An Analytics Approach to Hypertension Treatment

by

Christina Epstein

Submitted to the Sloan School of Management
in partial fulfillment of the requirements for the degree of

Master of Science in Operations Research

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2014

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Abstract

Hypertension is a major public health issue worldwide, affecting more than a third of the adult population and increasing the risk of myocardial infarction, heart failure, stroke, and kidney disease. Current clinical guidelines have yet to achieve consensus and continue to rely on expert opinion for recommendations lacking a sufficient evidence base. In practice, trial and error is typically required to discover a medication combination and dosage that works to control blood pressure for a given patient. We propose an analytics approach to hypertension treatment: applying visualization, predictive analytics methods, and optimization to existing electronic health record data to (1) find conjectures parallel and potentially orthogonal to guidelines, (2) hasten response time to therapy, and/or (3) optimize therapy selection. This thesis presents work toward these goals including data preprocessing and exploration, feature creation, the discovery of clinically-relevant clusters based on select blood pressure features, and three development spirals of predictive models and results.

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Acknowledgments

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# Contents

1 Introduction ...................................................... 13  
   1.1 Motivation .................................................. 13  
   1.2 Current Treatment Guidelines .............................. 13  
   1.3 Research Goals .......................................... 16  
   1.4 Structure ................................................ 17  

2 Data ........................................................................... 19  
   2.1 Boston Medical Center ........................................ 19  
   2.2 Patient Inclusion Criteria ................................... 19  
   2.3 Data Fields .................................................. 20  
      2.3.1 Demographics ............................................ 21  
      2.3.2 Blood pressure ........................................... 23  
      2.3.3 Weight and BMI ......................................... 23  
      2.3.4 Antihypertensive Medications ......................... 24  

3 Data Exploration ..................................................... 31  
   3.1 Feature Creation ............................................. 31  
   3.2 Blood Pressure Trajectory Clusters ......................... 31  

4 Predicting Blood Pressure Trajectory .......................... 39  
   4.1 Model 1: Initial Attempt .................................... 39  
   4.2 Model 2: Predict Cluster .................................... 40  
   4.3 Model 3: Median Initial and Final Blood Pressure ........... 47
List of Figures

2-1 Patient inclusion criteria ................................................. 20
2-2 Distribution of sex in selected patient population. .................. 21
2-3 Distribution of patient age at time of visit, and birth-date, in selected population. ......................................................... 22
2-4 Distribution of race in selected patient population................... 22
2-5 Example patient: clear blood pressure trajectory, three antihypertensive medication classes. .................................................... 24
2-6 Example patient: dense, noisy blood pressure measurements and many antihypertensive medications. ................................. 25
2-7 Distribution of blood pressure measurements in patient study population. 26
2-8 Duration of blood pressure measurement history in selected patient population. ............................................................. 27
2-9 Weight and BMI measurement for two example patients. .......... 27
2-10 Distribution of weight and BMI measurements in selected patient population. .............................................................. 28
2-11 Distribution of patient count by antihypertensive drug class prescribed ................................................................. 29
2-12 Distribution of patient count, by antihypertensive drug class and cumulative length of drug prescriptions. ............................... 30
3-1 Dendrogram for hierarchical clustering on blood pressure features .. 34
3-2 Clustering on blood pressure features: cluster sizes .................... 35
3-3 Final selection of (normalized) blood pressure variables for clustering: comparison between clusters ................................. 37
A-1 Start bin: 140+, CART classification .............................. 59
A-2 Start bin: 140+, RF classification ................................. 60
A-3 Random Forest classification for cluster 6 in <120 starting bin: variable importance for decreasing node impurity .................. 63
A-4 Random Forest regression for cluster 6 in <120 starting bin: variable importance for decreasing node impurity .................. 64
# List of Tables

1.1 Hypertension definitions from JNC 7 report ........................................ 14
1.2 Notes for demographic sub-populations from the JNC 7 report [2] .... 15
1.3 Complementary approaches: medical studies vs. analytics on EHR ... 16

2.1 Antihypertensive drug classes, as used in this work ......................... 28

3.1 Feature creation: options for summarizing temporal data ............... 32
3.2 Blood pressure features used for clustering ................................. 35
3.3 Cluster descriptions, plus trends by cluster for features not used in cluster creation ................................................................. 36

4.1 Non-blood-pressure features, used (or tried) as independent variables for prediction ................................................................. 41
4.2 Out-of-sample results: cluster by blood pressure features to create dependent variable, predict cluster using non-blood-pressure features. 43
4.3 Out-of-sample results: subset or group blood pressure clusters to create dependent variable for predictive models ......................... 44
4.4 Out-of-sample results: cluster by blood pressure features, split, predict cluster in each segment ......................................................... 46
4.5 Out-of-sample results: group (rather than cluster) by systolic blood pressure, predict group using other features ........................... 47
4.6 Count of patients, segmented by initial and final blood pressure (75% of total data) ................................................................. 48
4.7 Out-of-sample results: predict final blood pressure, segmented by starting blood pressure ........................................ 49

5.1 Feature importance for prediction: general trends from Sections 4.2 and 4.3, using CART, RF, and linear/logistic regression. .................. 52

A.1 Start bin: 140+, logistic regression (w/ sequential removal of high p-value variables) ................................................. 58

A.2 Best results for segmenting by initial blood pressure, clustering within each segment, and then predicting final-year blood pressure for each bin-cluster sub-group. ("class." is model accuracy minus baseline accuracy, "regress." is $R^2$) .................................................. 62

B.1 Results for predicting blood pressure trajectory separately for diabetic and non-diabetic patients ........................................... 66
Chapter 1

Introduction

1.1 Motivation

High blood pressure, or hypertension, is one of the major public health issues facing the world today. Of US adults, age 20 or older, 78 million, or 33% have hypertension, and only 53% of them have it controlled [4]. An additional 30% of the population is prehypertensive [5]. Worldwide, 40% of the over-25-year-old population has hypertension: with frequency ranging from 35% in the Americas to 46% in Africa [10]. High blood pressure increases the risk of myocardial infarction, heart failure, stroke, and kidney disease. In fact, the risk doubles for every 20 mm Hg systolic or 10 mm Hg diastolic increase, starting at 115/75 mm Hg (top end of “normal” range) [2]. Currently 1 in 3 deaths worldwide (17 million annually) are due to cardiovascular disease [10, 9]. The US spends an estimated $46.4 billion annually on the direct and indirect costs of hypertension [4]. The World Health Organization projects lost output due to cardiovascular disease for low and middle-income countries at approximately 2% of GDP in the years 2011 to 2025 [10].

1.2 Current Treatment Guidelines

In 2003, the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) issued a report reviewing and
Blood Pressure

<table>
<thead>
<tr>
<th>Normal</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehypertension</td>
<td>120 – 139</td>
<td>80 – 89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>≥ 140</td>
<td>90 – 99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥ 160</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Crisis</td>
<td>≥ 180</td>
<td>≥ 110</td>
</tr>
</tbody>
</table>

Table 1.1: Hypertension definitions from JNC 7 report

summarizing evidence and expert consensus into a concise guide for use by clinicians [2, 1]. In late 2013, multiple organizations released updated guidelines [7, 6, 11, 3]. While many aspects of these recent guidelines agree, with each other and the JNC 7 report, their differences highlight the uncertainty in best-practice for hypertension treatment [13].

Key points of the JNC 7 guidelines are:

1. Hypertension definitions as in Table 1.1.

2. Lifestyle modifications recommended for patients with prehypertension: weight reduction (if overweight or obese), adoption of a DASH diet (Dietary Approaches to Stop Hypertension), sodium reduction, increased physical activity, and moderation of alcohol consumption.

3. For hypertensive patients, treatment with medication (see Table 2.1) is advised (in addition to lifestyle modifications).

4. Patients should generally start with a thiazide diuretic, ACE inhibitor, ARB, calcium-channel blocker or β-blocker. Adjust treatment approximately monthly, until blood pressure goal is reached. Adjustments include increasing dosage, and adding or substituting an additional drug from the classes above.

5. Typically, patients will require two or more medications to achieve blood pressure control.

<table>
<thead>
<tr>
<th>Demographic Group</th>
<th>Prevalence</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minorities</td>
<td>“Blood pressure control rates vary in minority populations and are lowest in Mexican Americans and Native Americans.”</td>
<td>“In general, the treatment of hypertension is similar for all demographic groups, but socioeconomic factors and lifestyle may be important barriers to BP control in some minority patients.”</td>
</tr>
<tr>
<td>Blacks</td>
<td>“The prevalence, severity, and impact of hypertension are increased in blacks.”</td>
<td>“... somewhat reduced BP responses to monotherapy with β-blockers, ACE inhibitors, or ARBs compared with diuretics or CCBs [...] largely eliminated by drug combinations that include adequate doses of a diuretic.”</td>
</tr>
<tr>
<td>Over 65</td>
<td>“Hypertension occurs in more than two thirds of individuals after age 65 years. This is also the population with the lowest rates of BP control.”</td>
<td>“... follow the same principles outlined for the general care of hypertension. [...] lower initial drug doses may be indicated to avoid symptoms; however, standard doses and multiple drugs are needed in the majority ...”</td>
</tr>
<tr>
<td>Women</td>
<td>“Oral contraceptives may increase BP and the risk of hypertension increases with duration of use [...] hormone replacement therapy does not raise BP.”</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.2: Notes for demographic sub-populations from the JNC 7 report [2]

Adjustments are recommended for certain patients. The JNC 7 report includes a table of “compelling indications” for which the use or avoidance of particular drug classes is advised: heart failure, post-myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention. Other comorbidities with special treatment notes include: pregnancy, asthma, gout, history of significant hyponatremia, reactive airways disease, second or third-degree heart block, history of angioedema, and high potassium levels. Notes for demographic-based sub-populations are collected in Table 1.2.
Table 1.3: Complementary approaches: medical studies vs. analytics on EHR

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials and</td>
<td>• Expensive, limits size of study</td>
</tr>
<tr>
<td>prospective studies</td>
<td>population</td>
</tr>
<tr>
<td></td>
<td>• Limited insight for sub-</td>
</tr>
<tr>
<td></td>
<td>populations and questions not</td>
</tr>
<tr>
<td></td>
<td>included in study design</td>
</tr>
<tr>
<td></td>
<td>• High-quality data collection</td>
</tr>
<tr>
<td></td>
<td>• Statistical controls</td>
</tr>
<tr>
<td></td>
<td>• Larger study population</td>
</tr>
<tr>
<td></td>
<td>• Potentially longer patient history</td>
</tr>
<tr>
<td></td>
<td>• Flexibility in models and questions</td>
</tr>
<tr>
<td></td>
<td>considered</td>
</tr>
<tr>
<td></td>
<td>• Missing information</td>
</tr>
<tr>
<td></td>
<td>• Messier data</td>
</tr>
</tbody>
</table>

1.3 Research Goals

From Sections 1.1 and 1.2, it is clear that improvements in the treatment of hypertension would have a major impact, and there is disagreement and uncertainly in current evidence-based guidelines. Furthermore, experimentation is typically required to find an effective treatment for a given patient. We propose a complementary approach of applying analytics to patient electronic health record (EHR) data to accomplish one or more of the following goals:

1. Find conjectures parallel, and potentially orthogonal, to current treatment guidelines.

2. Hasten patient response time to therapy.

3. Optimize therapy selection.

Table 1.3 summarizes the benefits and drawbacks of this approach.

This thesis represents progress towards these goals. Most notably, the clusters described in Section 3.2 and the interpretation of the models in Chapter 4 reveal a number of known clinical trends – fulfilling the first part of goal one. This research has not yet clearly identified conjectures orthogonal to current guidelines. A predictive model of blood pressure trajectory is a key enabler for meeting these goals.
Such a model, if interpretable, might suggest treatment plans not common in current clinical practice, thereby meeting the second half of goal one, and hopefully goal two. Furthermore, good understanding of the factors influencing blood pressure trajectory, provided by a predictive model, is a prerequisite to the optimization model suggested by goal three. Creating a predictive model of blood pressure trajectory first requires a quantitative, data-based definition of blood pressure trajectory. The majority of this thesis is, in effect, spent grappling with this definition. Section 3.2 presents intriguing, clinically-relevant patient clusters, discovered by clustering on blood-pressure-related variables. Section 4.2 describes numerous attempts to translate this insight to prediction: using such clusters as the dependent variable of a predictive model. Unfortunately, the predictive power of these models is almost entirely due to differentiating patients with overall low versus high blood pressure – information already available to a physician after a patient’s initial visit. Finally, we developed the models described in Section 4.3, which do predict blood pressure changes in a clinically-relevant way. While the performance of these models is currently modest, there is potential in refining them further, as discussed in Section 5.3.

1.4 Structure

The structure of this thesis is as follows. Chapter two describes the data set: source, inclusion criteria, visualizations of example and aggregate data, and cleaning and preprocessing steps taken. Chapter three discusses feature selection as well as the result of clustering on select blood pressure features: clinically-relevant patient groups. Chapter four presents models and results for predicting blood pressure trajectory, over three spirals of development. Chapter five notes general trends, followed by concluding remarks and suggestions for future continuation of this work.
Chapter 2

Data

2.1 Boston Medical Center

This work is enabled by access to anonymized data from the Boston Medical Center (BMC), a 496-bed academic medical center, affiliated with Boston University School of Medicine, and located in Boston’s South End. BMC provides pediatric and adult care, including primary and family medicine, advanced specialty care, and trauma and emergency services. It is the largest safety-net hospital in New England. Available anonymized data comes from: up to 15 years of EHR (including visit history, vital signs, diagnoses, problem list, lab results, and prescriptions), billing data, demographics, and cancer registry information. Provider notes as well as diagnostic images and signals are not available. The anonymized data is linked by unique identifier numbers assigned to each patient and provider.

2.2 Patient Inclusion Criteria

Figure 2-1 shows the patient inclusion criteria for this analysis. We chose these criteria to select patients interacting with the BMC system regularly, without a known cause for their hypertension, and with sufficient blood pressure and medication information to address the goals stated in Section 1.3. We set aside a random 25% of these patients for eventual out-of-sample testing set. This data was not used at all in the
Figure 2-1: Patient inclusion criteria

analysis described in Chapters 3 and 4. The remaining 75% was used for training and validation.

Further filtering included steps such as removing missing and unreasonable values, requiring a minimum number, duration or density of blood pressure measurements, and excluding children. Several variants of such filtering were used throughout the analysis described in Chapters 3 and 4. In all cases, approximately 25,000 patients remained.

2.3 Data Fields

The EHR data fields used in this analysis are: date of birth, race, sex (demographics); blood pressure, weight, height, BMI (vitals); and antihypertensive medication prescriptions. All of these fields, except demographics, have a temporal element with irregular measurement intervals. The challenge of transforming this data into vari-
ables for exploratory and predictive analytics is discussed in Section 3.1

2.3.1 Demographics

Patient sex is directly available in the EHR. A histogram for the patient population described in Section 2.2 is shown in Figure 2-2. Age at time of visit is easily calculated from date of birth\(^1\). Histograms for both values are shown in Figure 2-3. Note the greater proportion of women in the age plot, and that the date-of-birth plot counts patients while the age plot counts visits: women visit the doctor more often than men. A number of race codes exist in the EHR. Same-race codes were combined (e.g. ”DEM\|RACE:a”, ”DEM\|RACE:asian”, ”DEM\|RACE:or”, and ”DEM\|RACE:oriental” all correspond to asian). The few patients coded as hispanic/black or hispanic/white were included in both categories. Codes for indian, middle eastern, native american, asian pacific islander, aleutian, eskimo, and multiracial were infrequent or nonexistent. These patients were combined with those coded as “other”. See Figure 2-4 for the

\(^1\)There is also an “age” field, which was not used. It indicates age at last database update.
Figure 2-3: Distribution of patient age at time of visit, and birth-date, in selected population.

Figure 2-4: Distribution of race in selected patient population.
resulting distribution.

2.3.2 Blood pressure

Blood pressure is measured in millimeters of mercury (mm Hg). It is typically reported as systolic pressure (pressure in arteries when heart contracts) over diastolic pressure (pressure in arteries between contractions). Others ways to report blood pressure are pulse pressure (systolic minus diastolic) and mean arterial pressure (average pressure throughout a heartbeat cycle). Mean arterial pressure can be estimated by: \[ \frac{2}{3} \text{diastolic} + \frac{1}{3} \text{systolic}. \]

The EHR includes systolic and diastolic blood pressure measurements. While a few of these are specifically marked as measured with patient lying, sitting, or standing; most are coded as “unknown”. Values greater than 300 mm Hg were removed to exclude obviously erroneous values. Of interest for this research is the trajectory of a patient’s blood pressure over time. For some patients, such as the example in Figure 2-5, this trend is fairly clear. More commonly, the variation in blood pressure measurements is greater than any increasing or decreasing trend. The patient in Figure 2-6 is such an example. Summarizing blood pressure trajectory is further discussed in Chapters 3 and 4. Figure 2-7 indicates the distribution of blood pressure measurements for the study population, by all four metrics described above. Note the “comb” pattern, suggesting doctors often round to the nearest increment of 5 or 10 when taking a reading. Figure 2-8 plots the duration of patient measurement history (difference between date of first and latest blood pressure measurement on record). The drop-off around 13 to 15 years is likely due to the phase-in of electronic record keeping at BMC.

2.3.3 Weight and BMI

Both weight and BMI are available in the EHR. They are typically less noisy than the blood pressure measurements, making trends clearer. Figure 2-9 shows these measurement for the same patients as in Figures 2-5 and 2-6. Figure 2-10 shows the
Figure 2-5: Example patient: clear blood pressure trajectory, three antihypertensive medication classes.

distribution of these measurements in the study population. Informed by exploratory scatter plots, erroneous data and extreme outliers were excluded by limiting data to: weight between 25 and 600 kg, height between 130 and 250 cm, and BMI between 10 and 75. Additional issues and solutions related to these fields are discussed in Section 5.3.1.

2.3.4 Antihypertensive Medications

Medication usage is reflected in the EHR by an entry every time a doctor writes or updates the prescription. Each entry includes an RxNorm[8] code that uniquely identifies the medication, the start date of the prescription, the end date of the prescription (typically the start date of the next entry for the same drug), dosage instructions (e.g. “take one by mouth once daily”), the drug name (e.g. “benazepril 5 MG / Hydrochlorothiazide 6.25 MG Oral Tablet (Lotensin HCT) (RXCUI:207881) (RXCUI:207881)”), the number of pills (or other units) per refill, and the number
of refills. We assume the patient is taking a drug the entire time between the listed start and end dates. As antihypertensive class is the clinically-relevant factor \cite{2}, we are able to simplify the 601 RxNorm codes (75 drug names) by grouping them into the classes in Table 2.1. Single-pill combination drugs are split into both relevant classes. Obtaining dosages required parsing the, relatively unstructured, instruction field to extract the number of pills per day\(^2\) and drug name to extract milligrams per pill (or unit). Currently, this parsing captures dosage for 92\% of the prescription entries. Additional processing to further utilize available drug data is discussed in Section 5.3.1.

Figures 2-5 and 2-6 show antihypertensive drug prescriptions for two example patients. Note, the classes here reflect the organization for the EHR database before additional sorting. One-pill combos are the legend entries with colons. Figures 2-11 and 2-12 show statistics of drugs prescribed, after sorting into the classes of Table 2.1.

\(^{2}\)Or, for clonidine, patches per week.
Figure 2.7: Distribution of blood pressure measurements in patient study population.

[Graphs showing distribution of blood pressure measurements for systolic, diastolic, pulse pressure, and estimated mean arterial pressure.]
Figure 2-8: Duration of blood pressure measurement history in selected patient population.

Figure 2-9: Weight and BMI measurement for two example patients.
Figure 2-10: Distribution of weight and BMI measurements in selected patient population.

| 1   | Thiazide diuretics                        |
| 2   | Other diuretics (loop, potassium-sparing, aldosterone-receptor blockers, carbonic anhydrase) |
| 3   | Angiotensin-converting enzyme (ACE) inhibitors |
| 4   | Angiotensin II receptor blocker (ARB)     |
| 5   | Calcium channel blocker (CCB)             |
| 6   | α-Blockers                                |
| 7   | β-Blockers                                |
| 8   | Centrally acting adrenergic agents        |
| Less common: |                                    |
| 9   | Peripheral vasodilators                   |
| 10  | Hydralazine hydrochloride                 |
| 11  | Minoxidil                                 |
| 12  | Reserpine                                 |

Table 2.1: Antihypertensive drug classes, as used in this work
Figure 2.11: Distribution of patient count by antihypertensive drug class prescribed
Figure 2.12: Distribution of patient count, by antihypertensive drug class and cumulative length of drug prescriptions.
Chapter 3

Data Exploration

3.1 Feature Creation

As mentioned in Section 2.3, one of the main challenges of this research was determining the best way to summarize temporal data with variable measurement density and spacing, start date, and length of history. Table 3.1 presents the various options considered. Note the use of residual standard error\(^1\) rather than \(R^2\) to indicate goodness of fit. Values of \(R^2\) near zero can indicate noisy data or a poor fit, but also correspond to a good fit of nearly constant data: a common pattern for blood pressure and weight. The use and evaluation of these features for data exploration and prediction is discussed in Section 3.2 and Chapter 4.

3.2 Blood Pressure Trajectory Clusters

One way to explore and evaluate the features presented in Section 3.1 is through clustering. First we discuss general preprocessing done, or tried, over the course of experimenting with various features, followed by details on the features ultimately selected for clustering.

Clustering algorithms operate on distances between data points, so the data must first be normalized, and possibly transformed. For example, the non-negative, skewed

\(^1\)Unbiased version: \(\sqrt{\text{sum of squared errors} / \text{degrees of freedom}}\)
**Blood Pressure** (very noisy)

Mean, median, standard deviation

Number, density (and timespan) of measurements

Polynomial fit:
- Linear: intercept, slope
- Quadratic: 3 coefficients
- Residual standard error (RSE)
- Value of fit at $t_0$
- Differences between 1st and 2nd order fit

**Weight and BMI**

Mean, median, standard deviation

Linear fit: intercept, slope, RSE

**Medications**, by drug class

Binary (after threshold for minimum script duration?)

Count of scripts

Cumulative script duration

Fraction of time: cumulative script duration / timespan

Max dose, pills/day, times/day

Use of two or more classes:
- Pairwise, triplet, etc.
- Full combination (e.g. sort and consider top 30 combinations, plus ”other”)

**Time period considered**

Entire patient history

Divide into discrete segments

Initial window (and final window), remaining record

---

Table 3.1: Feature creation: options for summarizing temporal data
distribution for residual standard error is more symmetric after a \( \ln() \) transform. When fitting blood pressure, weight, and BMI with a linear or quadratic equation, the slope and curvature coefficients for most patients are close to zero. Therefore, patients with larger values of these coefficients, often correlated with shorter measurement history, tend to dominate any clustering algorithm. The neglog transform \([12], \text{sign}(x) + \ln(|x| + 1),\) can be used to temper this effect. It is nearly linear close to zero, while pulling in extreme positive and negative values.

After applying transformations to some variables, we normalized all non-binary variables by subtracting the mean and dividing by the standard deviation. We then experimented with hierarchical, k-means, and spectral clustering, as well as weighting select variables to increase their influence. We first tried clustering on all non-drug variables, with the idea of then comparing medication usage by cluster. With so many variables, the clusters were hard to interpret. No striking drug trends emerged.

Next, we tried clustering with only blood pressure features, aiming to discover the best way to quantify “blood pressure trajectory” from the multitude of possible features listed in Table 3.1. We found hierarchical clustering with 8 clusters produced sensible, interpretable clusters. We then pared down the features used, while checking that the cluster distinctions remained. The seven blood pressure features ultimately used are presented in Table 3.2. Figure 3-1 shows the hierarchical clustering dendrogram, with a red box indicating the choice of 8 clusters. Figure 3-2 shows the resulting cluster sizes.

Each plot in Figure 3-3 shows one of the features used for clustering: a boxplot of its normalized values, separated along the x-axis by cluster. We studied this plot to determine a description for each cluster, which we present in the left column of Table 3.3. For example, consider Cluster 6. The median.sys and median.dia plots show that patients in this cluster tend to have lower systolic and diastolic blood pressures than the population average (indicated by the black line at zero). By considering the unnormalized, population average and standard deviation of median blood pressure, listed on the right of Figure 3-3, we further note that the middle 50% of Cluster 6 patients have median systolic blood pressure between approximately 120
Figure 3-1: Dendrogram for hierarchical clustering on blood pressure features.
<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 median.sys</td>
<td>median systolic blood pressure</td>
</tr>
<tr>
<td>2 median.dia</td>
<td>median diastolic blood pressure</td>
</tr>
<tr>
<td>3 B1.lin.sys</td>
<td>linear fit of systolic blood pressure, $\beta_1$ coefficient (slope)</td>
</tr>
<tr>
<td>4 B1.lin.dia</td>
<td>linear fit of diastolic blood pressure, $\beta_1$ coefficient (slope)</td>
</tr>
<tr>
<td>5 B2.quad.sys.negLog</td>
<td>quadratic fit of systolic blood pressure, $\beta_2$ coefficient ( curvature), transformed by: $sign(x) + ln(</td>
</tr>
<tr>
<td>6 B2.quad.dia.negLog</td>
<td>quadratic fit of diastolic blood pressure, $\beta_2$ coefficient ( curvature), transformed by: $sign(x) + ln(</td>
</tr>
<tr>
<td>7 BPdensity</td>
<td>total number of visits with blood pressure measurement divided by years between first and latest measurement</td>
</tr>
</tbody>
</table>

All features calculated by patient, over patient’s entire measurement history.

Table 3.2: Blood pressure features used for clustering

![Figure 3-2: Clustering on blood pressure features: cluster sizes](image-url)
Table 3.3: Cluster descriptions, plus trends by cluster for features not used in cluster creation.

<table>
<thead>
<tr>
<th>Characterization of cluster</th>
<th>Variables not used for clustering – trends by cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ok now, slowly getting in trouble</td>
<td>Younger, monotherapy (especially thiazide), heavier (gradual weight gain?)</td>
</tr>
<tr>
<td>2 Low and stable</td>
<td>Lighter, least noisy BP, more non-black men, tried 1-3 drugs (more non-thiazide diuretics)</td>
</tr>
<tr>
<td>3 Positive curvature, rapid decrease</td>
<td>Shorter history, losing weight, slightly older</td>
</tr>
<tr>
<td>4 High and stable, noisy</td>
<td>Heavier, noisy BP, tried several drugs (less non-thiazide diuretics), more blacks</td>
</tr>
<tr>
<td>5 Negative curvature, rapid increase</td>
<td>Shorter history, gaining weight, monotherapy or no drugs</td>
</tr>
<tr>
<td>6 Dense measurements, low and stable</td>
<td>Heavier, slightly older women, noisy weight/BMI, tried many drugs</td>
</tr>
<tr>
<td>7 Stable, elevated diastolic, least dense measurements</td>
<td>Heavier, younger, thiazide: alone or with one other class (less non-thiazide diuretics), more blacks</td>
</tr>
<tr>
<td>8 Low diastolic, elevated systolic</td>
<td>Older, more non-black women, tried many drugs</td>
</tr>
</tbody>
</table>

and 133 mm Hg and diastolic between 70 and 80 mm Hg: values corresponding to the low end of the prehypertension range. Next, looking at the B1.lin.sys, B1.lin.dia, B2.quad.sys.negLog, and B2.quad.dia.negLog plots, features which have unnormalized population mean close to zero, shows that the slope and curvature of blood pressure for Cluster 6 patients is typically close to zero. Finally, the BPdensity plot reveals that Cluster 6 patients have their blood pressure measured more frequently, on average, than patients in other clusters. Therefore, as shown in Table 3.3, we label this cluster, “Dense measurements, low and stable.”

We then made plots similar to Figure 3-3 of features not used for clustering. Notable trends in these features are recorded in the right column of Table 3.3. These additions to the cluster descriptions are clinically-consistent with the blood-pressure-
Figure 3-3: Final selection of (normalized) blood pressure variables for clustering: comparison between clusters.
only cluster labels, and enhance our understanding of the clusters. In particular, note the connection between weight loss (gain) and blood pressure decrease (increase), particularly in Clusters 3 and 5. Cluster 2 appears to be patients who responded well to initial treatment. Contrast this with Cluster 6: patients who required frequent visits and lots of experimentation to achieve blood pressure control. This cluster also contains more women, consistent with the observation in Section 2.3.1 that women go to the doctor more often. Cluster 4 seems to contain patients with difficult to treat blood pressure (and/or have poor adherence or irregular visits). A known subgroup, elderly patients with isolated systolic hypertension, appear in Cluster 8.
Chapter 4

Predicting Blood Pressure Trajectory

As discussed in Section 1.3, we view a predictive model of blood pressure trajectory as a key step to meeting our research goals. This chapter describes our efforts to build such a model. This research progressed in development spirals. We began with the minimal data processing required to try a simple predictive model. From this, we identified promising model improvements and the most pressing additional data processing tasks, and then repeated the process. This chapter presents details and results for three such spirals.

4.1 Model 1: Initial Attempt

In order to begin exploring the data and gauge the difficulty of this prediction problem, we started with a simple model, requiring minimal data processing:

1. Divide each patient’s record into 1-year or 6-month windows.

2. For each window, record independent variables: start date, age at start, most recent (prior) BMI and weight, count (by class) of drugs with a prescription valid anytime in the window; plus patient sex and race (black/not). For the dependent variable, record mean systolic blood pressure.
3. Use these data slices, over each patient’s history and multiple patients, to construct regression models.

We explored a variety of methods in step three: ordinary least squares (OLS), ridge regression (least squares with regularization), lasso regression ($l_1$ norm with regression, encourages sparsity), and lasso regression for variable selection followed by OLS on the chosen variables. We also compared these models across 8 sub-populations, constructed by splitting on three variables: male versus female, blacks versus other races, and age less than 45 versus 45-and-older.

The resulting models had $R^2$ values ranging from 0.06 to 0.20. The models were hard to interpret and no method, variable, or subgroup particularly stood out. Recognizing the need to capture patient blood pressure trajectories over timespans longer than 6 to 12 months led to the clustering analysis described in Section 3.2 and from there to the models described in Sections 4.2 and 4.3.

## 4.2 Model 2: Predict Cluster

Section 3.2 presents a promising definition of blood pressure trajectory: patient clusters on blood pressure features. Given the apparent clinical-relevance of these clusters, we next attempted to build a model that would predict a patient’s cluster, using non-blood pressure features as independent variables (see Table 4.1). In addition to the 8 clusters described in Section 3.2, we similarly constructed 4 clusters of blood pressure trajectory. We also created patient groups, inspired by insights from clustering, by thresholding on key blood pressure features. With these clusters or groups as dependent variables, we explored multiclass classification, as well as binary classification (by considering one-v-all, other groupings, and subsets of clusters/groups). Further details of these models are explained in the following paragraphs and tables.

We used 50% of the total data, further randomly split: 70% for training and 30% for out-of-sample evaluation and tried CART, Random Forest, and logistic regression (binary classification only). In almost all cases, Random Forest equaled or outperformed the other methods.
<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ageAtT0</td>
<td>patient age at time of first blood pressure measurement in EHR</td>
</tr>
<tr>
<td>race</td>
<td>factor variable with 6 levels, as in Figure 2-4</td>
</tr>
<tr>
<td>male</td>
<td>binary variable, 1=M, 0=F</td>
</tr>
</tbody>
</table>

*Calculated over patient’s entire EHR history*

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>median.weight</td>
<td>median of weight measurements</td>
</tr>
<tr>
<td>median.BMI</td>
<td>median of BMI measurements</td>
</tr>
<tr>
<td>B1.weight</td>
<td>$\beta_1$ (slope) coefficient of a linear fit to weight measurements</td>
</tr>
<tr>
<td>B1.BMI</td>
<td>$\beta_1$ (slope) coefficient of a linear fit to BMI measurements</td>
</tr>
<tr>
<td>residStdErr.weight</td>
<td>residual standard error of a linear fit to weight measurements</td>
</tr>
<tr>
<td>residStdErr.BMI</td>
<td>residual standard error of a linear fit to BMI measurements</td>
</tr>
<tr>
<td>numDrugs</td>
<td>number of different drug classes ever prescribed (0–12)</td>
</tr>
</tbody>
</table>

*Each line $\times$12, $<$drug class$>$ as listed in Table 2.1*

| $<$drug class$>$     | binary variable: 1 if cumulative length of prescriptions (for drug class) is longer than 3 months, 0 otherwise |
| $<$drug class$>$.frac | cumulative length of patient’s prescriptions (for drug class) divided by length of patient’s BP measurement history |
| $<$drug class$>$.maxDose | maximum dose (mg/day) the patient has ever been prescribed                 |

*Only used in Model 3 (Section 4.3)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>yearsBPhist</td>
<td>years between first blood pressure measurement in EHR and most recent measurement</td>
</tr>
<tr>
<td>numMeas.start</td>
<td>number of visits with a BP measurement in initial year of patient’s record</td>
</tr>
<tr>
<td>numMeas.end</td>
<td>number of visits with a BP measurement in year preceding latest BP measurement on record</td>
</tr>
</tbody>
</table>

Table 4.1: Non-blood-pressure features, used (or tried) as independent variables for prediction
Compared to the baseline model of predicting the most frequent cluster (or group), many of these models represent modest improvements in accuracy. However, when interpreted, nearly all of this performance is due to differentiating low-blood-pressure clusters from high-blood-pressure clusters. This is not particularly useful to a physician, who knows, within a visit or two, the current blood pressure of a patient being treated. Model 3, presented in Section 4.3, remedies this shortcoming by explicitly considering initial blood pressure. Nonetheless, the models in this section taught us about the data, and, reassuringly, highlighted known clinical trends.

Multiclass prediction with eight classes is a tall order, so, as previously mentioned, we also considered a smaller number of clusters (again using the 7 features in Table 3.2). Based on the hierarchical clustering dendrogram in Figure 3-1, we selected 4 clusters. These clusters can be described as: “increasing BP”, “decreasing BP”, “low-stable BP”, and “high-stable BP”. It turned out that features 5, 6 and 7 in Table 3.2 did not vary significantly between these clusters. Therefore, we re-ran hierarchical clustering using only features 1 through 4 in Table 3.2. These 4 clusters were consistent with the descriptions above, though the size of the clusters varied from those created with all seven features.

Our prediction experiments included multiple random train-validate splits, and experimentation with the different drug features listed in Table 4.1. The out-of-sample (validation set) results of the best-performing model (typically Random Forest) are presented in the following tables. Table 4.2 presents multiclass prediction and one-versus-all binary classification for the 8 clusters of Section 3.2, and the two versions of 4-clusters described above. Table 4.3 represents an attempt to tease apart prediction of blood pressure level versus change in blood pressure over time, using binary classification on subsets and groupings of the 4 blood pressure clusters (both versions).

Two main insights emerge from interpreting the models presented so far. First, prediction for problems with a high baseline (due to unbalanced classes) is, as expected, more difficult. For 2-class problems, AUC can be calculated, and shows that the models are somewhat out-performing the baseline. However, it is not clear if there is a cost difference between false positives and false negatives that would warrant se-
<table>
<thead>
<tr>
<th>Quantity predicted (dependent variable)</th>
<th>Baseline model</th>
<th>Baseline accuracy (%)</th>
<th>Improvement above baseline (% accuracy − baseline)</th>
<th>Main drivers of improvement (or lack of improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 clusters (as described in Section 3.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiclass prediction with 8 classes</td>
<td>predict Cluster 1: “Ok now, slowly getting in trouble”</td>
<td>21.3</td>
<td>4.5 to 9.7</td>
<td>age, weight, drug fraction</td>
</tr>
<tr>
<td>Binary classification, one-v-all for each of 8 clusters</td>
<td>predict: not in cluster</td>
<td>78.7 to 94.1</td>
<td>-0.1 to 0.5</td>
<td>high baseline</td>
</tr>
<tr>
<td>4 clusters (created using all 7 features in Table 3.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiclass prediction with 4 classes</td>
<td>predict: “decreasing BP”</td>
<td>37.2</td>
<td>11.2</td>
<td>thiazide Y/N</td>
</tr>
<tr>
<td>Binary classification, one-v-all for each of 4 clusters</td>
<td>predict: not in cluster</td>
<td>62.8 to 89.6</td>
<td>0.0 to 6.4</td>
<td>baseline</td>
</tr>
<tr>
<td>4 clusters (created using features 1–4 in Table 3.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiclass prediction with 4 classes</td>
<td>predict: “high-stable BP”</td>
<td>37.4</td>
<td>13.2</td>
<td>thiazide Y/N</td>
</tr>
<tr>
<td>Binary classification, one-v-all for each of 4 clusters</td>
<td>predict: not in cluster</td>
<td>62.6 to 87.1</td>
<td>-0.1 to 6.1</td>
<td>baseline</td>
</tr>
</tbody>
</table>

Table 4.2: Out-of-sample results: cluster by blood pressure features to create dependent variable, predict cluster using non-blood-pressure features.
<table>
<thead>
<tr>
<th>First-time drugs (Y/N)</th>
<th>Age, thiazide</th>
<th>(\text{AVC} = 0.71)</th>
<th>Improv. above baseline (%)</th>
<th>Baseline model</th>
<th>(60.4)</th>
<th>“High-stable BP”</th>
<th>vs.</th>
<th>“Increasing” or “Decreasing” BP</th>
<th>15.8</th>
<th>52.2</th>
<th>(AUC = 0.77)</th>
<th>“Low-stable BP”</th>
<th>(68.9)</th>
<th>“Increasing” or “Decreasing” BP</th>
<th>vs.</th>
<th>“Low-stable BP”</th>
<th>3.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Y)</td>
<td></td>
<td>(0.70)</td>
<td>(AUC = 0.070)</td>
<td></td>
<td></td>
<td>2.0</td>
<td>74.4</td>
<td>“High-stable BP”</td>
<td>vs.</td>
<td>“Low-stable BP”</td>
<td>1.9</td>
<td>63.5</td>
<td>(AUC = 0.67)</td>
<td>“High-stable BP”</td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N)</td>
<td></td>
<td>(0.72)</td>
<td>(AUC = 0.072)</td>
<td></td>
<td></td>
<td>2.6</td>
<td>71.4</td>
<td>“High-stable BP”</td>
<td>vs.</td>
<td>“Low-stable BP”</td>
<td>2.7</td>
<td>50.4</td>
<td>(AUC = 0.71)</td>
<td>“High-stable BP”</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.3: Out-of-sample results: subset or group blood pressure clusters to create dependent variable for predictive models.

† “low-stable BP” or “increasing”, ‡ “high-stable BP” or “decreasing BP” (created using features 1–4 in Table 3.2)
lecting a threshold different from 0.5. Second, for models with predictive power, it is largely due to obvious, clinically-known relationships such as:

- Low blood pressure is correlated with not having tried common first-line drugs, and even more likely for patients with stable weight who are not too heavy.
- High blood pressure is correlated with having tried a thiazide diuretic or calcium channel blocker, and even more likely for patients who have tried many drug classes.
- Among patients with low initial blood pressure, older patients are less likely to increase, perhaps because more of them have already been diagnosed and successfully treated.
- If initial blood pressure is high, losing weight is predictive of improvement.

These results are in-line with current knowledge, meeting the first half of goal one in Section 1.3, but don’t yet seem useful for the remaining goals. We further investigated these most-predictive variables by splitting the population on one or two at a time and predicting in each subset. Results are summarized in Table 4.4.

As previously mentioned, when constructing four clusters using seven or four blood pressure features, the interpretation of the clusters was the same, but the size of each cluster changed; a trend we also noticed during our clustering experiments in Section 3.2. This, and the many outliers in Figure 3-3, suggests the clusters overlap substantially and many patients only loosely fit their cluster description. To investigate the effect of this on cluster prediction, we compared the previous results with models predicting patient groups created by thresholding features 1 and 3 in Table 3.2. We selected the following five groups, with the dual goals of similarity to the 4-cluster descriptions and approximately equal group sizes:

1. “increasing BP”: \( \beta_1 > 0.0045 \) (mm Hg / day)
2. “decreasing’ BP”: \( \beta_1 < -0.0045 \) (mm Hg / day)
3. “low-stable BP”: median < 130, \( |\beta_1| \leq 0.0045 \)
4. “ok-stable BP”: 130 \( \leq \) median < 140, \( |\beta_1| \leq 0.0045 \)
5. “high-stable BP”: 140 \( \leq \) median, \( |\beta_1| \leq 0.0045 \)
### Table 4.4: Out-of-sample results: cluster by blood pressure features, split, predict cluster in each segment

<table>
<thead>
<tr>
<th>Feature</th>
<th>Baseline</th>
<th>Improvement above baseline (%)</th>
<th>Quantity predicted (dependent variable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, other drugs</td>
<td>69, 68</td>
<td>3.6, 3.8</td>
<td>Baseline model (biggest class vs. others)</td>
</tr>
<tr>
<td>Calcium</td>
<td>29, 33</td>
<td>4.7, 4.8</td>
<td>Split: Prescribed thiazide or calcium? (4-class classification)</td>
</tr>
<tr>
<td>Weight</td>
<td>13, 16</td>
<td>2.5, 2.8</td>
<td>Split: Prescribed thiazide or calcium? (binary: biggest class vs. others)</td>
</tr>
</tbody>
</table>

Note: “increasing BP” correlates with younger age.
4.3 Model 3: Median Initial and Final Blood Pressure

Informed by the previous results and observations, we focused on creating a model that would predict blood pressure changes in a clinically-useful way. The results presented in this section represent modest improvements over baseline models. More importantly, they predict blood pressure trajectory in a way that is useful for addressing the goals in Section 1.3 and offer a promising avenue for further development.

Here, instead of the blood pressure features in Table 3.2, we calculate the median systolic blood pressure in the initial and final year of each patient’s history. A one-year window was chosen based on average measurement density (total number of blood pressure measurements divided by years of measurement history). The population median is 4.5, suggesting 6-month windows often contain only 1 or 2 measurements, but a one-year window will typically contain at least a couple of measurements. We
Median systolic blood pressure in 1-year window

<table>
<thead>
<tr>
<th>first year</th>
<th>last year</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;120</td>
<td>[120, 130)</td>
<td>[130, 140)</td>
<td>140+</td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>1040</td>
<td>875</td>
<td>664</td>
<td>461</td>
<td>3040</td>
</tr>
<tr>
<td>[120, 130)</td>
<td>762</td>
<td>1309</td>
<td>1267</td>
<td>1140</td>
<td>4478</td>
</tr>
<tr>
<td>[130, 140)</td>
<td>573</td>
<td>1196</td>
<td>1467</td>
<td>1709</td>
<td>4945</td>
</tr>
<tr>
<td>140+</td>
<td>446</td>
<td>1065</td>
<td>1641</td>
<td>3131</td>
<td>6283</td>
</tr>
<tr>
<td>Total</td>
<td>2821</td>
<td>4445</td>
<td>5039</td>
<td>6441</td>
<td>18746</td>
</tr>
</tbody>
</table>

Table 4.6: Count of patients, segmented by initial and final blood pressure (75% of total data)

took median systolic pressure, rather than the mean as in Section 4.1, to reduce the influence of noisy, outlier values. Presuming doctors are basing treatment goals on the hypertension definitions in Table 1.1, we binned the one-year median blood pressure values accordingly. Since many values fall in the prehypertensive range, and being nearly-normal versus nearly-hypertensive is an important distinction, we further subdivided this bin. The resulting number of patients in each bin are shown in Table 4.6.

We then tried predicting the final blood pressure using non-blood-pressure features, for the whole population, and in each starting blood pressure bin. We used 75% of the overall data set, again with a 70/30% train/validate split. We experimented with predicting both the value (regression) and bin (classification) of the final-year median systolic blood pressure using CART, Random Forest, OLS (regression-only), and logistic regression (binary classification only). Considering the meaning of the predictions, while striving for balanced classes, we grouped the bins for the classification predictions as follows:

- Starting BP <120 or [120, 130): 4-class (all end bins separate)
- Starting BP [130, 140): combine first 2 bins (predict <130, [130-140), 140+)
- Starting BP 140+: combine first 3 bins (predict <140 versus 140+)
<table>
<thead>
<tr>
<th>Median systolic BP, initial year</th>
<th>Baseline model</th>
<th>Classification†</th>
<th>Regression†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline accuracy (%)</td>
<td>Improvement (%, accuracy – baseline)</td>
<td>(R²)</td>
</tr>
<tr>
<td>&lt; 120</td>
<td>4-class, predict &lt; 120</td>
<td>34.2</td>
<td>1.9 – 7.1</td>
</tr>
<tr>
<td>[120, 130)</td>
<td>4-class, predict [120, 130)</td>
<td>29.2</td>
<td>2.2 – 5.4</td>
</tr>
<tr>
<td>[130, 140)</td>
<td>3-class, predict &lt; 130</td>
<td>35.8</td>
<td>7.8 – 8.8</td>
</tr>
<tr>
<td>140+</td>
<td>2-class, predict &lt; 140</td>
<td>50.2</td>
<td>7.4 – 9.4</td>
</tr>
<tr>
<td>all</td>
<td>4-class, predict 140+</td>
<td>34.1</td>
<td>5.5</td>
</tr>
<tr>
<td>all</td>
<td>binary, predict &lt;= 140</td>
<td>68.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Table 4.7: Out-of-sample results: predict final blood pressure, segmented by starting blood pressure

- All patients: predict all 4 end bins, and 2-class (<=140 versus >140)

The best results for these experiments are summarized in Table 4.7. While these are modest improvements over the baseline models, they are models that predict clinically relevant blood pressure changes, and are reasonably interpretable. See Appendix A.1 for an exploration of one of these models. Also note the relative performance of classification and regression models. In comparison to 4-class classification, regression may be equal or better. For the 140+ starting bin, where one of the 2 predicted classes contains a wide range of values, binary classification appears stronger.

To explore if better predictions are possible for certain subgroups, we next tried clustering within each starting blood pressure bin, on non-blood-pressure features, and then predicting final blood pressure within each bin-cluster sub-group. Based on hierarchical cluster dendrograms, 5 to 6 clusters seemed a good choice: not too many, but enough to distinguish some interesting patient groups. In particular, across all
starting bins, one cluster contains a high proportion of black patients. Unfortunately, the cluster sizes are quite uneven, with the smallest containing as few as 98 patients. This led to significant variation in the results depending on the exact points in the training set. Moving up the dendrograms, 3 to 4 clusters also looked reasonable. Here the smallest cluster contained 410 patients. Comparing predictions for a cluster to predictions for all patients in the starting bin, the result was typically similar or worse. Some of the largest clusters performed a few percent better, presumably because they still had ample training data but didn’t have to contend with the most difficult-to-predict patients (isolated in the other clusters). Full results for these experiments are presented in Appendix A.2.
Chapter 5

Conclusion

5.1 General Observations

Throughout this work we noted several trends appearing across various experiments and methods. We hypothesize they represent underlying data structure and properties, and record them here for the benefit of future researchers.

One consistent trend was the relative importance of various features for prediction. That is, feature inclusion and position in CART trees, p-values in linear and logistic regression, and, for Random Forests, the average of total decrease in node impurities across all trees from splitting on a feature. Table 5.1 summarizes these observations.

Additional observations related to feature selection and importance are:

- Weight features are typically more predictive than BMI. However, as they are highly correlated, BMI will be used if weight is not included.

- Ages in the range of 56 to 61 seem important for this application. CART trees often split somewhere in this range.

- As suggested in Table 5.1, binary drug features are less useful than drug features which provide additional information: for example fraction-of-timespan-used or maximum dose.

When fitting a curve to blood pressure data, interpreting the coefficients of a quadratic fit is much more challenging than for a linear fit. Interpretation for either
fit is further complicated if the timespan of the data points varies. Considering the median of blood pressure values in an initial time window is therefore easier to understand and use than the intercept of a fitted curve.

More generally, the timespan considered for feature creation is quite important. Short timespans may not contain rich enough data, while long timespans may not adequately separate various stages of a patient’s disease progression and treatment. Furthermore, if timespans are unequal between patients, comparing features such as fit coefficients, number of drugs tried, and variability of weight is more difficult. Section 5.3.2 suggests model improvements based on these observations.

In terms of modeling, we emphasize the importance of including information about starting blood pressure so predictions can focus on changes rather than levels. We note that among all the experiments described in Chapter 4, Random Forest typically performed as-well, or better than CART and logistic or linear regression. In terms of results and interpretations, the (well-known) positive correlation between weight and blood pressure consistently appeared.

---

<table>
<thead>
<tr>
<th>Importance</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>most</td>
<td>age, $\beta_1$ (slope) of weight, length of history$^\dagger$</td>
</tr>
<tr>
<td>high</td>
<td>other weight/BMI features, number of BP measurements in first/last year$^\dagger$, thiazide diuretic$^\dagger$</td>
</tr>
<tr>
<td>medium</td>
<td>race, number of drug classes, ACE$^\dagger$, $\beta$-blocker$^\dagger$, CCB$^\dagger$, other diuretic$^\dagger$</td>
</tr>
<tr>
<td>low</td>
<td>sex, $\alpha$-blocker$^\dagger$, ARB$^\dagger$, centrally-acting agent$^\dagger$</td>
</tr>
<tr>
<td>very low</td>
<td>hydralazine hydrochloride$^\dagger$, minoxidil$^\dagger$, peripheral vasodilators$^\dagger$, reserpine$^\dagger$, binary variables for drug combinations</td>
</tr>
</tbody>
</table>

$^\dagger$fraction of history and/or max dose, $^\ddagger$only used in model 3

Table 5.1: Feature importance for prediction: general trends from Sections 4.2 and 4.3, using CART, RF, and linear/logistic regression.
5.2 Concluding Remarks

This thesis represents substantial work in accessing and processing electronic health record data from a Boston Medical Center research database. It presents data exploration results, particularly the discovery of clinically-relevant clusters of patient blood pressure trajectory. It discusses ways to tackle the challenge of constructing features and predictive models for this data. Section 4.3 presents a model with modest predictive power, for quantities relevant to the research goals stated in Section 1.3. My hope is that future researchers will continue progress towards these goals, aided by the groundwork I’ve laid.

5.3 Future Work

During the spiral-development approach described in Chapter 4, data processing and modeling steps were envisioned that have not yet been addressed.

5.3.1 Data Processing

Future development spirals may benefit from revisiting the assumptions and parameters laid out in this thesis, starting with the inclusion criteria described in Section 2.2. For example, further filtering could be done to explicitly exclude pregnant patients, or hypertension stemming from a known cause. Including hypertensive patients not on medication might provide a useful control group.

Data exploration in Chapter 2 revealed that weight is reported more often than BMI (as in Figure 2-9, Example 1), weight is occasionally misrecorded in pounds rather than kilograms, and a BMI calculated from height and weight is not necessarily consistent with the reported value. Currently, BMI features are constructed from available BMI data points, and dropped if no data is available. Processing which checks the consistency of weight, height, and BMI; against each other for the same visit, and against these measurements over time, could likely detect and correct many instances of the issues described above.
Medication dosage warrants further processing. Additional text parsing could fill in some of the prescriptions for which dosage is currently not captured. The handling of dosage for one-pill drug combinations needs to be verified, and possibly improved. Dosage would be more informative if compared to the typical dose for each drug, likely a manual table construction of 75-plus rows.

More information about medication usage may be available from other BMC database fields, or inferable with additional processing of data described in Section 2.3.4. Quantity per refill and number of refills could be parsed and combined with dosage to determine, and adjust, script end date. A closer look at patterns of patient prescriptions might yield rules to better infer actually usage dates. Some billing data is available in the database. This may indicate, for at least a subset of insurers, when patients refill prescriptions at the pharmacy – further refining script dates and speaking to adherence.

Other potentially useful BMC database fields include other medications (e.g. known to affect blood pressure or interact with antihypertensives), smoking status, illegal drug use, and codes indicating home blood pressure monitoring. Comorbidities such as: diabetes\(^1\), coronary artery disease, history of angina, myocardial infarction, heart failure, left ventricular hypertrophy, kidney disease, pregnancy, and menopause could be determined from diagnosis codes or patient problem lists. This information might be further enhanced by codes reflecting ECG test results and lab readings for blood urea nitrogen, creatinine, and glucose levels. Census tract and insurance provider can serve as socioeconomic proxies.

5.3.2 Models

To further explore the model presented in Section 4.3, we suggest considering timespans ranging from two years to full patient history. That is, consider blood pressure in the first year and predict blood pressure in the final year: over the first two years of each patient’s history, over the first three years for all patients with a history of

\(^1\)Appendix B explores adding diabetes information.
at least three years, etc\textsuperscript{2}. This removes the issues with varying timespan lengths discussed in Section 5.1. Additional modeling ideas to consider include:

- Tabulating number of patients as in Table 4.6, subdivided by other variables such as age, race, sex, BMI, and drug class. This could be framed as a “study” that presents treatment response percentages for various groups; a format familiar to clinicians and easily compared with the medical literature.

- Fitting blood pressure data with a more complex function. For example: continuous, piecewise-linear functions or higher-order polynomials, regularized somehow to balance goodness-of-fit and complexity.

- As noted in Section 5.1, Random Forest typically outperformed other methods tried. This suggests experimenting with additional methods sensitive to nonlinearities and resistant to over-fitting.

- Instead of systolic blood pressure, predicting pulse pressure or mean arterial pressure.

- Exploring other ways to use clustering results for prediction.

\textsuperscript{2}Median blood pressure features have already been constructed to allow this analysis. Processing of drug and weight/BMI features remains.
Appendix A

Additional Result Details

A.1 Example Model from Table 4.7

Here, as an example exploration of Table 4.7 results, we consider classification models for the 140+ bin. Recall, the baseline prediction of “< 140” has 50.2% accuracy. Figure A-1 shows the CART classification tree created for $cp=0.015$, with out-of-sample accuracy of 57.0%. Figure A-2 ranks the importance of variables for reducing node impurity in a corresponding Random Forest model, with out-of-sample accuracy of 60.9%. Table A.1 shows coefficient and p-values for a logistic regression model with out-of-sample accuracy of 58.7%.

First, note the difficulty of attributing predictive power to only a few variables, reflecting the complexity of this problem, and the correlation between many of the variables. A few variables stand out in at least two of these three models. More blood pressure measurements in the final year (numMeas.end) is correlated with decreasing blood pressure. This likely indicates greater engagement with healthcare providers to monitor and treat blood pressure, and perhaps better adherence as well. Age is clearly important. The logistic regression coefficient suggests younger, already-hypertensive patients have a harder time achieving control. Less easily interpreted: highly variable (or noisy) weight measurements (as indicated by residStdErr.weight) and shorter measurement history are correlated with decreasing blood pressure. A few correlations previously noted, which appear in these models, include: weight loss
<table>
<thead>
<tr>
<th>variable</th>
<th>coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>numMeas.end</td>
<td>-0.03</td>
<td>1.47e-11</td>
</tr>
<tr>
<td>ageAtT0</td>
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<td>1.25e-8</td>
</tr>
<tr>
<td>yearsBPhist</td>
<td>-0.06</td>
<td>1.22e-7</td>
</tr>
<tr>
<td>(Intercept)</td>
<td>-1.52</td>
<td>1.36e-5</td>
</tr>
<tr>
<td>raceblack</td>
<td>0.80</td>
<td>0.00157</td>
</tr>
<tr>
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<td>3.8e-4</td>
<td>0.00178</td>
</tr>
<tr>
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<td>-0.40</td>
<td>0.00598</td>
</tr>
<tr>
<td>ACE.maxDose</td>
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<tr>
<td>raceother</td>
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<td>0.01087</td>
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<tr>
<td>racehispanic</td>
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<td>0.01284</td>
</tr>
<tr>
<td>B1.weight</td>
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<tr>
<td>CALCIUM.frac</td>
<td>0.24</td>
<td>0.01543</td>
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<td>numDrugs</td>
<td>0.08</td>
<td>0.01763</td>
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<td>0.01</td>
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<td>Minoxidil.frac</td>
<td>2.77</td>
<td>0.09290</td>
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<td>0.11118</td>
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<tr>
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<td>0.14254</td>
</tr>
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</tr>
<tr>
<td>BETA.frac</td>
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<td>0.23618</td>
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<td>0.26581</td>
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<td>raceunknown</td>
<td>0.74</td>
<td>0.36085</td>
</tr>
</tbody>
</table>

Table A.1: Start bin: 140+, logistic regression (w/ sequential removal of high p-value variables)

($\beta_1$.weight) and decreasing blood pressure, as well as resistant hypertension and more medications (longer timespans, higher-doses, non-first-line classes). While race is of only medium importance in the Random Forest model, the logistic regression model indicates a significant, negative correlation between blacks and blood pressure control.
Figure A-1: Start bin: 140+, CART classification
Figure A-2: Start bin: 140+, RF classification

MeanDecreaseGini

- Hydralazine HCl frac
- CENTRAL ACT frac maxDose
- male
- CENTRAL frac
- ALPHA frac maxDose
- ARB frac maxDose
- ALPHA frac
- THIAZIDE frac maxDose
- ARB frac
- DIUR nonTHIAZ maxDose
- DIUR nonTHIAZ frac
- ACE frac maxDose
- DIUR nonTHIAZ frac
- ACE frac
- CALCIUM frac maxDose
- CALCIUM maxDose
- BETA frac
- numMeas start
- BETA frac
- numMeas end
- Median BMI
- Median weight
- B1.BMI
- B1.weight
- residStdErr BMI
- residStdErr weight
- bpRF
- MeanDecreaseGini

- race
- THIAZIDE frac
- THIAZIDE frac
- residStdErr BMI
- residStdErr weight
- residStdErr weight
- ageAtT0
- yearsBPhist
A.2 Clustering within Blood Pressure Bins: Full Results

Table A.2 presents results for predicting by cluster, within the starting blood pressure bins of “Model 3” (Section 4.3). While most of the results are similar or worse than predicting for the full bin (bottom row), a few slightly stronger results are highlighted in yellow. Note, as discussed in Section 4.3, that most of these correspond to the largest clusters.

One seeming outlier is cluster 6 in start bin “<120”. This cluster consists of older patients with fewer medications, shorter history, increasing weight, and slightly more measurements in the first year. The reported predictive power is from Random Forest; classification and regression with CART, even with parameter tuning by cross validation, and linear regression tend to perform poorly. Example plots of Random Forest variable importance for this cluster are presented in Figures A-3 (classification) and A-4 (regression). Of note, this cluster contains only 98 patients and predictive performance is highly dependent on the training set, making it difficult to tell if these stronger results are coincidence or a true trend.
Table A.2: Best results for segmenting by initial blood pressure, clustering within each segment, and then predicting final-year blood pressure for each bin-cluster subgroup. ("class." is model accuracy minus baseline accuracy, "regress." is $R^2$)

<table>
<thead>
<tr>
<th># clusters</th>
<th>Start BB bin</th>
<th>1.9–7.1</th>
<th>0–10</th>
<th>0.05–0.1</th>
<th>0.1–0.19</th>
<th>0.8–0.13</th>
<th>0.4–0.8</th>
<th>0.2–0.4</th>
<th>0–0.2</th>
<th>all in start BB bin, no clustering</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.05–0.10</td>
<td>0.05–0.10</td>
<td>0.1–0.19</td>
<td>0.8–0.13</td>
<td>0.4–0.8</td>
<td>0.2–0.4</td>
<td>0–0.2</td>
<td>0–0.2</td>
<td>3040 1.9–7.1 0.10–0.19 0.8–0.13 0.4–0.8 0.2–0.4 0–0.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.05–0.10</td>
<td>0.05–0.10</td>
<td>0.1–0.19</td>
<td>0.8–0.13</td>
<td>0.4–0.8</td>
<td>0.2–0.4</td>
<td>0–0.2</td>
<td>0–0.2</td>
<td>3040 1.9–7.1 0.10–0.19 0.8–0.13 0.4–0.8 0.2–0.4 0–0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.05–0.10</td>
<td>0.05–0.10</td>
<td>0.1–0.19</td>
<td>0.8–0.13</td>
<td>0.4–0.8</td>
<td>0.2–0.4</td>
<td>0–0.2</td>
<td>0–0.2</td>
<td>3040 1.9–7.1 0.10–0.19 0.8–0.13 0.4–0.8 0.2–0.4 0–0.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.05–0.10</td>
<td>0.05–0.10</td>
<td>0.1–0.19</td>
<td>0.8–0.13</td>
<td>0.4–0.8</td>
<td>0.2–0.4</td>
<td>0–0.2</td>
<td>0–0.2</td>
<td>3040 1.9–7.1 0.10–0.19 0.8–0.13 0.4–0.8 0.2–0.4 0–0.2</td>
<td></td>
</tr>
</tbody>
</table>

Median systolic blood pressure in initial year

### Class # regress.

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<tr>
<th>Class</th>
<th>#</th>
<th>regress.</th>
<th>Class</th>
<th>#</th>
<th>regress.</th>
<th>Class</th>
<th>#</th>
<th>regress.</th>
<th>Class</th>
<th>#</th>
<th>regress.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120</td>
<td>1</td>
<td>10.1</td>
<td>&gt;130</td>
<td>1</td>
<td>10.1</td>
<td>&gt;120</td>
<td>1</td>
<td>10.1</td>
<td>&gt;130</td>
<td>1</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Median systolic blood pressure in initial year
<table>
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<th>Variable</th>
<th>Importance</th>
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</tr>
<tr>
<td>B1.weight</td>
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<tr>
<td>B1.BMI</td>
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<td>median.BMI</td>
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<td>residStdErr.weight</td>
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<tr>
<td>yearsBPhist</td>
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<tr>
<td>numMeas.end</td>
<td></td>
</tr>
<tr>
<td>BETA.frac</td>
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<td>residStdErr.BMI</td>
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</tr>
<tr>
<td>ACE.maxDose</td>
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</tr>
<tr>
<td>numMeas.start</td>
<td></td>
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<tr>
<td>DIUR_nonTHIAZ.maxDose</td>
<td></td>
</tr>
<tr>
<td>race</td>
<td></td>
</tr>
<tr>
<td>BETA.maxDose</td>
<td></td>
</tr>
<tr>
<td>DIUR_nonTHIAZ.frac</td>
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</tr>
<tr>
<td>numDrugs</td>
<td></td>
</tr>
<tr>
<td>CALCIUM.frac</td>
<td></td>
</tr>
<tr>
<td>THIAZIDE.frac</td>
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</tr>
<tr>
<td>CALCIUM.maxDose</td>
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</tr>
<tr>
<td>ARB.frac</td>
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</tr>
<tr>
<td>male</td>
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<tr>
<td>ARB.maxDose</td>
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</tr>
<tr>
<td>THIAZIDE.maxDose</td>
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<tr>
<td>ALPHA.frac</td>
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<tr>
<td>ALPHA.maxDose</td>
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<tr>
<td>CENTRAL_ACT.frac</td>
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<td>Hydralazine_HCl.maxDose</td>
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<tr>
<td>Hydralazine_HCl.frac</td>
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</tr>
</tbody>
</table>

Figure A-3: Random Forest classification for cluster 6 in <120 starting bin: variable importance for decreasing node impurity
Figure A-4: Random Forest regression for cluster 6 in >120 starting bin. Variable importance for decreasing node impurity.
Appendix B

Impact of Including Diabetes Variable

To begin investigating the importance of comorbidities, we queried the BMC database for patients with diabetes codes (ICD9 250.*) in their problem list and converted this to an “is diabetic” binary variable. Overall, 36% of the study population is diabetic. Of the patient clusters presented in Section 3.2, clusters 6 and 8 (and 4, slightly) have more diabetics than average, while cluster 7 has the smallest proportion. This is consistent with the other noted features of these clusters. In particular, the density of measurements in cluster 6 may be partially explained by patients visiting the doctor more frequently for management of diabetes.

Tabulating diabetic patients, as in Table 4.6, indicates they are somewhat more likely to have higher blood pressure, by both starting and ending bin. We then re-ran “Model 3” with this additional variable. The results were no better than those in Table 4.7. The diabetic variable seemed to be of similar importance to the “low” class in Table 5.1.

Finally, we made predictions for diabetic and non-diabetic patients separately. These results are reported in Table B.1 and show slightly stronger predictions in the diabetic population.
<table>
<thead>
<tr>
<th>Starting BP</th>
<th># classes</th>
<th>baseline (%)</th>
<th>CART</th>
<th>RF</th>
<th>log. reg.</th>
<th>CART</th>
<th>RF</th>
<th>lin. reg.</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diabetic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>4</td>
<td>35.6</td>
<td>4.0</td>
<td>3.0</td>
<td>0.11</td>
<td>0.13</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[120, 130)</td>
<td>4</td>
<td>30.0</td>
<td>-2.2</td>
<td>1.4</td>
<td>0.04</td>
<td>0.09</td>
<td>0.04</td>
<td></td>
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<tr>
<td>[130, 140)</td>
<td>3</td>
<td>35.5</td>
<td>3.3</td>
<td>5.7</td>
<td>-0.01</td>
<td>0.06</td>
<td>0.03</td>
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<td></td>
</tr>
<tr>
<td>140+</td>
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<td>51.1</td>
<td>5.0</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.57</td>
<td>0.62</td>
<td>0.60</td>
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<td></td>
</tr>
<tr>
<td>Diabetic patients</td>
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<td></td>
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<td>&lt;120</td>
<td>4</td>
<td>31.3</td>
<td>3.4</td>
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<td>0.13</td>
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</tr>
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<td>140+</td>
<td>2</td>
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<td>0.01</td>
<td>0.05</td>
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<td>0.65</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
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</table>

Table B.1: Results for predicting blood pressure trajectory separately for diabetic and non-diabetic patients
Bibliography


