the same way as Figure 10c.

The modifications of the parameters in the `FPCA()` function provided more flexibility, increasing the precision of estimated curve trajectories when compared to the observed data. However, PACE still fails to capture obvious dynamics, as seen in Figure 13b and c. The estimated mean seems like the driving force in the individual curve fitting to such an extent that much of the variability in the data is lost.

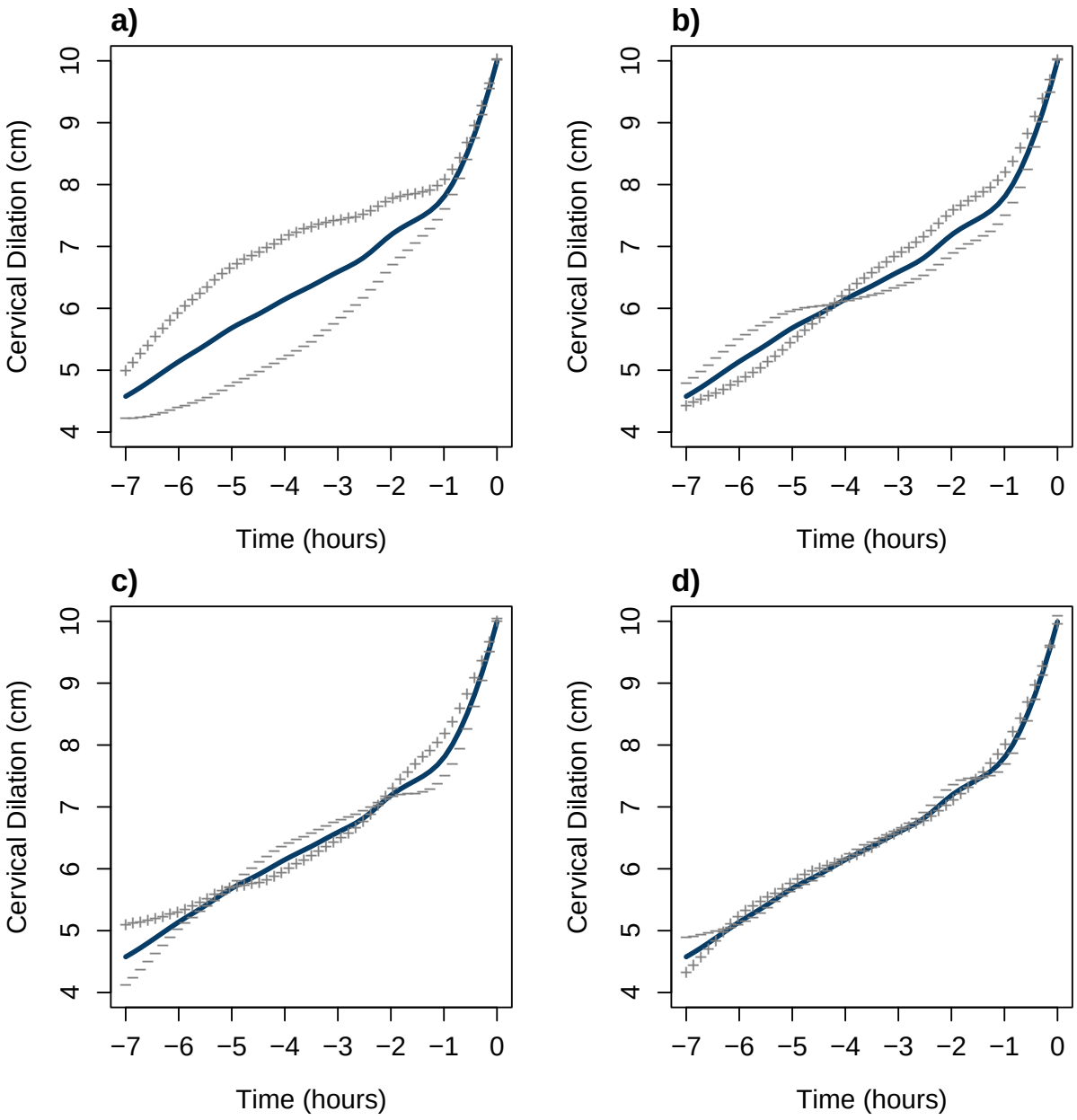

Figure 12: Results from FPCA, based on curves fitted using PACE with a ridge parameter for regularisation, and a user defined bandwidth value of 0.5 for the smoothed covariance function. The figures depics FPC-scores relative to the estimated mean. The solid blue line is the estimated mean curve, while the lines marked by with plus and minuses marks the shape of the trajectory when one SD of the FPC-score is added or subtracted from the mean curve. a) The first FPC with FVE: 80.1 %. b) The second FPC with FVE: 11.6 %. c) The third FPC with FVE: 6.8 %. d) The fourth FPC with FVE: 1.5 %.

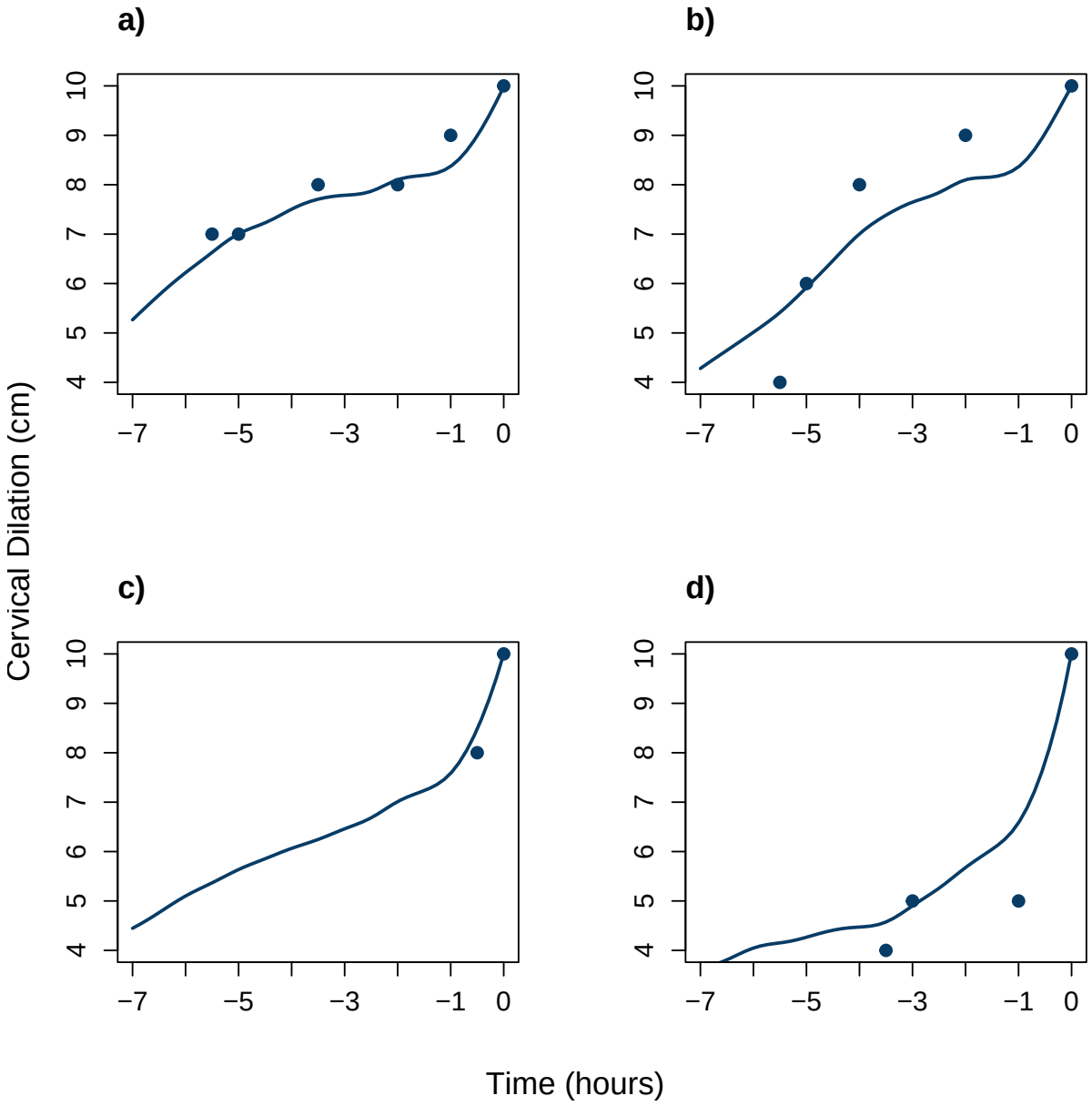

Figure 13: a-d) Estimated path trajectories of the cervical dilation in four participants fitted using PACE with a ridge parameter for regularisation, and a user defined bandwidth value of 0.5 for the smoothed covariance function. The dots are the participants respective measurment observed at a certain time.

3.5 Curve Fitting Simulated Data with PACE

The simulated data consist of n=4800 collections of discrete measures, with an equal proportion of data from an exponential, sigmoid and linear function as seen in Figure 14.

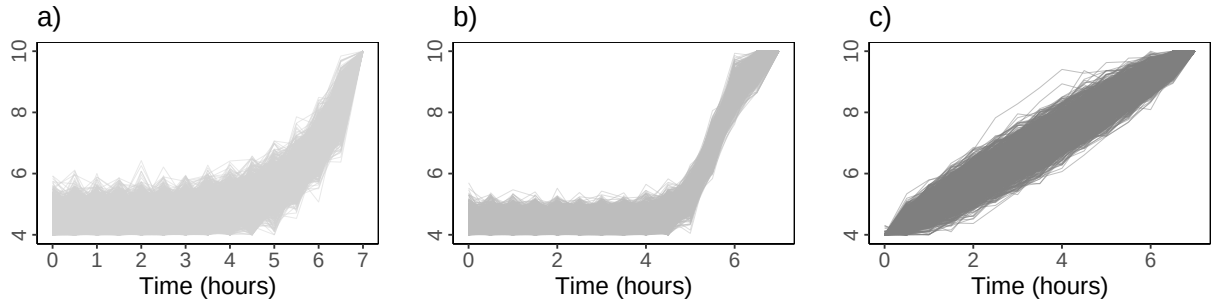

Figure 14: Simulated dense data with added noise and restricted to the domain of the selected study sample from LaPS. The discrete observations are linearly interpolated for each row. a) Exponential shaped cuvres. b) Curved with a sigmoid shape. c) Linearly shaped curves.

Figure 15 consist of the complete simulated dataset, linearly interpolated for comparisons with Figure 7. Using PACE to estimate the curve trajectories of the complete data effectively distinguishes between the three groups, as seen in Figure 16.

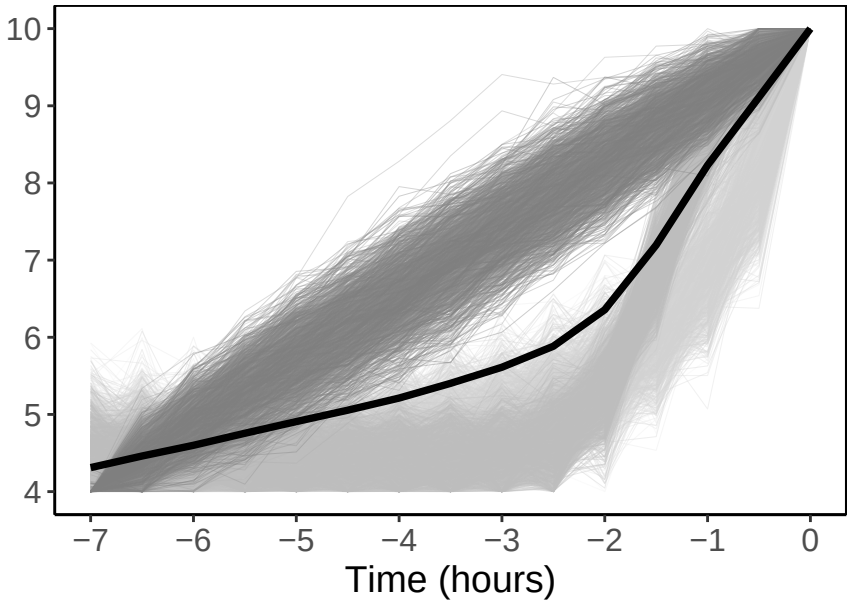

Figure 15: Simulated data combined. Each collection of discrete measures are linearly interpolated (n=4800). The arithmetic mean for each time point is also linearly interpolated in black.

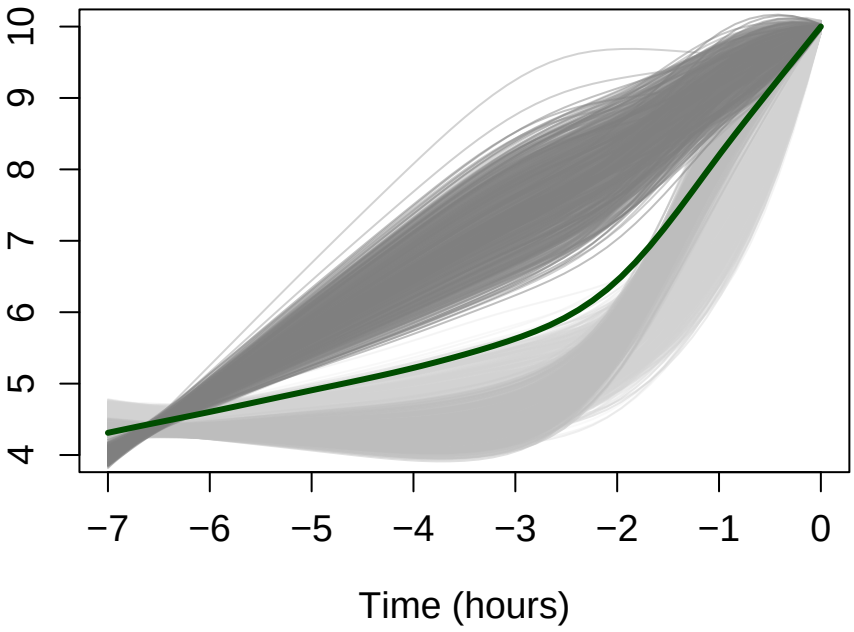

Figure 16: Estimated path trajectories of simulated dense data with PACE. The solid dark green curve is the eatimated mean.

By rounding the values to the nearest integer and introducing a random number of missing values in the range $[1, 13]$ for each collection of discrete measures, we get a slightly different fit. The results are presented in Figure 17. These data are more similar to the cervical dilation data, but has a uniform distribution of missing values. In the case of left censoring the first value is always 5, in contrast to the LaPS dataset where the initial measure could be anywhere between 4-10. This ensures that the domain is well-covered. The estimated path trajectories in Figure 17 capture most of the dynamics, but seem to struggle in separating the exponentially shaped curves from the sigmoidal. These are very similar in shape, so this is expected. However, looking closely, some of the linearly shaped curves that lies above the estimated mean curve in Figure 16, is now below. The slight gap between the curves have also decreased in size.

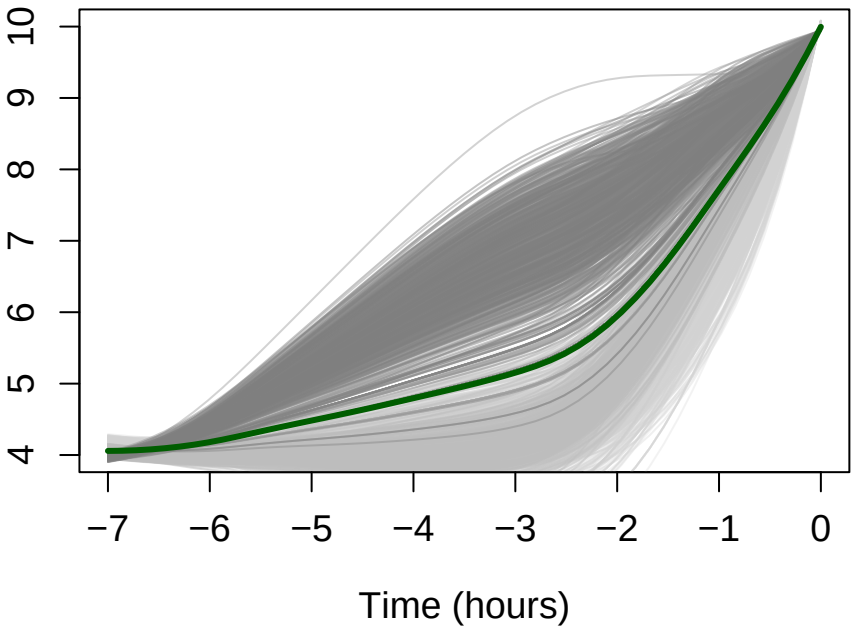

Figure 17: Estimated path trajectories of slightly sparse simulated data with PACE.

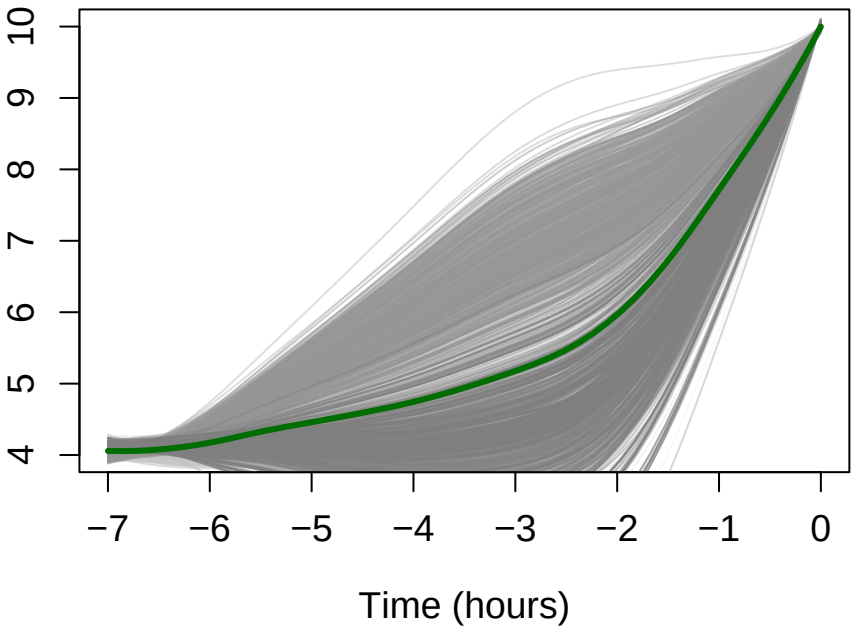

Figure 18: Estimated path trajectories of the very sparse simulated data with PACE.

In the final examination of the simulated data, the number of missing values in the selected study sample from the LaPS dataset is random sampled to achieve the same distribution of missing values (see Figure 6). The estimated path trajectories are presented in Figure 18, and the three groups are no longer recognizable. The gap between the curves are absent, and the curves have some characteristics that are not present in the original simulated data. E.g. the deep dip in the curves that lies low on the y-axis. The deep grey linear curves are also stretched towards the lowermost curves. Even though these data have a common domain along both the x- and y-axis, PACE fails to fit curves to data that are as sparse as the cervical dilation data in the selected study sample presented in Section 3.3.

4 Discussion

This thesis's primary objective is to determine if the PACE algorithm is suitable for curve fitting cervical dilation data from VEs for FDA purposes. The results presented indicate that this is not the case.

To explore the PACE algorithm, FPCA with various parameter options were used to estimate curve trajectories for cervical dilation data. The results from using the default options and an improved fit after parameter tuning are presented in this thesis. However, the FPCA with PACE produced inaccurate curve trajectories and failed to capture obvious patterns of progression.

A consequential aim was to diagnose the issues. Data with a known underlying trajectory were simulated to explore the limits of PACE, and then noise and missing values were added stepwise. Using a random number of missing values, PACE produced an acceptable fit. By random sampling the distribution of missing values in the clinical data, the simulated data obtained the same degree of sparseness. This produced inaccurate results and made the method unable to distinguish between the groups with common underlying distributions. Primarily, the severe sparseness of the data, with few repeated measurements, is an obstacle for PACE to capture the complete variability, and the outcome is that the method heavily relies on central tendencies. This is particularly evident in the incomplete cases, where the data takes on an unnatural path towards the estimated mean curve. However, the estimated mean curves seem to capture the central tendencies even in sparse cases, but have limited usefulness without an accompanying measure of the dispersion.

A secondary aim was to give a thorough description of the LaPS cervical dilation data by highlighting important features and their potential implications. These features are discussed in the thesis and can be summarised by the following terms:

- Sparseness
- Irregularity
- Censoring
- Misalignment

- Not randomly sampled

A third aim was to highlight the potential of FDA in describing the cervical dilation during the active phase of labour. Unlike summary measures, such as the duration of the active phase or mean rates of progression, FDA provides a method that can incorporate the raw data collection as a whole. Since labour is a continuous process, it is possible that the different phases and stages of labour will have mutual dependence. Provided access to the data, FDA could be used to study a labour from the onset and throughout, independent of the current definitions. Furthermore, FDA enables the possibility of identifying both phase- and amplitude variation, and incorporate explanatory variables.

The main challenge of curve fitting with traditional techniques is that irregularity is not supported. Another issue is that these procedures rely on pre-smoothing, which can be problematic in sparsely sampled data because of the potential loss of features or the introduction of additional noise. Yao et al. (2005)'s proposed solution to these shortcomings is performing FPCA via the PACE algorithm, which yields covariance- and mean functions, harmonic curves with corresponding scores and estimated path trajectories for each subject. PACE does not rely on pre-smoothing of the trajectories but derives the harmonics by modelling the conditional expectation given the observed data to capture the underlying temporal patterns.

The package `fdapace` was used to implement PACE in `R`. It was straightforward to realise and had computational efficiency. The approach to parameter tuning was by visual inspection, which provided seemingly better results than using model selection methods, such as cross-validation, but left the curve fitting process sensitive to human error. However, the nature of the data limited the number of possible parameters, and the final options were obtained by a systematic selection, testing the various combinations. If not for the apparent challenges in estimating the path trajectories, assessing the fit could present a problem. In that case, a measure for evaluating the goodness of fit could be applied.

The PACE method requires the domain to be well-covered with observations for each time point. If not, the covariance estimate will be unreliable and produce untrustworthy results.

This is not the case in cervical dilation data from VEs, which is restricted to different subintervals of the domain. Therefore, it was necessary to align the observations.

The choice of 10 cm to align the curves handled the differences between participants due to time shifts but effectively excluded all participants with an ICS. Furthermore, the assumption of a common domain required restrictions on the time interval. PACE stretches the estimated path trajectories to fit the time span, which has important ramifications on the curve fitting: For example, it does not make sense to force a 5-hour long active phase to span 26 hours. A 7-hour threshold was therefore chosen based on the following reasons:

- In terms of data preservation, it is close to the third quartile of 8 hours of active phase duration
- It corresponds to the median of the uncensored active phase duration, which indicates that it is a representative value for the central tendency of the data
- Participants with an active phase duration >7 hours have a low relative frequency and a high variability in labour progression patterns and duration

The implication is that shorter labours are stretched to fit the 7-hour domain, and n=1939 participants were excluded. During preliminary tests, these were attempted to be retained in the study sample by choosing a cutoff point of 7 hours in reversed time. I.e., creating more left-censored cases. However, this violated the assumption of a common domain also along the y-axis, introducing a time gap between the functional data that exceeded the allowable threshold. Another approach that was explored is grouping the labours after length before applying PACE. However, as mentioned, some of the shorter labours were left-censored, and the left tail needs to be predicted to obtain a complete set of functional data. When presented with censored data, PACE will project the incomplete cases onto a fitting harmonic curve, which effectively aligns the tail with the dominant modes of variation. However, this presupposes that the incomplete data share similar patterns with the variability captured in the harmonics. In certain cases, this may not hold, leading to potential inaccuracies in the predicted curves. A proposed solution is to combine the curve fitting with a clustering algorithm to categorise similar labours. In this specific case, with the irregular and

sparse sampling of cervical dilation data, comparing trajectories might present challenges. Nevertheless, this is worth exploring in future research.

Some of the recordings of cervical dilation were fluctuating. E.g., if a participant reaches 10 cm, then 8 cm is recorded sometime later on before increasing again. This phenomenon is known as cervical reversal, or recoil, and might occur if the parturient is experiencing, e.g., stress due to a change in the environment or other factors (Weckend et al., 2022). It is unknown whether the fluctuations in these particular data are caused by inaccurate measurements or actual cervical recoil. However, they presented some challenges during the preprocessing stage, and since they were not a significant proportion, these data were omitted from the selected study sample.

The precluding of certain data does have implications for potential further analysis. The aim of excluding the mentioned participants was to simplify preprocessing, reduce the data set to a more homogeneous and manageable size, and minimise the effect of domain stretching or shrinking by the PACE method. However, this was a trade-off with potential disadvantages. The chosen sample could be missing valuable information relevant to further analysis. Specifically, the labours that concluded with an ICS are of interest for risk assessment. Participants with prolonged labour might also contain important patterns that would help understand the dynamics of labour progression, and potential systematic differences between retained and omitted data can introduce additional bias. This will, in turn, have an impact on the validity of potential further analysis of the reduced data set, and the impact would need assessment. Data with a smaller sample size will also decrease the precision of analysis and may not capture the full range of variability. Addressing the specific research questions in this thesis, primarily fitting functional curves to the cervical dilation data using PACE, the reduction in sample size was necessary but is considered a weakness of the approach.

It is possible that some of the issues faced with PACE could be addressed with a combination of methods, such as clustering and group-wise fitting of curves. A proposed alternative to PACE is presented by Nie et al. (2021), called Sparse Orthonormal Approximation (SOAP), a method which avoids estimating the mean and covariance function but estimates the harmonics by finding the best approximation in a Hilbert space. Nie et al. (2021) argues

that this makes the method more stable with sparse and irregular data. When comparing their method to PACE in a simulation study, Nie et al. (2021) found that SOAP outperforms PACE in predicting individual trajectories and recovering the harmonics. Despite promising results, the SOAP method is not as accessible as PACE, with little documentation beyond what is described by Nie et al. (2021), and it would require manual implementation in `R`. The performance of SOAP on data similar to the present cervical dilation data remains to be explored.

Another alternative would be to discard the idea of evaluating cervical dilation data as functional data. E.g., by using a mixed-effects model similar to the approach by Zhang et al. (2010). Survival analysis is another branch of statistics widely used for assessing risk, which incorporates time and where censoring is a known term. Still, FDA provides a unique ability to assess temporal patterns, describe curve dynamics through derivatives and perform inference with functional regression models. Thus, developing methods that address the issues faced here would be valuable in studying the patterns of labour progression.

The LaPS data also contains detailed information about each participant, neonate and labour in categorical and numerical variables. The descriptive analysis presents the study sample as representative of Norwegian nullipara: The BMI has a distribution analogue to the general Norwegian woman (Folkehelseinstituttet, 2022), while the average age is slightly lower. During the last decade, the average age of Norwegian nullipara has been converging towards 30, exceeding this age last year. A likely explanation of the younger population in this data set is the location of the obstetric units because the maternal age tends to be lower in more sparsely populated areas (Statistics Norway, 2022a, 2022b). These explanatory variables can be used to quantify associations and identify possible predictors for labour progression patterns in future research, together with the cervical dilation data.

There are some limitations to how well cervical dilation data can be sampled through a VE. The frequency of VEs depends on the course of labour and the preferences of the parturient. In some cases, an uncomplicated and progressing labour may require few or no VEs. In other cases, such as in the presence of labour dystocia or by request of the parturient, VEs may be performed more often. The procedure is invasive and might cause the parturient discomfort

(G et al., 2022). A high number of VEs is also associated with a risk for infection (Gluck et al., 2022). Therefore it is general practice to restrict the number of VEs to a minimum. This is reflected in this particular dataset, which is very sparse. Because of individual differences, the measurements are made at irregular time points, which, together with the sparseness of the data, had inevitable implications on the approach. As presented in the results, the timing of measurements is related to the outcome, i.e., the cervical dilation. This introduces bias. One way to address the issue could be to have a pre-specified schedule for measurements that are applied consistently to all participants, regardless of progression, to ensure that other factors do not influence the timing of measurements. However, in the specific case of the VE, this is not possible because of the procedure's invasiveness.

Subjectively measuring cervical dilation using two fingers is also bound to present significant measurement error, as the accuracy is limited. The error may depend on the examiner's training, experience and technique, so if personnel change during labour, it could influence the measure. The parturients anatomy or position may also affect the examiner's accessibility of the cervix, and the measurement error can be dependent on the progress of labour, as the cervix becomes softer and thinner as labour advances, which will make it harder to measure accurately (Jackson et al., 1992). In addition, the dilation is approximated in integers, making it somewhat rough. The measurement error might also be correlated with time, as repeated measurements can be influenced by expectations due to previous measurements. It is evident that the digital cervical exam has some disadvantages from a statistical point of view. However, it also has significance for the parturient because examination of the cervix can cause distress or pain (Mohaghegh et al., 2021) and increases the risk of chorioamnionitis, an infection due to bacteria entering the uterus (Oberman et al., 2023). An alternative to the VE is using transperinal ultrasound, which is non-invasive, and leaves less room for subjective interpretation by the examiner. Brancadoro et al. (2018) systematic review and meta-analysis for devices measuring cervical dilation introduce ultrasound as the most promising technology, being both accurate in distance measuring and having potential for further development. However, during a 2021 review comparing transperineal ultrasound to the VE, Mohaghegh et al. (2021) found the ultrasound reliable for assessing labour progression in multipara but concluded that the application needs further studies for

nullipara.

The utilisation of VEs has remained a part of intrapartum care for a long time. For instance, during the 1st-2nd. century A.D. Soranus of Ephesus suggested that midwives should have soft hands with long slim fingers and short nails (Feltovich, 2017). The procedure is not only used to determine cervical dilation, but also to assess the effacement, position and consistency of the cervix and the fetal station. The VE is a part of current practice and is accessible, cost-effective and thoroughly tested. A statistical approach to studying cervical dilation data has the potential to create positive change with minimal disruption. Therefore, further development of methods for curve fitting sparse data is desirable. The application of such a method extends beyond intrapartum care, e.g., in areas such as medical trials, meteorological data analysis, and financial records. In the future, valuable insights from FDA might also be obtained in the very sparse, irregular and incomplete cases.

5 Conclusion

In conclusion, FDA has interesting potential in the study of labour progression. However, this thesis has highlighted some hindrances to accomplishing curve fitting cervical dilation data obtained from VEs: Primarily, the nature of the observed data means that traditional FDA is unsuitable. Yao et al. (2005) has proposed the PACE framework to address the issues, and this approach was tested but presented several concerns. To align the data, excluding all participants without an observed endpoint at 10 cm of cervical dilation was necessary. Further, the assumption of a common domain resulted in manually choosing a domain to fit the curves. It was discovered that the few repeated observations per subject were causing the method to estimate inaccurate curve trajectories by using simulated data with known underlying trajectories. The method effectively captured central tendencies of the data, but these have limited clinical usefulness.

A proper description of the temporal variations could be used to address the issue of defining true labour dystocia. At the present time, PACE is not a sensible approach to curve fitting cervical dilation data from VEs. There are promising developments in the FDA field, such as the SOAP method (Nie et al., 2021). Still, some advancement is necessary in terms of documentation and accessibility. Techniques from other statistical fields could provide insight into the participants' labour progression in the selected study sample, but some of the advantages FDA present would then be lost.

The cervical dilation data presented here serves as a practical example of data that is very sparse, irregular, and censored. The unsuccessful application of PACE for FDA purposes highlight the need for further methodological advancements addressing these types of data. The descriptions of the challenges encountered while working with the cervical dilation data might contribute to the understanding of PACE and guidance in future research attempts. By striving for methodological improvements, we can enhance the understanding of labour progression and possibly improve clinical decision making, promoting maternal and neonatal well-being.

Appendix

Appendix A

Functional data analysis (FDA) as described by J. O. Ramsay & Silverman (2005), J. Ramsay & Silverman (2002) and Frøslie (2014).

A.1 Traditional Approach to Curve Fitting in FDA

It can be shown that the smooth curve $x_i(t_j)$ can be well approximated by a linear combination of K weighted *basis functions*, $\phi_k(t)$, where $k = 1, 2, ..., K$. The number of basis functions is an exogenous parameter, decided outside the model.

$$x_i(t_j) \approx \sum_{k=1}^{K} c_{ki}\phi_k(t) = \mathbf{c}_i^T \phi(t), \tag{3}$$

where $\mathbf{c}_i = [c_{1i}, ..., c_{Ki}]$ is the unknown coefficients weighing each of the basis functions, $\phi(t) = [\phi_1(t), ..., \phi_K(t)]$. This means that the relationship between the original points of measure and the basis functions can be written as:

$$\hat{y}_i(t_j) = \sum_{k=1}^{K} c_{ki}\phi_k(t) + \varepsilon_{ij}, \tag{4}$$

which in matrix notation reads:

$$\mathbf{Y} = \mathbf{C\Phi} + \mathbf{E}. \tag{5}$$

In the hypothetical example where we have a complete, regularly sampled data set, $\mathbf{Y}$ is the 53×7277 matrix of observed cervical dilation measurements, $\mathbf{\Phi}$ is the $53 \times K$ matrix of the values of the K basis functions evaluated at time t_j, and $\mathbf{E}$ is the 53×7277 matrix of error terms. Finally, $\mathbf{C}$ is the $K \times 7277$ matrix of linear coefficients c_{ki}, which can be estimated by penalized least square estimation, minimizing:

$$(\mathbf{Y} - \mathbf{\Phi C})^T(\mathbf{Y} - \mathbf{\Phi C}) + \lambda \mathbf{C}^T \mathbf{R C}. \tag{6}$$

The roughness penalty term in the above expression compensate for random error, where λ is the smoothing parameter defining the degree of regularization, and $\mathbf{R}$ is the $K \times K$ matrix describing the curvature.

A.2 Traditional Functional Principal Component Analysis

Similarly to traditional PCA, each fitted curve can be expressed in terms of K principal components, as:

$$\hat{x}_i(t) = \sum_{k=1}^{K} f_{ik} \xi_k(t), \tag{7}$$

where f_{ik} is the score for parturient i in the principal component k, and $\xi_k(t)$ is the harmonic curve for principal component k.

To estimate the harmonic curves and the corresponding score, the weight function $\xi(t)$ is estimated by maximizing the variance of the corresponding FPC-score, given by $f_i = \int \xi(t) x_i(t) dt$. The first harmonic have the constraint $\int \xi_1(t)^2 = 1$, while subsequent harmonics have the additional constraint of being orthogonal to the previous harmonics, ensuring that every harmonic curve represent independent modes of variation.

Appendix B

Principal Analysis by Conditional Expectation (PACE) as described by Yao et al. (2005).

B.1 Details on Principal Analysis by Conditional Expectation (PACE)

As with the more traditional approach we use the model given in equation (1). Applying the Karhunen-Loève expansion, the smooth curve $x_i(t_j)$ can be disassembled into:

$$x_i(t_j) = \mu(t) + \sum_{k=1}^{\infty} \xi_{ik}\phi_k(t), \tag{8}$$

where $\mu(t)$ is the average curve evaluated at t, ξ_{ik} is the k'th FPC-score for individual i, and ϕ_k is the k'th harmonic. We assume that the unknown trajectories are well approximated by a set of K harmonics:

$$\hat{x}_i(t_j) = \hat{\mu}(t) + \sum_{k=1}^{K} \hat{\xi}_{ik}\hat{\phi}_k(t). \tag{9}$$

The mean curve, $\mu(t)$, is estimated based on the pooled data from all individuals using a local linear smoother. The harmonics and the FPC-scores are estimated based on the covariance surface:

$$G(s,t) = \text{cov}(X(s), X(t)), \tag{10}$$

which describes the variability and correlation of the functional data across time points s and t. First, the discrete covariances are caluculated seperately for each participant. These are given by:

$$G_i(T_{ij}, Til) = (Yij - \hat{\mu}(T_{ij}))(Y_{ij} - m\hat{u}(T_{il})). \tag{11}$$

Next, we can estimate the smooth covariance surface, $\hat{G}(s,t)$, using a local weighted bilinear smoother that aggregates the raw covariances from the participant.

Once the smooth covariance surface is estimated, the harmonic curves, ϕ_k, and eigenvalues, λ_k can be estimated by solving the following eigenequation:

$$\int_{\mathcal{T}} \hat{G}(s,t)\hat{\phi}_k(s)ds = \hat{\lambda}_k\hat{\phi}_k(t), \tag{12}$$

for $m < k$, under the constraints $||\hat{\phi}_k(t)|| = \int_{\mathcal{T}} \hat{\phi}_k(t)^2 dt = 1$ and $\int_{\mathcal{T}} \hat{\phi}_k(t) \times \hat{\phi}_m(t)dt = 0$, which ensures that the harmonics are orthonormal and independent.

Finally, known as the PACE-step, we can estimate the FPC-scores, ξ_{ik}. The estimated FPC-scores are expected values of the true, unknown FPC-scores, conditioned on the pooled set of weight measures for the given participant, i.

$$\hat{\xi}_{ik} = \hat{\mathrm{E}\mathrm{x}\mathrm{p}}[\hat{\xi}_{ik}|\mathbf{Y}_i] = \hat{\lambda}_k \hat{\boldsymbol{\phi}}_{ik}^T \hat{\boldsymbol{\Sigma}}_{\boldsymbol{Y}_i}^{-1}(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i), \tag{13}$$

where $\hat{\lambda}_k$ is the estimated eigenvalue for the harmonic k, $\hat{\boldsymbol{\phi}}_{ik}$ are vector corresponding to the estimated harmonic itself, $\hat{\boldsymbol{\Sigma}}_{\boldsymbol{Y}_i}$ is the estimated covariance matrix for the observed dilation measures of parturient i, and finally, $\hat{\boldsymbol{\mu}}_i$ is the vector that contain the estimated mean function.

Appendix C

C.1 Fraction of Variance Explained

The Fraction of Variance Explained is a measure of how much of the total variance each harmonic describes. It is given by the coefficient of determination, R^2, defined by:

$$R^2 = \frac{\mathrm{SSE}}{\mathrm{SST}}, \tag{14}$$

where SSE denotes the error sum of squares associated with the specific harmonic, and SST the total sum of squares (J. O. Ramsay & Silverman, 2005).

C.2 Min-max normalization

Also known as feature scaling, min-max normalisation is a method for rescaling the range of a set of values to a certain domain. The general formula maps the values to the interval $[0, 1]$, and is given by:

$$x' = \frac{x - \min(x)}{\max(x) - \min(x)}, \tag{15}$$

where x is a given value, $\max(x)$ is the maximum value in the set and $\min(x)$ is the minimum. Min-max normalization will squeeze or stretch the set of values to fit a given range (Zheng & Casari, 2002). In the specific case presented in this thesis, we wish to map the values to the active phase domain of $[4, 10]$ cm, in which case the equation becomes:

$$x' = 4 + \frac{(x - \min(x))(10 - 4)}{\max(x) - \min(x)}. \tag{16}$$

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