Event Based Models for Disease Progression

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1 Introduction

Event-based Model (EBM) is used to model the order of degenerative diseases. In another word, we want to estimate the order in which different biological factors ("biomarkers") get affected by a specific disease. The order is categorized by multiple **stages** in the disease progression.

For instance, Alzheimer may have the following stages:

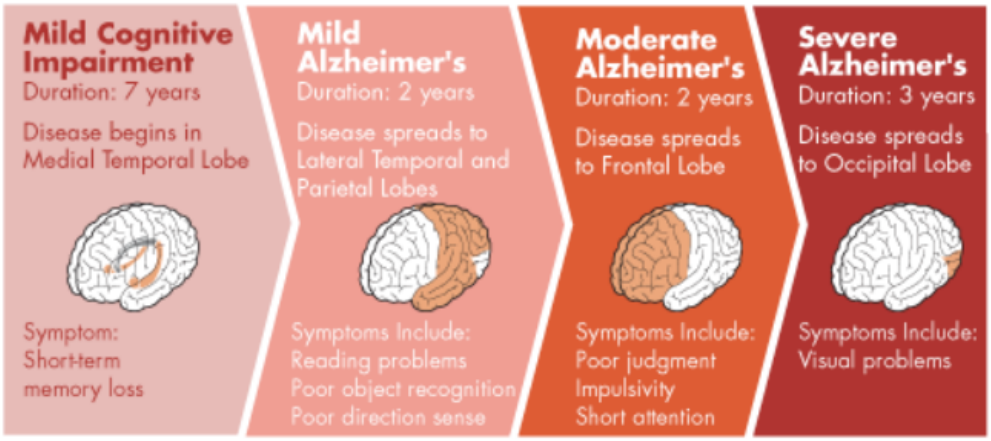


Figure 1.1: Alzheimer Disease Progression (Credit: https://preventad.com/alzheimers-disease/)

We estimate this order based on the biomarker data from patients' visits. These data are typically results of neuropsych (e.g., MMSE) and/or biological examiations (e.g., blood pressure). Visits data can be longitudinal and/or cross-sectional, i.e., single visits from a cohort of patients.

Knowing the disease progression is important because it helps prevent and hopefully cure the disease. It also helps health professionals prepare for the disease's further development.

We have several assumptions in EBM:

- The disease is irreversible (i.e., a patient cannot go from stage 2 to stage 1)
- The order in which different biomarkers get affected by the disease is the same across all patients.
- Biomarker data can be approximated by a Gaussian distribution.

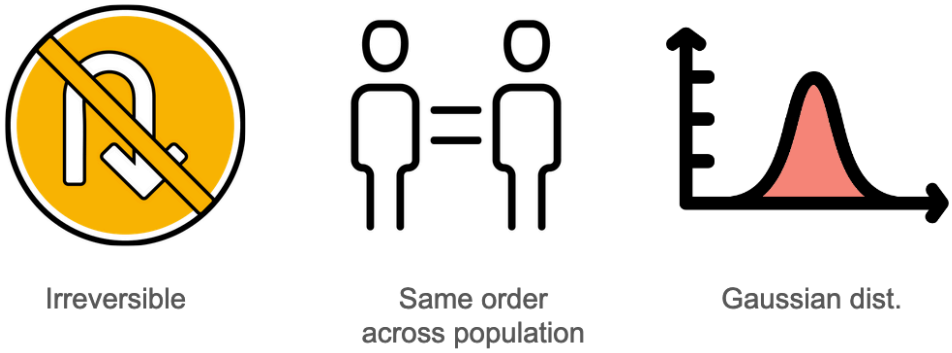


Figure 1.2: Assumptions of EBM

This book contains chapters that explain step by step how we use the event-based model to estimate the order of disease progression based on cross-sectional patients' biomarker data.

2 EBM as A Generative Model

We can use EBM to generate synthetic biomarker data if we know:

- The order (S) in which different biomarkers get affected by the disease.
- Parameters (i.e., mean and standard deviation) of biomarkers' distribution when they are affected (θ) and not affected (ϕ) by the disease.
- Stages (k_j) that each participant is in.

Data we can generate looks like this:

	participant	biomarker	measurement	k_j	S_n	affected_or_not	Diseased
0	67	HIP-FCI	22.478591	2	1	affected	True
1	67	HIP-GMI	-5.102497	2	3	not_affected	True
2	67	FUS-FCI	322.304772	2	5	not_affected	True
3	67	PCC-FCI	-5.690280	2	2	affected	True
4	67	FUS-GMI	6.345347	2	4	not_affected	True

Figure 2.1: Sample Data

This data is from a single participant.

As we mentioned above, to generate this data, we need to know:

- S, i.e., the order of biomarkers. In the above example, S is HIP-FCI, PCC-FCI, HIP-GMI, FUS-GMI, FUS-FCI.
- $\mathcal{N}(\theta_\mu, \theta_\sigma)$ and $\mathcal{N}(\phi_\mu, \phi_\sigma)$ for each of the five biomarkers, which are known but not shown directly here in the dataset.
- k_j, which is 2 in the above example.

We explain how this data is constructed in the following, column by column.

First, the `participant` id is 67. The `biomarker` indicates each of the five biomarkers examined and measured. The `measurement` is the biomarkers' measurement. `k_j` is the participant's stage. If this stage is above 0, it means `Diseased = True`. `S_n` indicates the n-th rank in the order. If `k_j < S_n`, it means the participant's stage hasn't reached that biomarker's rank; therefore, this biomarker is `not affected`. If `k_j >= S_n`, then this biomarker is `affected`.

If a biomarker is `affected`, then its measurement comes from $\mathcal{N}(\theta_\mu, \theta_\sigma)$ of that biomarker; if `not_affected`, $\mathcal{N}(\phi_\mu, \phi_\sigma)$.

2.1 Generative Process

The generative process of biomarker measurements can be described as:

$$X_{nj} \mid S, k_j, \theta_n, \phi_n \sim I(z_j = 1)\Big[I(S(n) \leq k_j)\, p(X_{nj} \mid \theta_n) + I(S(n) > k_j)\, p(X_{nj} \mid \phi_n)\Big] + \big(1 - I(z_j = 1)\big)\, p(X_{nj} \mid \phi \tag{2.1}$$

This model says that given that we know $S, k_j, \theta_n,$ and ϕ_n, we can draw the biomarker measurement from a distribution.

$S \sim \text{UniformPermutation}(\cdot)$

S follows a distribution of uniform permutation. That means the ordering of biomarkers is random.

$k_j \sim \text{DiscreteUniform}(N)$

k_j follows a discrete uniform distribution, which means a participant is equally likely to fall in a progression stage (e.g., from 0 to 5, where 0 indicate this participant is healthy.)

2.2 Graphical Explanation

In the following, we explain the generative model in three different scenarios using graphical models: (1) All participants are healthy; (2) Both healthy and diseased participants, but all biomarkers are affected among diseased people; (3) Both healthy and diseased participants, but we do not whether biomarkers are affected or not among patients.

2.2.1 Scenario 1

If all participants are healthy:

$$X_{nj} \sim p(X_{nj} \mid \phi_n) \tag{2.2}$$

Where

X_{nj} indicates the measurement of biomarker n in participant j.

ϕ_n represents $\mathcal{N}(\phi_\mu, \phi_\sigma)$ for biomarker n.

The graphical model would look like:

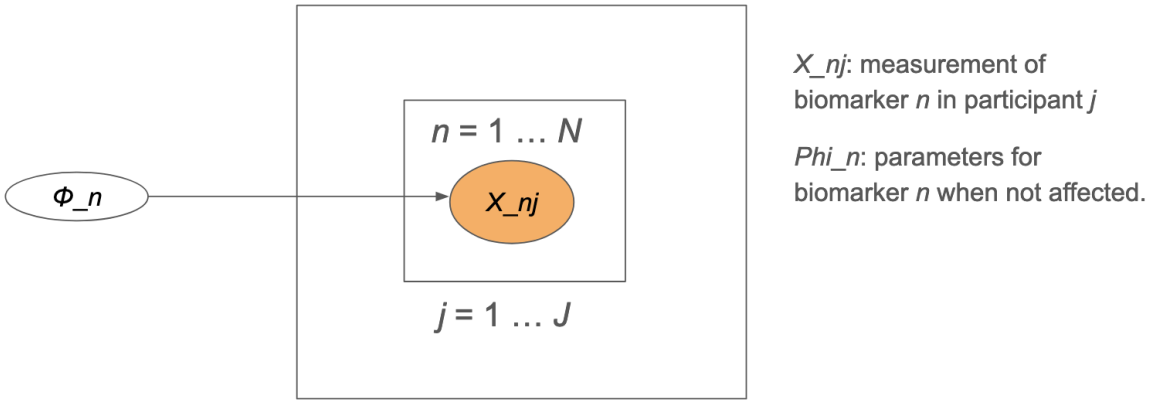


Figure 2.2: Graphical Model of Scenario 1

2.2.2 Scenario 2

If we have oth diseased and healthy participants, and all biomarkers are affected among diseased participants.

$$X_{nj} \sim I(z_j == 1)p(X_{nj} \mid \theta_n) + (1 - I(z_j == 1))p(X_{nj} \mid \phi_n) \tag{2.3}$$

Where:

$z_j = 1$ indicates this participant is diseased and $z_j = 1$ represents a healthy participant.

$I(True) = 1$ and $I(False) = 0$.

θ_n represents $\mathcal{N}(\theta_\mu, \theta_\sigma)$ for biomarker n.

The graphical model would look like:

2.2.3 Scenario 3

If we have both healthy and diseased participants, but we do not whether biomarkers are affected or not among patients, see Equation 2.1.

This is the model in usual cases.

The graphical model looks like:

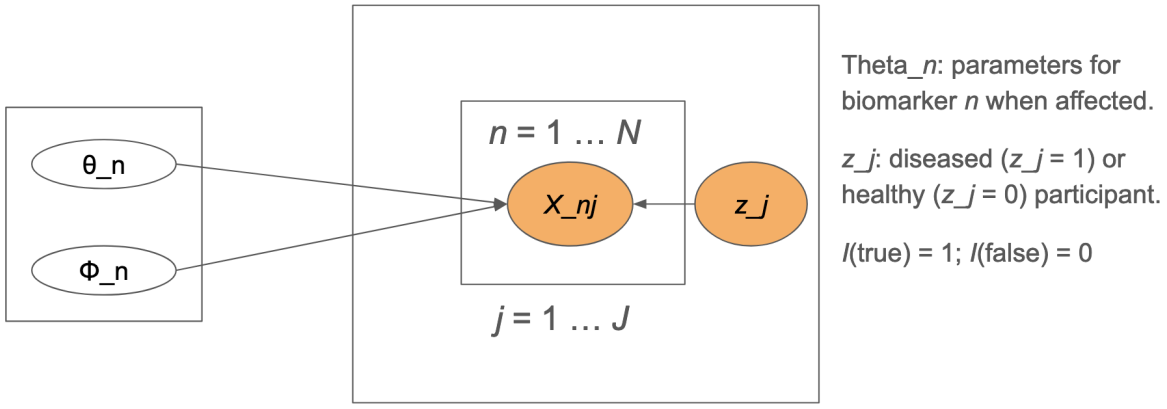


Figure 2.3: Graphical Model of Scenario 2

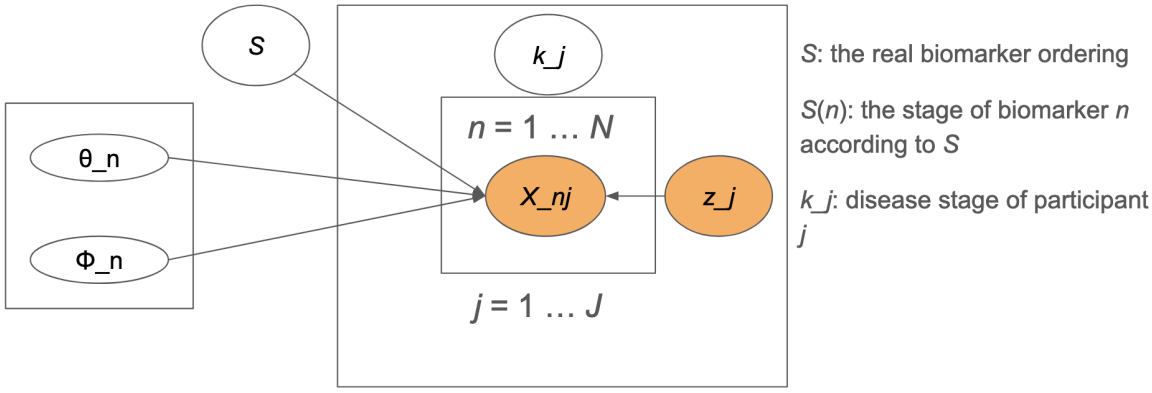


Figure 2.4: Graphical Model of Scenario 3

3 Calculating the Likelihood of Biomarker Measurements

Suppose we have a participant's data, for example, Figure 2.1. Now, the question is:

> What is the likelihood of this participant having this sequence of biomarker data, given that we know S, k_j, θ, ϕ.

In the following, we explain how to calculate this likelihood in two scenartios: (1) known k_j and (2) unknown k_j.

3.1 Known k_j

$$p(X_j|S, z_j = 1, k_j) = \underbrace{\prod_{i=1}^{k_j} p(X_{S(i)j} \mid \theta_{S(i)})}_{\text{Affected biomarker likelihood}} \underbrace{\prod_{i=k_j+1}^{N} p(X_{S(i)j} \mid \phi_{S(i)})}_{\text{Non-affected biomarker likelihood}} \tag{3.1}$$

This equation compuates the likelihood of the observed biomarker data of a specific participant, given that we know the disease stage this patient is at (k_j).

- S is an **orded array** of biomarkers that are affected by the disease, for example, $[b, a, d, c]$. This means that biomarker b is affected at stage 1. At stage 2, biomarker b and a will be affected.
- $S(i)$ is the i^{th} biomarker according to S. For example S_1 will be biomarker b.
- k_j indicates the stage the patient is at, for example, $k_j = 2$. This means that the disease has effected biomarker a and b. Biomarker c and d have not been affected yet.
- $\theta_{S(i)}$ is the parameters for the probability density function (PDF) of observed value of biomarker $S(i)$ when this biomarker has been affected by the disease. Let's assume this distribution is a Gaussian distribution with means of $[45, 50, 55, 60]$ and a standard deviation of 5 for biomarker b, a, d, and c.

- $\phi_{S(i)}$ is the parameters for the probability density function (PDF) of observed value of biomarker $S(i)$ when this biomarker has **NOT** been affected by the disease. Let's assume this distribution is a Gaussian distribution with means of $[25, 30, 35, 40]$ and a standard deviation of 3 for biomarker b, a, d, and c.
- X_j is an array representing the patient's observed data for all biomarker. Assume the data is $[77, 45, 53, 90]$ for biomarker b, a, d, and c.

We assume that the patient is at stage 2 of this disease; hence $k_j = 2$.

Next, we are going to calculate $p(X_j|S, z_j = 1, k_j)$:

When $i = 1$, we have $S_{(i)} = b$ and $X_{S_{(i)}} = X_b = 45$. So

$$p(X_{S_{(i)}}|\theta_{S(i)}) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{X_b - \mu}{\sigma}\right)^2}$$

Because $k_j = 2$, so biomarker b and a are affected. We should use the distribution of θ_b; therefore, we should plug in $\mu = 45, \sigma = 5$ in the above equation.

We can do the same for $i = 2$, 3, and 4.

So

$$p(X_j|S, k_j = 2) = p(X_b|\theta_b) \times p(X_a|\theta_a) \times p(X_d|\phi_d) \times p(X_c|\phi_c)$$

The above is the likelihood of the given biomarker data when $k_j = 2$.

Note that $p(X_b|\theta_b)$ is probability density, a value of a probability density function at a specific point; so it is not a probability itself.

Multiplying multiple probability densities will give us a likelihood.

3.2 Unknown k_j

$$P(X_j|S) = \sum_{k_j=0}^{N} P(k_j) p(X_j \mid S, k_j) \tag{3.2}$$

Suppose we have the same information above, except that we do not know at which disease stage the patient is, i.e., we do not know k_j. We have the observed biomarker data: $X_j = [77, 45, 53, 90]$. And I wonder: what is the likelihood of seeing this specific ovserved data?

We assume that all five stages (including $k_j = 0$) are equally likely.

We do not know k_j, so the best option is to calculate the "average" likelihood of all the biomarker data.

Based on Equation 3.1, we can calculate the following:

$L_1 = p(X_j|S, k_j = 1)$

$L_2 = p(X_j|S, k_j = 2)$

$L_3 = p(X_j|S, k_j = 3)$

$L_4 = p(X_j|S, k_j = 4)$

Also note that we need to consider L_0 because in the equation above, k_j starts from 0.

$$L_0 = p(X_j|S, k_j = 0) = p(X_b|\phi_b) \times p(X_a|\phi_a) \times p(X_d|\phi_d) \times p(X_c|\phi_c)$$

$$L_1 = p(X_j|S, k_j = 1) = p(X_b|\theta_b) \times p(X_a|\phi_a) \times p(X_d|\phi_d) \times p(X_c|\phi_c)$$

$$L_2 = p(X_j|S, k_j = 2) = p(X_b|\theta_b) \times p(X_a|\theta_a) \times p(X_d|\phi_d) \times p(X_c|\phi_c)$$

$$L_3 = p(X_j|S, k_j = 3) = p(X_b|\theta_b) \times p(X_a|\theta_a) \times p(X_d|\theta_d) \times p(X_c|\phi_c)$$

$$L_4 = p(X_j|S, k_j = 4) = p(X_b|\theta_b) \times p(X_a|\theta_a) \times p(X_d|\theta_d) \times p(X_c|\theta_c)$$

$P(k_j)$ is the prior likelihood of being at stage k. **Event based models assume a uniform prior on** k_j. Therefore:

$P(X_j|z_j = 1, S) = \frac{1}{5}(L_0 + L_1 + L_2 + L_3 + L_4)$

4 Generate Synthetic Data

In this chapter, we talk about how we generate the synthetic data of participants' biomarker measurements. These data are used to test our algorithms.

4.1 Obtain Estimated Distribution Parameters

In Chapter 2, we mentioned that EBM can be used as a generative model and we need to know S, θ, ϕ and k_j.

First, we obtained S, θ, ϕ from Chen et al. (2016):

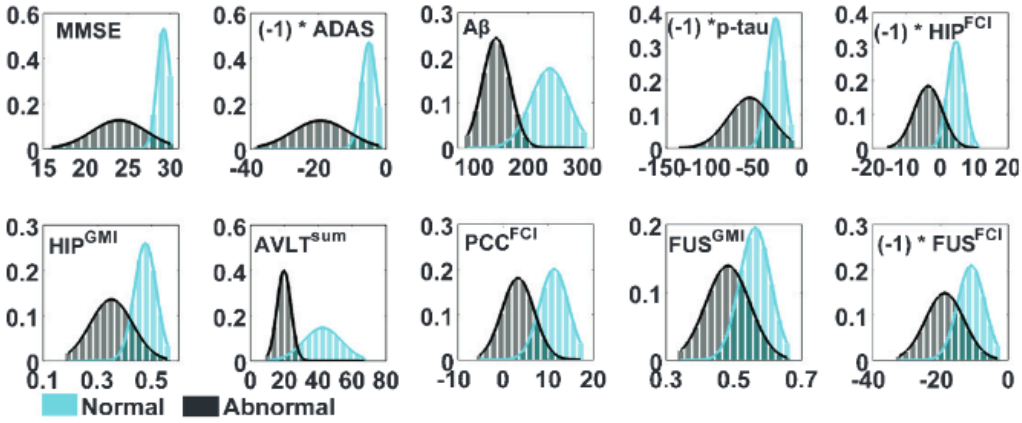


Fig. 1. Probability distributions of normal (cyan) and abnormal (black) events measured by biomarkers from the AD and CN populations. The y-axis denotes the proportion of subjects, while the x-axis indicates the detected value of each biomarker measurement. The (–1) is employed to reverse the signs of the biomarker, indicating the left distribution is an event that occurred and the right distribution is an event that did not occur.

Figure 4.1: Theta and Phi from Chen's Paper

This is our estimation:

```
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
import json
```

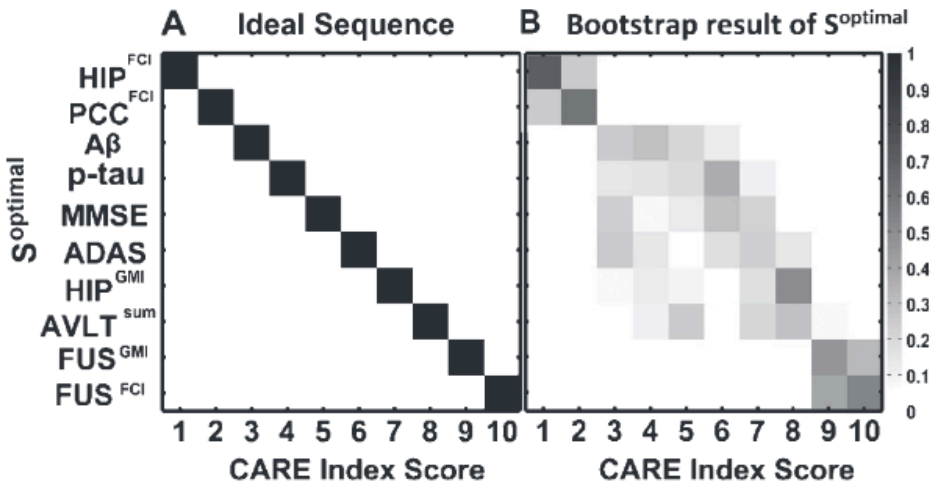


Fig. 2. Optimal temporal order, $S^{optimal}$, of the 10 AD biomarkers estimated by the EBP model. A) The y-axis shows the $S^{optimal}$ and the x-axis shows the CARE index score at which the corresponding event occurred. B) Bootstrap cross-validation of the $S^{optimal}$. Each entry in the matrix represents the proportion of the $S^{optimal}$ during 500 bootstrap samples. The proportion values range from 0 to 1 and correspond to color, from white to black. The CARE index scores with their corresponding biomarkers follow: 1, increased HIP^{FCI}; 2, decreased PCC^{FCI}; 3, decreased Aβ concentration; 4, increased p-tau concentration; 5, decreased MMSE score; 6, increased ADAS score; 7, decreased HIP^{GMI}; 8, decreased AVLT score; 9, decreased FUS^{GMI}; 10, increased FUS^{FCI}.

Figure 4.2: S from Chen's Paper

```
import scipy.stats as stats
from typing import List, Optional, Tuple, Dict
import os
import seaborn as sns
import altair as alt
```

```
all_ten_biomarker_names = np.array([
    'MMSE', 'ADAS', 'AB', 'P-Tau', 'HIP-FCI',
    'HIP-GMI', 'AVLT-Sum', 'PCC-FCI', 'FUS-GMI', 'FUS-FCI'])
# in the order above
# cyan, normal
phi_means = [28, -6, 250, -25, 5, 0.4, 40, 12, 0.6, -10]
# black, abnormal
theta_means = [22, -20, 150, -50, -5, 0.3, 20, 5, 0.5, -20]
# cyan, normal
phi_std_times_three = [2, 4, 150, 50, 5, 0.7, 45, 12, 0.2, 10]
phi_stds = [std_dev/3 for std_dev in phi_std_times_three]
# black, abnormal
theta_std_times_three = [8, 12, 50, 100, 20, 1, 20, 10, 0.2, 18]
theta_stds = [std_dev/3 for std_dev in theta_std_times_three]
```

```
# to get the real_theta_phi means and stds
hashmap_of_dicts = {}
for i, biomarker in enumerate(all_ten_biomarker_names):
    dic = {}
    # dic = {"biomarker": biomarker}
    dic['theta_mean'] = theta_means[i]
    dic['theta_std'] = theta_stds[i]
    dic['phi_mean'] = phi_means[i]
    dic['phi_std'] = phi_stds[i]
    hashmap_of_dicts[biomarker] = dic
hashmap_of_dicts

real_theta_phi = pd.DataFrame(hashmap_of_dicts).transpose().reset_index(names=['biomarker'])
real_theta_phi
```

	biomarker	theta_mean	theta_std	phi_mean	phi_std
0	MMSE	22.0	2.666667	28.0	0.666667
1	ADAS	-20.0	4.000000	-6.0	1.333333
2	AB	150.0	16.666667	250.0	50.000000
3	P-Tau	-50.0	33.333333	-25.0	16.666667
4	HIP-FCI	-5.0	6.666667	5.0	1.666667
5	HIP-GMI	0.3	0.333333	0.4	0.233333
6	AVLT-Sum	20.0	6.666667	40.0	15.000000
7	PCC-FCI	5.0	3.333333	12.0	4.000000
8	FUS-GMI	0.5	0.066667	0.6	0.066667
9	FUS-FCI	-20.0	6.000000	-10.0	3.333333

Store the parameters to a `JSON` file:

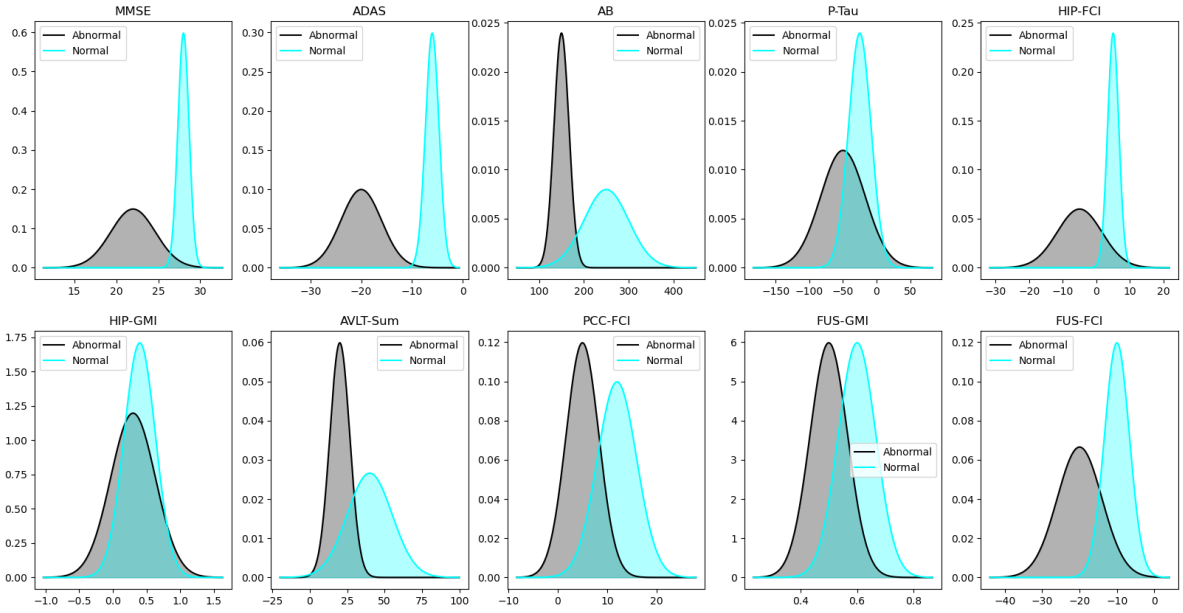
```
with open('files/real_theta_phi.json', 'w') as fp:
    json.dump(hashmap_of_dicts, fp)
```

```
biomarkers = all_ten_biomarker_names
n_biomarkers = len(biomarkers)

def plot_distribution_pair(ax, mu1, sigma1, mu2, sigma2, title):
    """mu1, sigma1: theta
    mu2, sigma2: phi
    """
```

```
    xmin = min(mu1 - 4*sigma1, mu2-4*sigma2)
    xmax = max(mu1 + 4*sigma1, mu2 + 4*sigma2)
    x = np.linspace(xmin, xmax, 1000)
    y1 = stats.norm.pdf(x, loc = mu1, scale = sigma1)
    y2 = stats.norm.pdf(x, loc = mu2, scale = sigma2)
    ax.plot(x, y1, label = "Abnormal", color = "black")
    ax.plot(x, y2, label = "Normal", color = "cyan")
    ax.fill_between(x, y1, alpha = 0.3, color = "black")
    ax.fill_between(x, y2, alpha = 0.3, color = "cyan")
    ax.set_title(title)
    ax.legend()

fig, axes = plt.subplots(2, n_biomarkers//2, figsize=(20, 10))
for i, biomarker in enumerate(biomarkers):
    ax = axes.flatten()[i]
    mu1, sigma1, mu2, sigma2 = real_theta_phi[
        real_theta_phi.biomarker == biomarker].reset_index().iloc[0, :][2:].values
    plot_distribution_pair(
        ax, mu1, sigma1, mu2, sigma2, title = biomarker)
```



You can compare this to Figure 4.1.

4.2 The Generating Process

In the following, we explain our data generation process.

We have the following parameters:

J: Number of participants.

R: The percentage of healthy participants.

M: Number of datasets per combination of j and r.

We set these parameters:

```
js = [50, 200, 500]
rs = [0.1, 0.25, 0.5, 0.75, 0.9]
num_of_datasets_per_combination = 50
```

So, there will be $3 \times 5 \times 50 = 750$ datasets to be generated.

We define our `generate_data_from_ebm` function:

```
def generate_data_from_ebm(
    n_participants: int,
    S_ordering: List[str],
    real_theta_phi_file: str,
    healthy_ratio: float,
    output_dir: str,
    m,  # combstr_m
    seed: Optional[int] = 0
) -> pd.DataFrame:
    """
    Simulate an Event-Based Model (EBM) for disease progression.

    Args:
    n_participants (int): Number of participants.
    S_ordering (List[str]): Biomarker names ordered according to the order
        in which each of them get affected by the disease.
    real_theta_phi_file (str): Directory of a JSON file which contains
        theta and phi values for all biomarkers.
        See real_theta_phi.json for example format.
    output_dir (str): Directory where output files will be saved.
    healthy_ratio (float): Proportion of healthy participants out of n_participants.
    seed (Optional[int]): Seed for the random number generator for reproducibility.
```

```
    Returns:
    pd.DataFrame: A DataFrame with columns 'participant', "biomarker", 'measurement',
        'diseased'.
    """
    # Parameter validation
    assert n_participants > 0, "Number of participants must be greater than 0."
    assert 0 <= healthy_ratio <= 1, "Healthy ratio must be between 0 and 1."

    # Set the seed for numpy's random number generator
    rng = np.random.default_rng(seed)

    # Load theta and phi values from the JSON file
    try:
        with open(real_theta_phi_file) as f:
            real_theta_phi = json.load(f)
    except FileNotFoundError:
        raise FileNotFoundError(f"File {real_theta_phi} not fount")
    except json.JSONDecodeError:
        raise ValueError(
            f"File {real_theta_phi_file} is not a valid JSON file.")

    n_biomarkers = len(S_ordering)
    n_stages = n_biomarkers + 1

    n_healthy = int(n_participants * healthy_ratio)
    n_diseased = int(n_participants - n_healthy)

    # Generate disease stages
    kjs = np.concatenate((np.zeros(n_healthy, dtype=int),
                          rng.integers(1, n_stages, n_diseased)))
    # shuffle so that it's not 0s first and then disease stages bur all random
    rng.shuffle(kjs)

    # Initiate biomarker measurement matrix (J participants x N biomarkers) with None
    X = np.full((n_participants, n_biomarkers), None, dtype=object)

    # Create distributions for each biomarker
    theta_dist = {biomarker: stats.norm(
        real_theta_phi[biomarker]['theta_mean'],
        real_theta_phi[biomarker]['theta_std']
    ) for biomarker in S_ordering}
```

```
    phi_dist = {biomarker: stats.norm(
        real_theta_phi[biomarker]['phi_mean'],
        real_theta_phi[biomarker]['phi_std']
    ) for biomarker in S_ordering}

    # Populate the matrix with biomarker measurements
    for j in range(n_participants):
        for n, biomarker in enumerate(S_ordering):
            # because for each j, we generate X[j, n] in the order of S_ordering,
            # the final dataset will have this ordering as well.
            k_j = kjs[j]
            S_n = n + 1

            # Assign biomarker values based on the participant's disease stage
            # affected, or not_affected, is regarding the biomarker, not the participant
            if k_j >= 1:
                if k_j >= S_n:
                    # rvs() is affected by np.random()
                    X[j, n] = (
                        j, biomarker, theta_dist[biomarker].rvs(random_state=rng), k_j, S_n,
                else:
                    X[j, n] = (j, biomarker, phi_dist[biomarker].rvs(random_state=rng),
                               k_j, S_n, 'not_affected')
            # if the participant is healthy
            else:
                X[j, n] = (j, biomarker, phi_dist[biomarker].rvs(random_state=rng),
                           k_j, S_n, 'not_affected')

    df = pd.DataFrame(X, columns=S_ordering)
    # make this dataframe wide to long
    df_long = df.melt(var_name="Biomarker", value_name="Value")
    data = df_long['Value'].apply(pd.Series)
    data.columns = ['participant', "biomarker",
                    'measurement', 'k_j', 'S_n', 'affected_or_not']

    # biomarker_name_change_dic = dict(
    #     zip(S_ordering, range(1, n_biomarkers + 1)))
    data['diseased'] = data.apply(lambda row: row.k_j > 0, axis=1)
    # data.drop(['k_j', 'S_n', 'affected_or_not'], axis=1, inplace=True)
    # data['biomarker'] = data.apply(
    #     lambda row: f"{row.biomarker} ({biomarker_name_change_dic[row.biomarker]})", axis=
```

```
    if not os.path.exists(output_dir):
        os.makedirs(output_dir)

    filename = f"{int(healthy_ratio*n_participants)}|{n_participants}_{m}"
    data.to_csv(f'{output_dir}/{filename}.csv', index=False)
    # print("Data generation done! Output saved to:", filename)
    return data
```

```
S_ordering = np.array([
    'HIP-FCI', 'PCC-FCI', 'AB', 'P-Tau', 'MMSE', 'ADAS',
    'HIP-GMI', 'AVLT-Sum', 'FUS-GMI', 'FUS-FCI'
])

# where the generated data will be saved
output_dir = 'data'

# We run the following only once; once the data is generated, we no longer run it
# We still show the codes to present our generation process
torun = False
```

```
if torun:
    real_theta_phi_file = 'files/real_theta_phi.json'
    for j in js:
        for r in rs:
            for m in range(0, num_of_datasets_per_combination):
                generate_data_from_ebm(
                    n_participants=j,
                    S_ordering=S_ordering,
                    real_theta_phi_file=real_theta_phi_file,
                    healthy_ratio=r,
                    output_dir=output_dir,
                    m=m,
                    seed = int(j*10 + (r * 100) + m),
                )
        print(f'Done for J={j}')
```

4.3 Visualize Synthetic Data

Above, we have generated 750 datasets, named in the fashion of `150|200_3`, which means the third dataset when $j = 200$ and $r = 0.75$.

Next, we try to visualize this dataset.

```
df = pd.read_csv(f"{output_dir}/150|200_3.csv")
df.head()
```

	participant	biomarker	measurement	k_j	S_n	affected_or_not	diseased
0	0	HIP-FCI	3.135981	0	1	not_affected	False
1	1	HIP-FCI	12.593704	2	1	affected	True
2	2	HIP-FCI	6.220776	0	1	not_affected	False
3	3	HIP-FCI	3.545100	0	1	not_affected	False
4	4	HIP-FCI	3.966541	0	1	not_affected	False

```
df.shape
```

```
(2000, 7)
```

This dataset has 2000 rows because we have 200 participants and 10 biomarkers.

4.3.1 Distribution of all biomarker values

```
alt.renderers.enable('png')
alt.Chart(df).transform_density(
    'measurement',
    as_=['measurement', 'Density'],
    groupby=['biomarker']
).mark_area().encode(
    x="measurement:Q",
    y="Density:Q",
    facet = alt.Facet(
        "biomarker:N",
        columns = 5
    ),
    color=alt.Color(
        'biomarker:N'
    )
).properties(
    width= 100,
    height = 180,
```

```
).properties(
    title='Distribution of biomarker measurments'
)
```

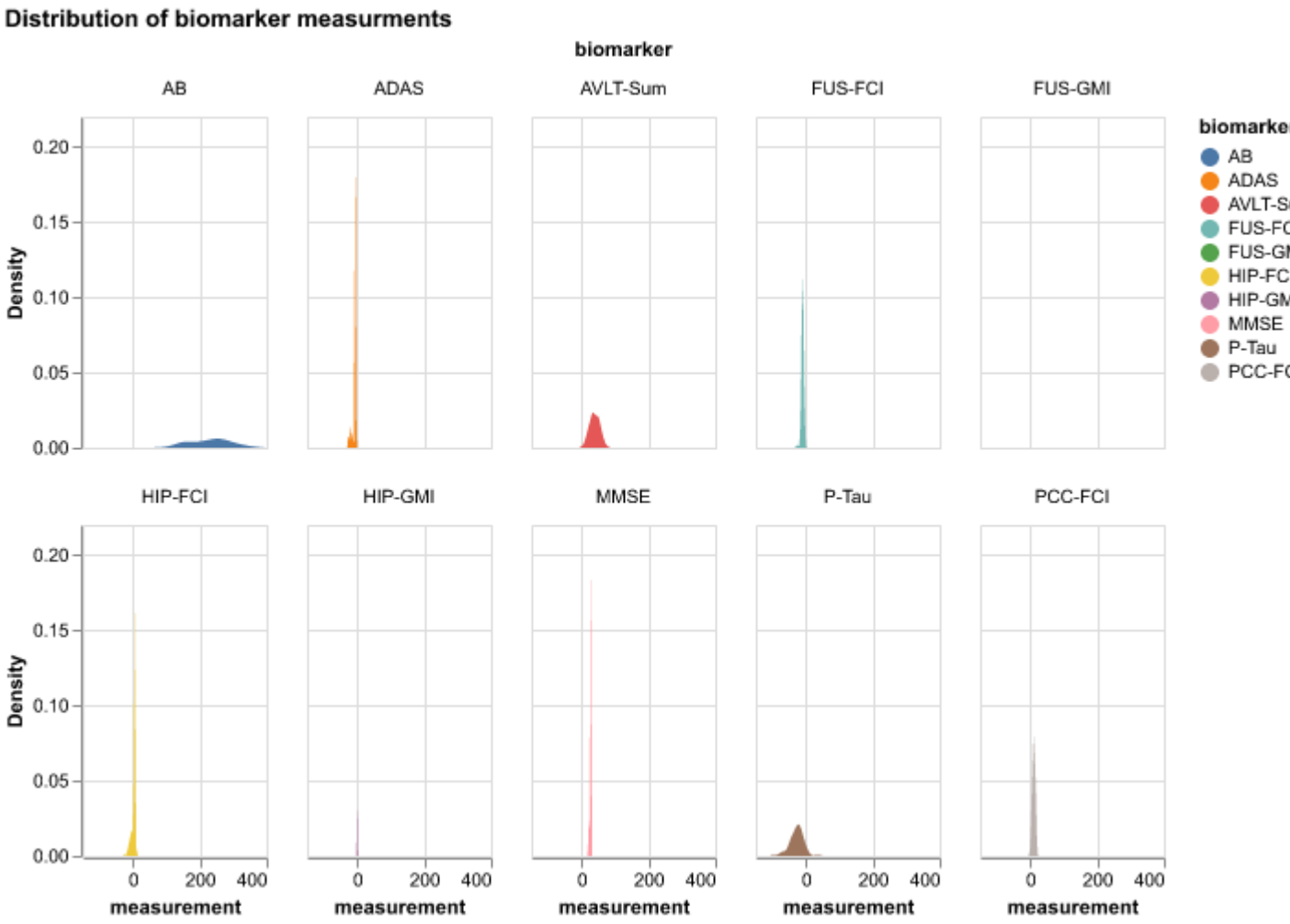


Figure 4.3: Distribution of biomarker measurments

4.3.2 Distribution of A Specific Biomarker

```
idx = 1
biomarkers = df.biomarker.unique()
bio_data = df[df.biomarker==biomarkers[idx]]
```

```
alt.Chart(bio_data).transform_density(
    'measurement',
    as_=['measurement', 'Density'],
    groupby=['affected_or_not']
).mark_area().encode(
    x="measurement:Q",
    y="Density:Q",
    facet = alt.Facet(
        "affected_or_not:N",
    ),
    color=alt.Color(
        'affected_or_not:N'
    )
).properties(
    width= 240,
    height = 200,
).properties(
    title=f'Distribution of {biomarker} measurements'
)
```

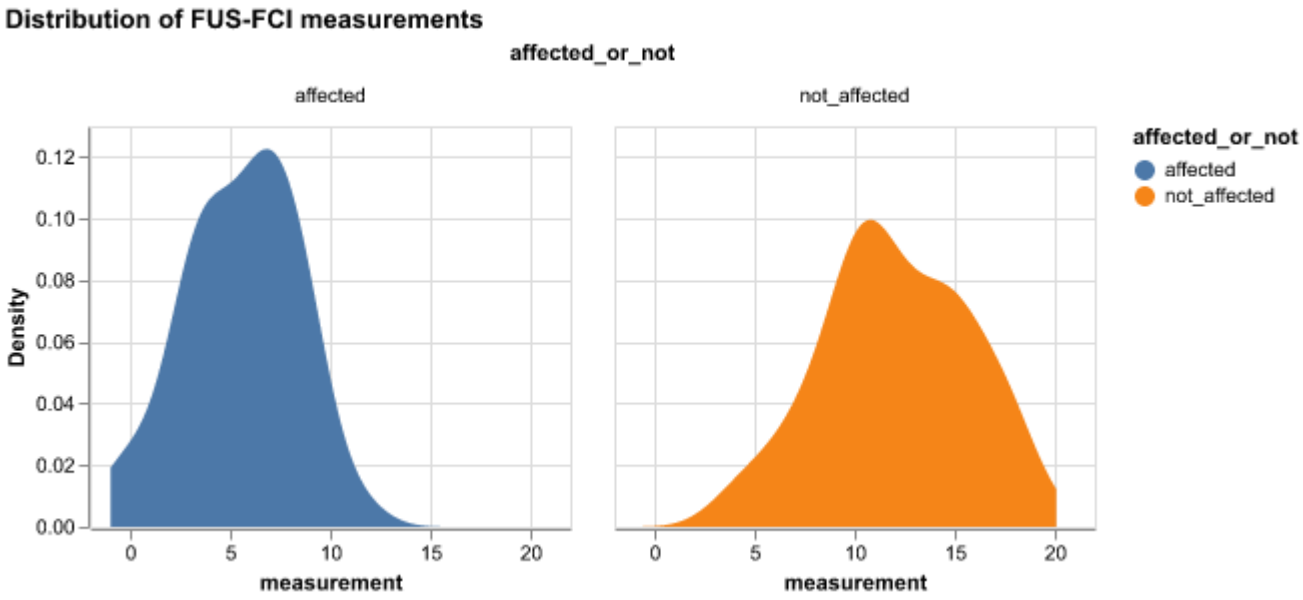


Figure 4.4: Distribution of HIP-FCI measurements, compring bewteen affected and non-affected group

4.3.3 Looking into A Specific Participant

```
pidx = 1
p_data = df[df.participant == pidx]
p_data
```

	participant	biomarker	measurement	k_j	S_n	affected_or_not	diseased
1	1	HIP-FCI	12.593704	2	1	affected	True
201	1	PCC-FCI	7.164017	2	2	affected	True
401	1	AB	182.033823	2	3	not_affected	True
601	1	P-Tau	-25.345325	2	4	not_affected	True
801	1	MMSE	27.600823	2	5	not_affected	True
1001	1	ADAS	-4.920415	2	6	not_affected	True
1201	1	HIP-GMI	0.099052	2	7	not_affected	True
1401	1	AVLT-Sum	30.270797	2	8	not_affected	True
1601	1	FUS-GMI	0.658954	2	9	not_affected	True
1801	1	FUS-FCI	-11.701559	2	10	not_affected	True

```
pidx =1 # participant index
p_data = df[df.participant == pidx]
alt.Chart(p_data).mark_bar().encode(
    x='biomarker',
    y='measurement',
    color=alt.Color(
        'affected_or_not:N'
    ),
    tooltip=['biomarker', 'affected_or_not', 'measurement']
).interactive().properties(
    title=f'Distribution of biomarker measurements for participant #{idx} (k_j = {p_data.k_j
)
```

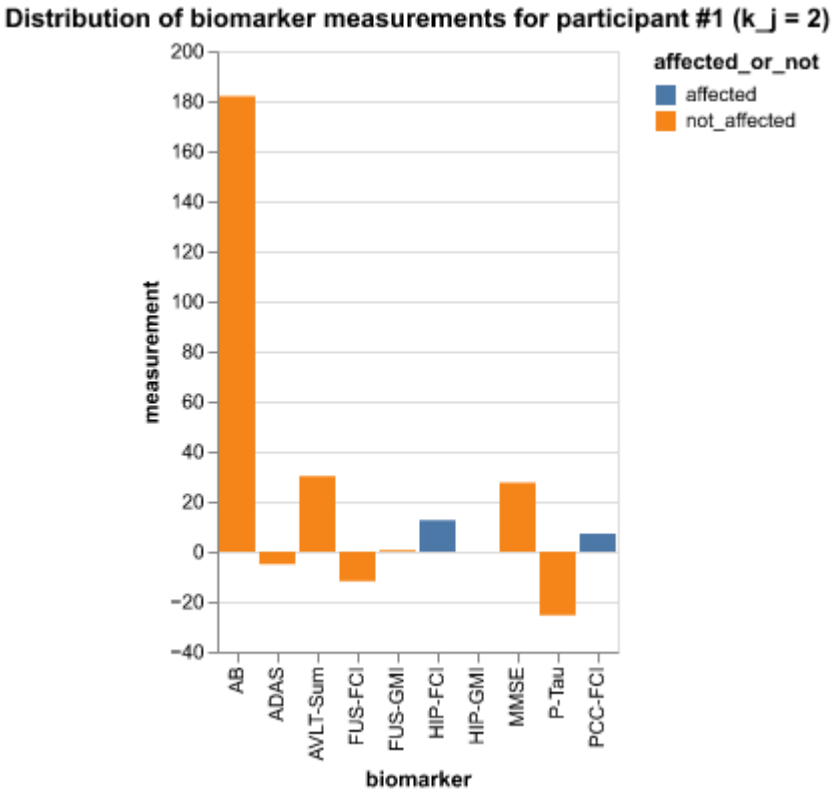


Figure 4.5: Distribution of biomarker measurements for a specific participant

5 Estimate Distribution Parameters

Given a biomarker's measurements, how can we estimate $\mathcal{N}(\theta_\mu, \theta_\sigma)$ and $\mathcal{N}(\phi_\mu, \phi_\sigma)$?

```
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
import altair as alt
import math
from scipy.stats import norm
from copkmeans.cop_kmeans import cop_kmeans
from typing import Dict
import re
import json
```

```
output_dir = 'data'
df = pd.read_csv(f"{output_dir}/150|200_3.csv")
biomarkers = df.biomarker.unique()
idx = 1
biomarker_df = df[df.biomarker==biomarkers[idx]]
biomarker_df.sample(10)
```

	participant	biomarker	measurement	k_j	S_n	affected_or_not	diseased
348	148	PCC-FCI	7.290860	6	2	affected	True
345	145	PCC-FCI	12.898988	0	2	not_affected	False
224	24	PCC-FCI	14.715956	0	2	not_affected	False
257	57	PCC-FCI	17.010971	0	2	not_affected	False
311	111	PCC-FCI	11.618309	0	2	not_affected	False
246	46	PCC-FCI	7.404043	6	2	affected	True
277	77	PCC-FCI	9.669905	0	2	not_affected	False
305	105	PCC-FCI	3.762252	7	2	affected	True
332	132	PCC-FCI	15.006273	0	2	not_affected	False
297	97	PCC-FCI	6.230812	0	2	not_affected	False

```
biomarker_df.shape
```

```
(200, 7)
```

5.1 Constrained K-Means

The first method we can use is constrained K-means, implemented by Babaki (2017).

We choose constrained K-Means instead of the standard K-Means algorithm because we know all healthy participants have to belong to the same cluster. The constrained K-Means algorithm can satisfy this constraint.

```
def compute_theta_phi_for_biomarker(biomarker_df):
    """get theta and phi parameters for this biomarker using constrained k-means
    input:
        - biomarker_df: a pd.dataframe of a specific biomarker
    output:
        - a tuple: theta_mean, theta_std, phi_mean, phi_std
    """
    n_clusters = 2
    measurements = np.array(biomarker_df['measurement']).reshape(-1, 1)
    healthy_df = biomarker_df[biomarker_df['diseased'] == False]
    must_link = [(x, 0) for x in healthy_df.index]
    # imeplement Constrained K-means algorithm
    # https://github.com/Behrouz-Babaki/COP-Kmeans
    clusters, centers = cop_kmeans(dataset=measurements, k=n_clusters, ml=must_link)
    predictions = np.array(clusters)
    healthy_predictions = predictions[healthy_df.index]

    # double check the result
    cluster_counts = np.bincount(predictions)
    if not all(c > 1 for c in cluster_counts):
        raise ValueError(f"Not all clusters have more than one node.")
    if len(cluster_counts) != n_clusters:
        raise ValueError(f"Number of clusters is not equal to {n_clusters}.")
    if len(set(healthy_predictions)) > 1:
        raise ValueError("Not all healthy participants belong to one cluster.")

    phi_cluster_idx = healthy_predictions[0]
    theta_cluster_idx = 1 - phi_cluster_idx
```

```
    # two empty clusters to strore measurements
    clustered_measurements = [[] for _ in range(2)]
    # Store measurements into their cluster
    for i, prediction in enumerate(predictions):
        clustered_measurements[prediction].append(measurements[i][0])

     # Calculate means and standard deviations
    theta_mean, theta_std = np.mean(
        clustered_measurements[theta_cluster_idx]), np.std(
            clustered_measurements[theta_cluster_idx])
    phi_mean, phi_std = np.mean(
        clustered_measurements[phi_cluster_idx]), np.std(
            clustered_measurements[phi_cluster_idx])

    # check whether the prior_theta_phi contain 0s or nan
    if math.isnan(theta_std) or theta_std == 0:
        raise ValueError(f"Invalid theta_std: {theta_std}")
    if math.isnan(phi_std) or phi_std == 0:
        raise ValueError(f"Invalid phi_std: {phi_std}")
    if theta_mean == 0 or math.isnan(theta_mean):
        raise ValueError(f"Invalid theta_mean: {theta_mean}")
    if phi_mean == 0 or math.isnan(phi_mean):
        raise ValueError(f"Invalid phi_mean: {phi_mean}")

    return theta_mean, theta_std, phi_mean, phi_std

def get_theta_phi_estimates(
    data: pd.DataFrame,
) -> Dict[str, Dict[str, float]]:
    """
    Obtain theta and phi estimates (mean and standard deviation) for each biomarker.

    Args:
    data (pd.DataFrame): DataFrame containing participant data with columns 'participant',
        'biomarker', 'measurement', and 'diseased'.
    # biomarkers (List[str]): A list of biomarker names.

    Returns:
    Dict[str, Dict[str, float]]: A dictionary where each key is a biomarker name,
        and each value is another dictionary containing the means and standard deviations
        for theta and phi of that biomarker, with keys 'theta_mean', 'theta_std', 'phi_mean'
        and 'phi_std'.
```

```
    """
    # empty hashmap of dictionaries to store the estimates
    estimates = {}
    biomarkers = data.biomarker.unique()
    for biomarker in biomarkers:
        # Filter data for the current biomarker
        # reset_index is necessary here because we will use healthy_df.index later
        biomarker_df = data[data['biomarker']
                            == biomarker].reset_index(drop=True)
        theta_mean, theta_std, phi_mean, phi_std = compute_theta_phi_for_biomarker(
            biomarker_df)
        estimates[biomarker] = {
            'theta_mean': theta_mean,
            'theta_std': theta_std,
            'phi_mean': phi_mean,
            'phi_std': phi_std
        }
    return estimates
```

```
estimates = get_theta_phi_estimates(data = df)
estimates_df = pd.DataFrame.from_dict(estimates, orient='index')
estimates_df.reset_index(names = 'biomarker', inplace=True)
estimates_df
```

	biomarker	theta_mean	theta_std	phi_mean	phi_std
0	HIP-FCI	-8.587833	5.365053	4.903437	2.008974
1	PCC-FCI	16.330398	0.720160	10.507041	4.427907
2	AB	288.610990	9.079334	229.407086	61.967583
3	P-Tau	-71.767059	15.231429	-23.737466	16.637657
4	MMSE	22.164115	1.555676	27.994652	0.832845
5	ADAS	-20.582091	3.853234	-6.002048	1.487443
6	HIP-GMI	0.114735	0.106857	0.404924	0.235082
7	AVLT-Sum	23.638988	5.848744	42.028039	14.229989
8	FUS-GMI	0.645942	0.019813	0.579887	0.067980
9	FUS-FCI	-19.200644	4.688806	-9.568412	3.003514

```
with open('files/real_theta_phi.json', 'r') as f:
    truth = json.load(f)
truth_df = pd.DataFrame.from_dict(truth, orient='index')
truth_df.reset_index(names = 'biomarker', inplace=True)
truth_df
```

	biomarker	theta_mean	theta_std	phi_mean	phi_std
0	MMSE	22.0	2.666667	28.0	0.666667
1	ADAS	-20.0	4.000000	-6.0	1.333333
2	AB	150.0	16.666667	250.0	50.000000
3	P-Tau	-50.0	33.333333	-25.0	16.666667
4	HIP-FCI	-5.0	6.666667	5.0	1.666667
5	HIP-GMI	0.3	0.333333	0.4	0.233333
6	AVLT-Sum	20.0	6.666667	40.0	15.000000
7	PCC-FCI	5.0	3.333333	12.0	4.000000
8	FUS-GMI	0.5	0.066667	0.6	0.066667
9	FUS-FCI	-20.0	6.000000	-10.0	3.333333

Now let's compare the results using plots:

```
def obtain_theta_phi_params(biomarker, estimate_df, truth):
    '''This is to obtain both true and estimated theta and phi params for each biomarker '''
    biomarker_data_est = estimate_df[estimate_df.biomarker == biomarker].reset_index()
    biomarker_data = truth[truth.biomarker == biomarker].reset_index()
    # theta for affected
    theta_mean_est = biomarker_data_est.theta_mean[0]
    theta_std_est = biomarker_data_est.theta_std[0]

    theta_mean = biomarker_data.theta_mean[0]
    theta_std = biomarker_data.theta_std[0]

    # phi for not affected
    phi_mean_est = biomarker_data_est.phi_mean[0]
    phi_std_est = biomarker_data_est.phi_std[0]

    phi_mean = biomarker_data.phi_mean[0]
    phi_std = biomarker_data.phi_std[0]

    return theta_mean, theta_std, theta_mean_est, theta_std_est, phi_mean, phi_std, phi_mean_

def make_chart(biomarkers, estimate_df, truth, title):
    alt.renderers.enable('png')
    charts = []
    for biomarker in biomarkers:
        theta_mean, theta_std, theta_mean_est, theta_std_est, phi_mean, phi_std, phi_mean_est
        biomarker, estimate_df, truth)
        mean1, std1 = theta_mean, theta_std
```

```
        mean2, std2 = theta_mean_est, theta_std_est

        # Generating points on the x axis
        x_thetas = np.linspace(min(mean1 - 3*std1, mean2 - 3*std2),
                               max(mean1 + 3*std1, mean2 + 3*std2), 1000)

        # Creating DataFrames for each distribution
        df1 = pd.DataFrame({'x': x_thetas, 'pdf': norm.pdf(x_thetas, mean1, std1), 'Distribut
        df2 = pd.DataFrame({'x': x_thetas, 'pdf': norm.pdf(x_thetas, mean2, std2), 'Distribut

        # Combining the DataFrames
        df3 = pd.concat([df1, df2])

        # Altair plot
        chart_theta = alt.Chart(df3).mark_line().encode(
            x='x',
            y='pdf',
            color=alt.Color('Distribution:N', legend=alt.Legend(title="Theta"))
        ).properties(
            title=f'{biomarker}, Theta',
            width=100,
            height=100
            )

        mean1, std1 = phi_mean, phi_std
        mean2, std2 = phi_mean_est, phi_std_est

        # Generating points on the x axis
        x_phis = np.linspace(min(mean1 - 3*std1, mean2 - 3*std2),
                               max(mean1 + 3*std1, mean2 + 3*std2), 1000)

        # Creating DataFrames for each distribution
        df1 = pd.DataFrame({'x': x_phis, 'pdf': norm.pdf(x_phis, mean1, std1), 'Distribution
        df2 = pd.DataFrame({'x': x_phis, 'pdf': norm.pdf(x_phis, mean2, std2), 'Distribution

        # Combining the DataFrames
        df3 = pd.concat([df1, df2])

        # Altair plot
        chart_phi = alt.Chart(df3).mark_line().encode(
            x='x',
            y='pdf',
```

```
            color=alt.Color('Distribution:N', legend=alt.Legend(title="Phi"))
        ).properties(
            title=f'{biomarker}, Phi',
            width=100,
            height=100
            )

        # Concatenate theta and phi charts horizontally
        hconcat_chart = alt.hconcat(chart_theta, chart_phi).resolve_scale(color="independent"

        # Append the concatenated chart to the list of charts
        charts.append(hconcat_chart)
    # Concatenate all the charts vertically
    final_chart = alt.vconcat(*charts).properties(title = title)

    # Display the final chart
    final_chart.display()
```

```
make_chart(biomarkers[0:4],
           estimates_df,
           truth_df,
           title = "Comparing Theta and Phi Distributions Using Constrained K-Means")
```

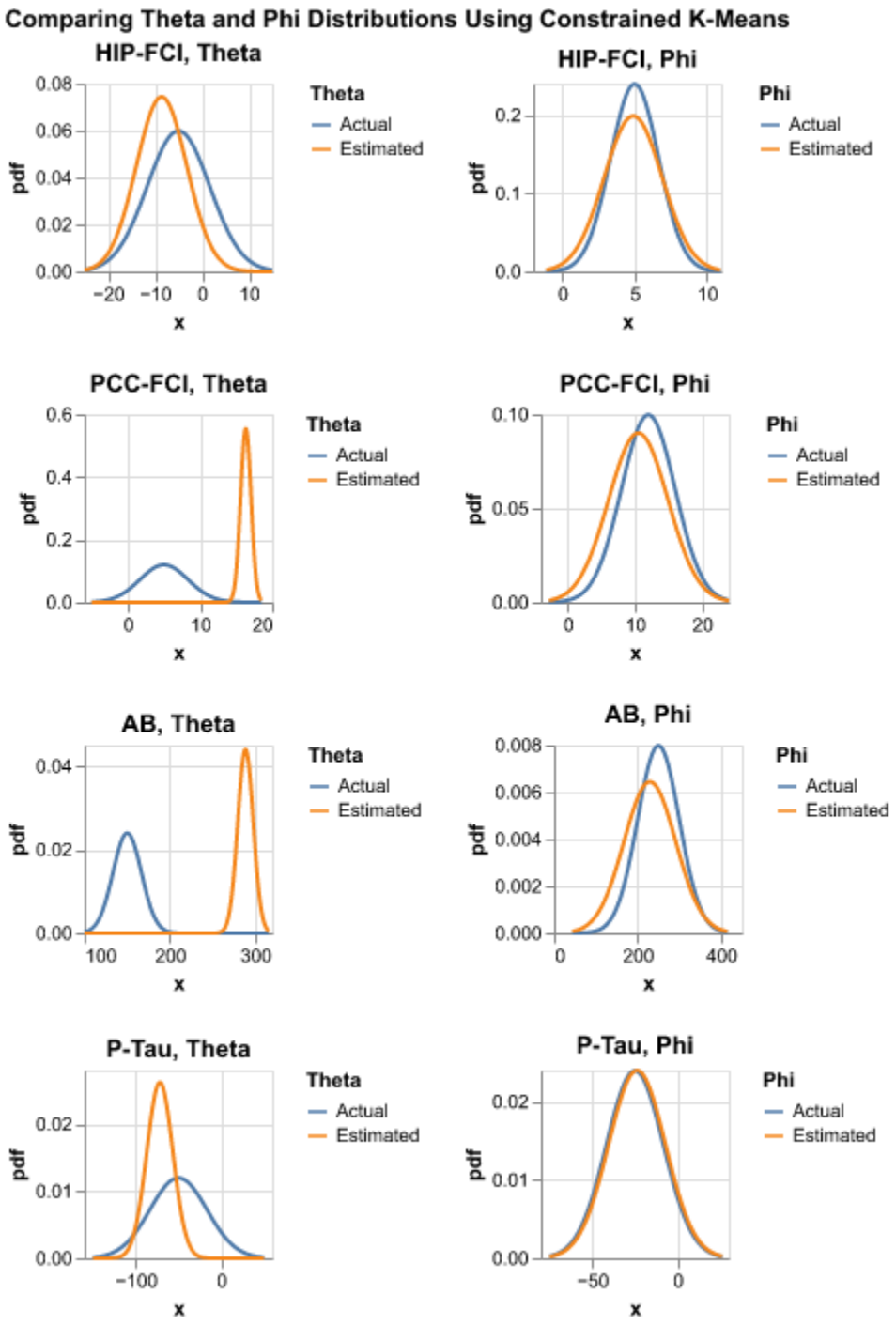


Figure 5.1: Comparing Theta and Phi Distributions Using Constrained K-Means

It turns out the result is generally okay.

5.2 Conjugate Priors

The second method we may utilize is conjugate priors. Conjugacy occurs when the posterior distribution is in the same family of distribution as the prior distribution, but with new parameter values.

Why conjugacy is important? Because without it, one has to do the integration, which oftentimes is hard.

Three major conjugate families:

- Beta-Binomial
- Gamma-Poisson
- Normal-Normal

In our example, we assume that the measurement data for each biomarker follows a normal distribution; however, we do not know the exact μ and σ. Our job is to estimate the two parameters for each biomarker based on the data we have.

According to *An Introduction to Bayesian Thinking* by Clyde et al. (2022), if the data comes from a normal distribution with unknown μ and σ, the conjugate prior for μ has a normal distribution with mean m_0 and variance $\frac{\sigma^2}{n_0}$. The conjugate prior for $\frac{1}{\sigma^2}$ has a Gamma distribution with shape $\frac{v_0}{2}$ and rate $\frac{v_0 s_0^2}{2}$ where

- m_0: prior estimate of μ.
- n_0: how strongly is the prior belief in m_0 is held.
- s_0^2: prior estimate of σ^2.
- v_0: prior degress of freedome, influencing the certainty of s_0^2.

That is to say:

$$\mu|\sigma^2 \sim \mathcal{N}(m_0, \sigma^2/n_0)$$

$$1/\sigma^2 \sim Gamma\left(\frac{v_0}{2}, \frac{v_0 s_0^2}{2}\right)$$

Combined, we have:

$$(\mu, 1/\sigma^2) \sim NormalGamma(m_0, n_0, s_0^2, v_0)$$

The posterior also follows a Normal-Gamma distribution:

$$(\mu, 1/\sigma^2)|data \sim NormalGamma(m_n, n_n, s_n^2, v_n)$$

More specifically

$$1/\sigma^2|data \sim Gamma(v_n/2, s_n^2 v_n/2)$$

$$\mu|data, \sigma^2 \sim \mathcal{N}(m_n, \sigma^2/n_n)$$

Based on the above two equations, we know that the mean of posterior mean is m_n and the mean of the posterior variance is $(s_n^2 v_n/2)/(v_n/2)$. This is beceause the expected value of $Gamma(\alpha, \beta)$ is $\frac{\alpha}{\beta}$.

where

- m_n: posterior mean, mode, and median for μ
- n_n: posterior sample size
- s_n^2: posterior variance
- v_n: posterior degrees of freedome

The updating rules to get the new hyper-parameters:

$$m_n = \frac{n}{n+n_0}\bar{y} + \frac{n_0}{n+n_0}m_0$$

$$n_n = n_0 + n$$

$$v_n = v_0 + n$$

$$s_n^2 = \frac{1}{v_n}\left[s^2(n-1) + s_0^2 v_0 + \frac{n_0 n}{n_n}(\bar{y} - m_0)^2\right]$$

where

- n: sample size
- $\bar{y}$: sample mean
- s^2: sample variance

```
def estimate_params_exact(m0, n0, s0_sq, v0, data):
    '''This is to estimate means and vars based on conjugate priors
    Inputs:
        - data: a vector of measurements
        - m0: prior estimate of $\mu$.
        - n0: how strongly is the prior belief in $m_0$ is held.
        - s0_sq: prior estimate of $\sigma^2$.
        - v0: prior degress of freedome, influencing the certainty of $s_0^2$.

    Outputs:
        - mu estiate, std estimate
    '''
    # Data summary
    sample_mean = np.mean(data)
    sample_size = len(data)
    sample_var = np.var(data, ddof=1)  # ddof=1 for unbiased estimator

    # Update hyperparameters for the Normal-Inverse Gamma posterior
    updated_m0 = (n0 * m0 + sample_size * sample_mean) / (n0 + sample_size)
    updated_n0 = n0 + sample_size
    updated_v0 = v0 + sample_size
    updated_s0_sq = (1 / updated_v0) * ((sample_size - 1) * sample_var + v0 * s0_sq +
                                        (n0 * sample_size / updated_n0) * (sample_mean - m0)
    updated_alpha = updated_v0/2
    updated_beta = updated_v0*updated_s0_sq/2

    # Posterior estimates
    mu_posterior_mean = updated_m0
    sigma_squared_posterior_mean = updated_beta/updated_alpha

    mu_estimation = mu_posterior_mean
    std_estimation = np.sqrt(sigma_squared_posterior_mean)

    return mu_estimation, std_estimation

def get_theta_phi_conjugate_priors(biomarkers, data_we_have, theta_phi_kmeans):
    '''To get estimated parameters, returns a hashmap
    Input:
    - biomarkers: biomarkers
    - data_we_have: participants data filled with initial or updated participant_stages
    - theta_phi_kmeans: a hashmap of dicts, which are the prior theta and phi values
        obtained from the initial constrained kmeans algorithm
```

```
    Output:
    - a hashmap of dictionaries. Key is biomarker name and value is a dictionary.
    Each dictionary contains the theta and phi mean/std values for a specific biomarker.
    '''
    # empty list of dictionaries to store the estimates
    hashmap_of_means_stds_estimate_dicts = {}

    for biomarker in biomarkers:
        # Initialize dictionary outside the inner loop
        dic = {'biomarker': biomarker}
        for affected in ['affected', 'not_affected']:
            data_full = data_we_have[(data_we_have.biomarker == biomarker) & (
                data_we_have.affected_or_not == affected)]
            if len(data_full) > 1:
                measurements = data_full.measurement
                s0_sq = np.var(measurements, ddof=1)
                m0 = np.mean(measurements)
                mu_estimate, std_estimate = estimate_params_exact(
                    m0=m0, n0=1, s0_sq=s0_sq, v0=1, data=measurements)
                if affected == 'affected':
                    dic['theta_mean'] = mu_estimate
                    dic['theta_std'] = std_estimate
                else:
                    dic['phi_mean'] = mu_estimate
                    dic['phi_std'] = std_estimate
            # If there is only one observation or not observation at all, resort to theta_phi
            # YES, IT IS POSSIBLE THAT DATA_FULL HERE IS NULL
            # For example, if a biomarker indicates stage of (num_biomarkers), but all partic
            # are smaller than that stage; so that for all participants, this biomarker is no
            else:
                print('not enough data here, so we have to use theta phi estimates from const
                # print(theta_phi_kmeans)
                if affected == 'affected':
                    dic['theta_mean'] = theta_phi_kmeans[biomarker]['theta_mean']
                    dic['theta_std'] = theta_phi_kmeans[biomarker]['theta_std']
                else:
                    dic['phi_mean'] = theta_phi_kmeans[biomarker]['phi_mean']
                    dic['phi_std'] = theta_phi_kmeans[biomarker]['phi_std']
        # print(f"biomarker {biomarker} done!")
        hashmap_of_means_stds_estimate_dicts[biomarker] = dic
    return hashmap_of_means_stds_estimate_dicts
```

```
conjugate_prior_theta_phi = get_theta_phi_conjugate_priors(
    biomarkers = biomarkers,
    data_we_have = df,
    theta_phi_kmeans = estimates
)
cp_df = pd.DataFrame.from_dict(conjugate_prior_theta_phi, orient='index')
cp_df.reset_index(drop=True, inplace=True)
cp_df
```

	biomarker	theta_mean	theta_std	phi_mean	phi_std
0	HIP-FCI	-5.378366	7.233991	5.092800	1.514402
1	PCC-FCI	5.521792	2.777207	12.071769	3.671679
2	AB	151.143708	14.806694	251.973564	51.382188
3	P-Tau	-41.768257	34.857945	-24.739527	14.928907
4	MMSE	23.122406	2.446874	28.049683	0.718493
5	ADAS	-19.633304	4.582900	-5.902198	1.278311
6	HIP-GMI	0.425625	0.272876	0.379542	0.235348
7	AVLT-Sum	21.664360	3.755735	40.700638	14.480463
8	FUS-GMI	0.482745	0.055585	0.590434	0.063730
9	FUS-FCI	-18.566905	5.781937	-9.648705	3.099195

```
make_chart(
    biomarkers[0:4],
    cp_df,
    truth_df,
    title = "Comparing Theta and Phi Distributions Using Conjugate Priors"
)
```

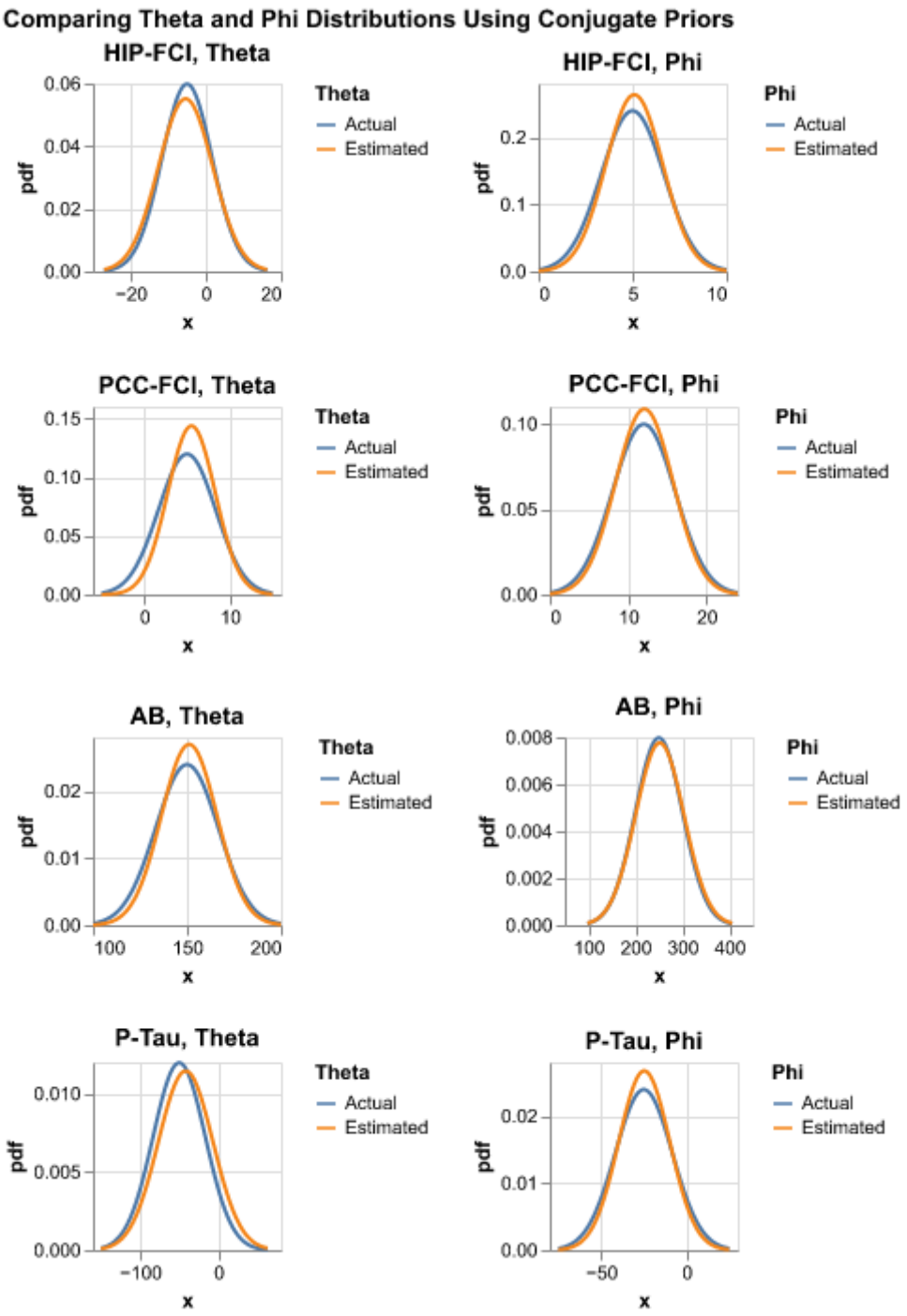


Figure 5.2: Comparing Theta and Phi Distributions Using Conjugate Prior

5.3 Conclusion

The result from conjugate priors looks better than that from constrained kmeans. However, to use conjugate priors, we assume that we know S and k_j for each participant, which are very hardly known. The constrained kmeans algorithm does not require any prior knowledge of S nor k_j.

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