

# Constructing Decision Models for Diabetes Using Clinical Data

by  
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Submitted to the Department of Electrical Engineering and Computer Science  
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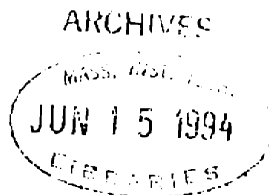
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**Abstract:** Clinicians often have to make decisions under uncertainty. Decision analysis provides a framework for reasoning about such problems. Markov modeling is a formalism for decision analysis that is desirable because of its simplicity and ease of use in calculating prognosis. Constructing realistic and comprehensive models, however, can be challenging. We would like to include all the factors relevant to the problem and yet keep the model simple enough such that calculation is possible. Further, estimates of the parameters of a Markov model, i.e., the transition probabilities, are frequently supplied subjectively by medical experts or derived from medical literature. When the decision situations are complex or the decision dimensions are large, such estimations may not be possible. On the other hand, calculating objective probabilities from clinical data may be complicated by data formats, measurement assumptions, and recording errors. Finally, there needs to be some way of measuring the success of a model and its parameters.

This project addresses these issues by constructing decision models for Type I diabetes and uses clinical data to determine the model parameters. In constructing decision models, I had to constantly balance model complexity with comprehensiveness. Using clinical data introduced additional complications as I had to deal with recording errors and missing data. Several heuristics for dealing with imperfect data were used. A number of methods, including simulation, expert opinion, and confidence measures, were used to evaluate the models. While the models greatly simplified the decision problem, results were obtained which corresponded to clinical practice. Thus, with more comprehensive models and cleaner data, Markov modeling may be a useful tool for the management of Type I diabetes.

Thesis Supervisor: Peter Szolovits

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# Chapter 1

## Introduction

A doctor or clinician frequently has to make decisions in the face of uncertainty. He has to consider possible treatments and weigh the risks and benefits of each treatment. Decision analysis provides a framework for reasoning about such problems. Decision analysis has two components: utility theory and probability theory. Utility theory provides a mechanism for comparing or expressing preferences for particular outcomes by assigning numerical values to all possible outcomes. Probability theory captures the uncertainty in a decision problem and allows us to determine mathematically which outcome is likely to occur. By combining utility and probability theory, decision analysis allows us to evaluate alternative actions and decide on the actions which optimize the outcome.

Markov modeling is one mathematical formalism used in decision analysis. A Markov model describes all the possible states of health a patient can be in. Different treatments or therapies, with a certain probability, can cause a patient to change from one state of health to another. After assigning utilities to each state, we can determine a solution which optimizes a patient's overall health. Constructing a realistic model, however, can be challenging. We would like to include all the factors relevant to determining proper treatment and yet keep the model simple enough such that calculation is possible. Furthermore, estimates of the parameters of a Markov model, i.e., the transition probabilities, are frequently supplied subjectively by medical experts or derived from medical literature. When the decision situations are complex or the decision dimensions are large, such estimations may not be possible. On the other hand, calculating objective

probabilities from clinical data may be complicated by data formats, measurement assumptions, and recording errors. Furthermore, there needs to be some way of measuring the success of a model and its parameters.

This project aimed to explore these issues by applying Markov modeling techniques to the treatment of Type I diabetes. Clinical data were used to determine transition probabilities. Goals of this project were:

- Evaluate the use of Markov processes in representing insulin therapy for Type I diabetes.
- Construct simple models representing the decision problem.
- Develop and implement methodologies for extracting transition probabilities from clinical data.
- Develop and implement methodologies for working with imperfect data.
- Determine ways to measure the success or effectiveness of the model and its parameters.

The clinical data used were logs obtained from 80 Type I diabetes patients. I constructed Markov model which could recommend adjustments in insulin dosages in response to glucose measurements. There was a constant trade-off between keeping the model simple and yet comprehensive. Later, I used a more complex model in an attempt to improve the recommendations. A simple counting method was used to determine the transition probabilities. The data supplied were sufficient for deriving the transition probabilities and determining an optimal policy of actions, although initially some of the probabilities were inaccurate and caused errors in the recommended policy. Additional rejection and error-checking mechanisms were added to improve the accuracy of the probabilities. Finally, several methods, including expert opinion, simulation, and confidence measures, were used to assess the probabilities and resulting policy.

Experts were consulted for their assessment of the models, probabilities and recommended actions. The general response was that the models were too simplified to be useful for diabetic treatment. Nonetheless, useful lessons were learned from building simple



Markov models and experimenting with clinical data. Factors such as data requirements, model complexity, and clinical use imposed constraints on the model. Counting transitions from clinical data was an acceptable method for calculating transition probabilities. However, this method did not deal with errors well. Error-checking mechanisms were needed to make the transition probabilities more reliable. Despite problems with the complexity of the decision problem and imperfect clinical data, reasonable actions were determined for the states in the model.

Chapter 2 will provide some background information on Type I diabetes, Markov modeling, and the clinical data used. Chapter 3 will give an overview of the system and describe the modules of the system. Chapter 4 will describe methods for evaluating the results and present an analysis. Chapter 5 will discuss the issues raised by this project. Finally, Chapter 6 will summarize the project and describe possible future work.

# Chapter 2

## Background

This chapter will provide some background information on Type I diabetes, Markov modeling, and the clinical data used.

### 2.1 Type I Diabetes

Type I diabetes, or Insulin Dependent Diabetes Mellitus (IDDM), results from the failure of the pancreas to produce the hormone insulin in response to raised blood glucose levels. Patients rely on injections of insulin, as well as diet and exercise, to keep their blood glucose levels under control [2].

#### 2.1.1 Complications

The goal of therapy for Type I diabetes is to lower average blood glucose (BG) and keep it within as narrow a range as possible. However, glucose-insulin interaction is a difficult control problem. In a normal human, insulin varies minute by minute to maintain glucose homeostasis. In contrast, a diabetic patient typically receives 2-4 injections per day, resulting in large, and sometimes dangerous, swings in BG. Chronic hyperglycemia (high blood glucose) over a number of years puts the patient at risk for problems such as ketosis, acidosis, and retinopathy. On the other hand, hypoglycemia (low blood glucose), caused by missed meals, excessive insulin dosage, or unplanned exercise, can cause headaches, dizziness, and sweating. If blood glucose falls to too low a level, the patient's brain is inadequately supplied with glucose, and the patient may become unconscious or fall into a coma. While lowering average BG levels is beneficial to the patient in the long term, in the short term it can increase the risk for hypoglycemic episodes.

### 2.1.2 Insulin Therapy

Three types of insulin are typically used: short-acting, intermediate-acting, and long-acting. The profiles of each type of insulin are listed in Table 1 [1]. Short-acting (regular) insulin has the shortest onset and duration of action and can be administered several times a day. Intermediate-acting insulins, such as neutral protamine Hagedorn (NPH) and Lente, have a longer onset and duration of action, and are given once or twice a day. Long-acting insulins, such as Ultralente and protamine zinc insulin (PZI), have a slow onset of action and a flat peak of action that can last for up to 60 hours. They are used to provide a “basal” level of insulin, and dosages are changed infrequently.

Insulin Type	Onset (hr.)	Peak (hr.)	Duration (hr.)
Regular	0.5-1	2-4	6-8
NPH	1.5	4-12	18-24
Lente	2.5	6-14	18-28
Ultralente	4-6	18-24	36-40
Protamine zinc	4-6	12-24	36-40

**Table 1:** Action profiles of different types of insulin

### 2.1.3 Computer-based Methods for Insulin Adjustment

There are several computer-based methods for adjusting insulin to maintain stable BG levels. They can be classified into rule-based, model-based, or probabilistic approaches.

Rule-based approaches are used for routinely adjusting dosage, following if-then rules such as those published in [9]:

- If pre-lunch blood glucose is greater than 130 mg/dl for 2-4 days in a row, increase your pre-breakfast regular insulin by 1 or 2 units.
- If pre-lunch blood glucose is less than 70 mg/dl or if you have a hypoglycemic reaction between lunch and supper, reduce your pre-lunch regular insulin by 1 or 2 unit.

These rules are easy to program. However, they cannot predict future behavior, i.e. future BG levels or hypoglycemic symptoms. Conflicts can arise when several rules' conditions are satisfied. Also, the rule set does not take into account the differences between

individuals and cannot learn additional knowledge about the patient.

Model-based approaches use mathematical models which reflect the underlying physiology of insulin action, insulin sensitivity, absorption rate, etc. These models provide a framework for characterizing a patient quantitatively and predicting BG levels. Actions are chosen by determining which actions yields the best BG levels according to the model. For example, Roman Hovorka and others [4] used an adaptive approach, where the patient-specific parameters of the model, basal insulin requirement and insulin sensitivity, were continually re-adjusted based on the difference between predicted and observed BG. Model-based strategies have the benefit of being based on physiological models. However, they must be very comprehensive to be useful in clinical situations. This complexity makes models difficult to construct and analyze.

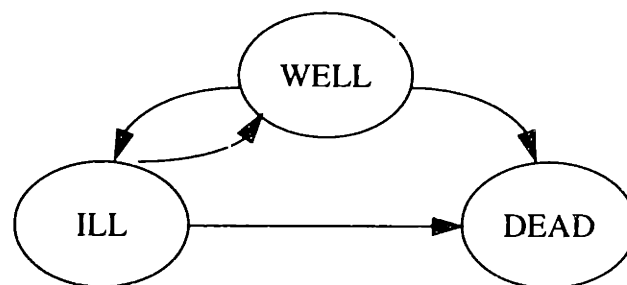
Probabilistic approaches rely on an underlying physiological model while taking into account the uncertainty of glucose-insulin interaction. One probabilistic strategy for diabetic management [5] used causal probabilistic networks (CPNs), also known as belief networks, to model glucose metabolism. Such an approach is able to represent uncertain knowledge, predict BG values, and compare competing therapies. The limitation of CPNs is similar to that of a modeling approach. As the underlying model becomes more comprehensive, the number of nodes in the network increases, and it becomes more difficult to determine the necessary conditional probabilities. Markov and semi-Markov modeling are other formalisms used in probabilistic approaches.

## **2.2 Markov Modeling**

A Markov decision process is composed of a set of states, actions, transitions between states, and values (utilities) assigned to the states. States capture a patient's health status or physiological state, e.g., blood glucose levels. Utility values express the desirability of being in each state. A patient can occupy only one state at any point in time, but transitions, or changes of state, may occur over time. Actions are different treatments or inter-

ventions which can cause a transition from one state to another. The transition probability between states  $i$  and  $j$ ,  $P_{ij}^a$ , is defined to be the probability that a transition occurs from  $i$  to  $j$ , given action  $a$ . By maximizing the expected or average utilities achievable in each state, an optimal course of actions, or policy, can be determined for the decision process. For each state, the policy specifies the action which, when taken, optimizes the expected or average utility of the outcome. In a Markov process, transitions are governed only by the current state and action taken. No knowledge of prior history is needed. It is this property of a Markov process that makes the solution easy to calculate.

Figure 1 illustrates Markov modeling. The states are WELL, ILL, and DEAD. Obviously, WELL has the highest utility and DEAD has the lowest. A patient can make a transition from WELL to ILL and vice versa, as well as from WELL or ILL to DEAD. There is no transition from the DEAD state. At each state, a patient can choose between alternate actions which may cause a transition. Therefore, we would like to determine a policy of actions which tends to keep the patient in a WELL state and avoid the DEAD state



**Figure 1:** Example of a Markov model

### 2.3 Clinical Data

Dr. Michael Kahn of Washington University, St. Louis, Mo., supplied data on 80 outpatients, covering several weeks to several months of therapy. Each record in the data has the following format:

1. Date in MM-DD-YYYY format

2. Time in HH:MM format
3. Code--indicating what quantity is being measured, i.e. insulin dosage, blood glucose measurement, meal size, etc.
4. Value--value of the measurement indicated by the code.

The types of insulin used were regular, NPH, and Ultralente. Records also indicated whether blood glucose measurements were taken before or after breakfast, lunch, and supper. Unspecified measurements (no indication of whether they were taken before or after a meal) were also recorded. Some information was provided as to the size of meals and amount of exercise, but because there were so few entries of this information, it was not used in my model.

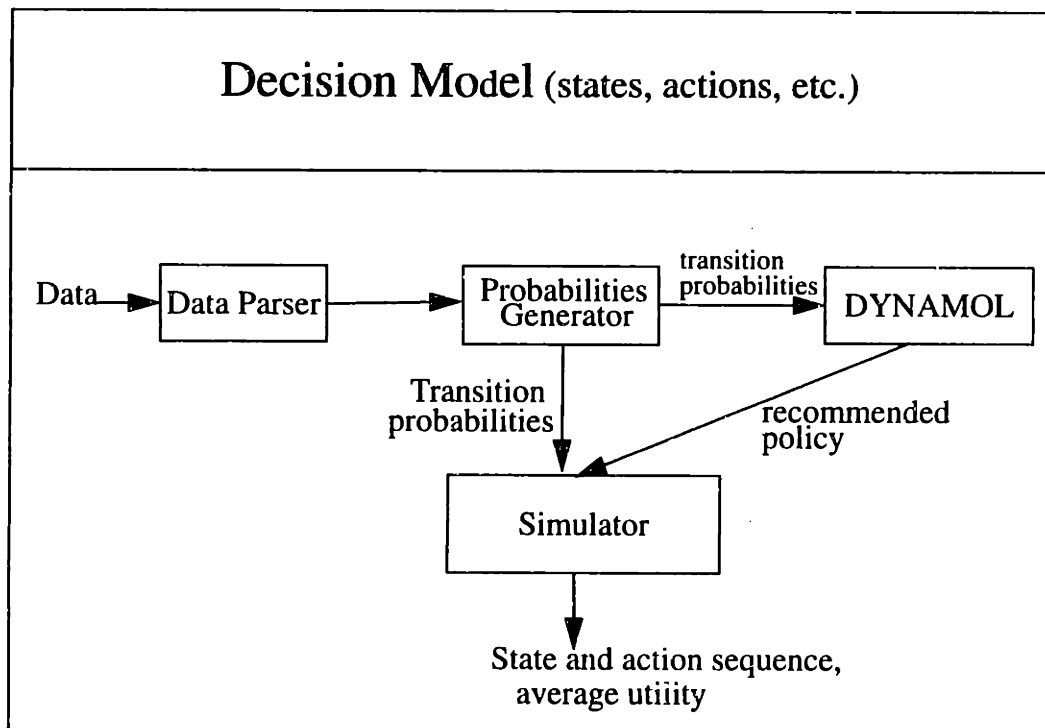
The data was based on patient logs, thus, there may be errors or gaps in each data, or the patient may not record certain information. For example, some data sets contained only unspecified BG measurements, with no information on when meals were eaten, while others contained no records of insulin dosages for part of the data set. Finally, there was no information on the patient's age, health, insulin regimen, etc.

# Chapter 3

## System Description

This chapter will describe the system design. Because the data format, underlying model, and probability generation algorithm may change, the functions of the system are organized into modules which can be replaced easily.

### 3.1 Overview



**Figure 2:** System modules

Figure 2 shows the modules of the system. The Data Parser converts data into a sequence of states and actions to be used by the Probabilities Generator. The Probabili-

ties Generator determines the transition probabilities. DYNAMOL (DYNAMIC MODELing Language) determines a policy from the decision model and its probabilities. The Simulator simulates the behavior of a patient following the policy generated by DYNAMOL. Finally, all modules depend on the decision model.

### 3.2 Decision Model

The fundamental issue in designing the decision model is creating a useful model while keeping the number of states and transitions small. A partial list of factors in glucose-insulin interaction include:

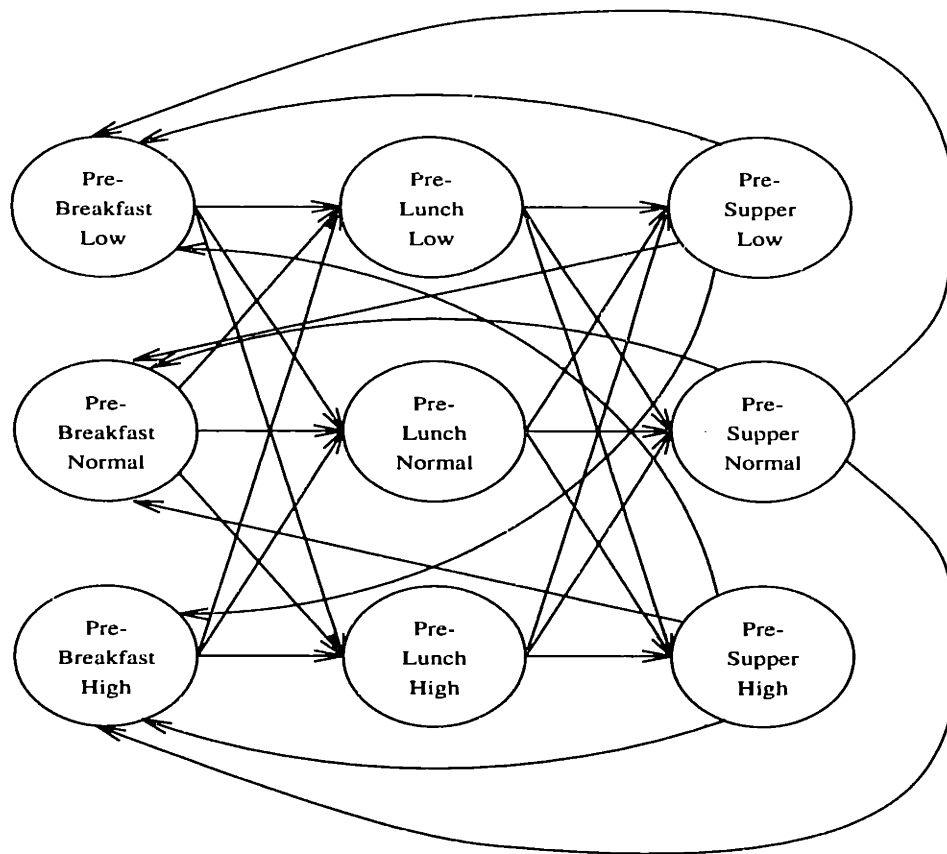
- age and physiological state of the patient
- insulin sensitivity
- insulin action
- insulin absorption
- diet
- exercise
- previous history of BG measurements

It is important to keep the model simple and the number of states small, although this sometimes comes at the expense of comprehensiveness. Doctors at New England Medical Center who are building Markov models suggest that models with at most 20 states are manageable. Markov models of as few as three states have been used for medical practice [8]. Therefore, I took many simplifications to keep the number of states manageable. Diet and exercise were ignored because there were insufficient data on these factors. Further, the state variables of the model must be of observable quantities, as the data were obtained from patient logs of measurements and actions taken. Thus, the model was unable to capture unobservable quantities such as insulin sensitivity. However, some of these factors could be learned indirectly from the data by observing how a patient's glucose levels responded to insulin therapy. If the transition probabilities of a model could be determined for an individual patient, the system would also learn the patient's response to various



insulin therapies, which would take into account some of these unobservable factors.

A state-transition diagram of our decision model is shown in Figure 3:



**Figure 3: State-Transition Diagram**

States are defined by two state variables, or dimensions along which the patient's health are defined:

- blood glucose (BG) level = {HIGH, NORMAL, LOW}
- time of measurement = {PRE-BREAKFAST, PRE-LUNCH, PRE-SUPPER}

BG levels are continuous values, however, they must be divided into intervals in the model. BG levels below 80 mg/dl are considered to be low. BG levels from 80-120 mg/dl are normal, and anything above that is high. Dividing BG into these three intervals results in a very coarse-grained model, but it does keep the number of states manageable. Times

of measurement are defined to be pre-meal because those are the times when the patients in the data sets took BG measurements. This model divides the day into three time slices: pre-breakfast, pre-lunch, and pre-supper. Transitions can only occur from one time slice to the one immediately following it. This is done because in a Markov process, states have no memory of past states and actions--transitions depend only on the current state. To have any memory, some history variables have to be added to the state variables, greatly increasing the number of states. Ramoni [7] and others took a similar approach when using Bayesian networks to predict blood glucose in diabetes patients.

Each arrow in the figure corresponds to a possible transition, conditional upon nine actions. Actions are defined by two variables:

- change in regular insulin = {MORE, SAME, LESS}
- change in NPH insulin = {MORE, SAME, LESS}

Changes in insulin dosage are used instead of actual dosages because patients take varying amounts of insulin. Unfortunately, there were not enough data to apply the model to individual patients. In the future, if enough data are supplied for each patient, it may be possible to use actual dosages as actions. Ultralente insulin is ignored because it is used to deliver a basal level of insulin and is seldom changed. There are 243 possible transitions--9 states, 3 possible states to transition to, and 9 actions. This model deals with insulin therapy in the short term. It can predict BG levels and recommend insulin dosage adjustments at each meal.

### **3.2.1 Alternate Model**

The model described in the previous section is a useful prototype model. However, it ignores an important aspect of insulin action. NPH has a long duration of action which extends beyond a single time slice. In the original model, an action's effect extends for only one time slice. Thus, a subsequent implementation of the decision model added a "history" variable which kept track of whether NPH insulin was taken in the time slice before. This new model can capture the effects of NPH insulin for longer than one time

slice. With the new state variable, there are now 18 possible states:

- blood glucose (BG) level = {HIGH, NORMAL, LOW}
- time of measurement = {PRE-BREAKFAST, PRE-LUNCH, PRE-SUPPER}
- previous NPH = {YES, NO}

The actions now have to be actual dosages because changes in dosage give no indication whether any NPH is taken or not. However, using actual dosages is difficult when data from many patients are used. Different patients take varying amounts of insulin. In fact, the same patient can have very different dosages at different times during the day. Thus, dosage is represented as a percentage of the average dosage for an individual patient in each time slice. Insulin dosages are divided into three categories (low, medium, and high) to keep the number of actions the same as before. Various ways of dividing regular and NPH dosages into intervals were tried. The one that yields the best results is:

- Regular: 0-75%, 75-125%, above 125%
- NPH: 0-50%, 50-150%, above 150%

NPH Dosages that are within 0-50% of normal is considered to be a zero dosage because NPH is seldom reduced to 50% of the average. Using this division, only the number of states is doubled, and the number of transition probabilities is twice that of the original model (486).

### **3.3 Data Parser**

The Data Parser reads in the patient data sets and converts them into a format readable by the system. It parses the data codes, converts the date and time to a decimal number, and filters out extraneous data. The output is a list of BG measurements, insulin dosages, and the time that each quantity is recorded. The module deals with the different data formats. Alternative modules, such as one which normalizes insulin dosage, can be coded and used when different data are used.

### 3.4 Probabilities Generator

The Probabilities Generator identifies the states and actions from the parsed data and generates a sequence of states and actions. It computes changes in dosage by comparing the current dosage with the dosage a day ago. To determine the transition probability from states  $i$  to  $j$ , given action  $a$ , the system counts all the transitions from  $i$  to  $j$  given action  $a$  and divides that by the total number of transitions out of  $i$  for action  $a$ .

Although counting transitions is a sufficient method for calculating transition probabilities, multiple regression models may also be used. One possible regression method is normal probit regression [3], which assumes a normal distribution for the dependent variable, future BG level. Regression analysis determines the distribution for BG levels from previous BG levels and insulin dosages. The distribution can then be used to determine the probability that future BG falls within a certain interval. This was not implemented in my system, although Brian Kan of the New England Medical Center has used this technique.

### 3.5 DYNAMOL

DYNAMOL (DYNAmic MOdeling Language) [6] is a prototype implementation of a modeling framework where a decision problem is formulated in terms of a high-level decision grammar, visualized via a set of graphical presentation conventions, and solved with respect to its formal mathematical representation as a semi-Markov or Markov decision process. A semi-Markov process is similar to a Markov process except that it has an additional parameter, holding time distribution. The holding time distribution describes the time it takes to make a transition after an action has been taken. A Markov process is simply a semi-Markov process where holding time distributions are defined as unit time steps. Given a Markov model, the transition probabilities, and a set of utilities for the states, DYNAMOL determines an optimal policy of actions to be taken in each state. The optimal policy can be solved for various time horizons, from one cycle (one time slice) to infinity. Because the decision problem is a short term one, I used a time horizon of three

cycles, equivalent to one day.

### **3.6 Simulator**

After determining a policy using DYNAMOL, the simulator is used to evaluate the model and its parameters. Given the model, transition probabilities, utilities, and policy of optimal actions, the simulator generates a sequence of patient states. In the simulator, a patient only takes the recommended action in each state, and the transitions are determined according to their probabilities. The simulator takes in the duration (in days) for the simulation and outputs a sequence of states and an average utility value--the average utility value of all the states occupied by the simulated patient.

This average utility is used to evaluate different models and probabilities. As the model is refined or the probabilities become more accurate, it should be more likely to maintain control over blood glucose, which would result in higher average utilities. Other methods for evaluating decision models will be discussed in the next chapter.

# Chapter 4

## Results

After implementing the system described in the previous chapter, I used the system to determine the transition probabilities and policy. This chapter will present the results and discuss methods for evaluating them.

### 4.1 Methods for Verifying Results

How does one verify the transition probabilities and recommended policies without trying them on actual patients? Transition probabilities were evaluated by simulation and varying the utilities. Policies were evaluated by comparing them to expert opinion, matching them to clinical data, and determining a “confidence” measure for each action.

#### 4.1.1 Simulation

The models and probabilities were evaluated by medical experts--Isaac Kohane of Children’s Hospital and Mark Eckman of New England Medical Center. They felt that the models were too simplified to be useful for clinical practice, but they were useful for experimenting with Markov modeling for the diabetes domain. The transition probabilities were mostly found to be reasonable; the incorrect values may be due to errors in the data or an oversimplification of the decision model. The probabilities were further verified through simulation. If the method of estimating transition probabilities is correct, then a simulated patient should have transition probabilities close to those of real patients. Using the simulator to generate a sequence of states and actions, I was able to re-derive the transition probabilities from that sequence to within 5-10% of the original. This indicated that, at least, the implementation of the transition counting algorithm and

simulator was correct.

#### 4.1.2 Varying the utilities

Another method for verifying transition probabilities is to vary the utilities and examine the resulting policy. Utilities are supposed to express the desirability of being in each state, but it is ambiguous whether high BG or low BG is better. The long term goal of insulin therapy is to lower BG levels. However, in the short term, it is desirable to avoid the unpleasant, and sometimes dangerous, symptoms caused by low BG levels. The utilities, shown in Table 2, are supplied by Dr. Isaac Kohane of Children's Hospital. These utility values give preference to low BG. Thus, the recommended policy should be biased towards increasing insulin and lowering BG levels. If utility values are changed to give preference to high BG, however, then the recommended policy should shift towards decreasing insulin to avoid hypoglycemic episodes. In one experiment, the utilities for high and low BG are swapped to give preference to high BG. And as expected, there were fewer actions which increase insulin and more actions which decrease insulin.

State	Utility
pre-breakfast low	0.4
pre-breakfast normal	1.0
pre-breakfast high	0.1
pre-lunch low	0.3
pre-lunch normal	1.0
pre-lunch high	0.1
pre-supper low	0.4
pre-supper normal	1.0
pre-supper high	0.1

**Table 2:** Utility values

#### 4.1.3 Evaluation criteria for policies

It is more difficult to prove that the policies are clinically correct. Since the models are

very simplified, they cannot be compared to medical literature. I consulted a teaching nurse at Children's Hospital as to what she would do in each situation. She said if no other information other than current BG is known, then a general rule of thumb is to decrease regular insulin by 10% if BG is low, increase by 10% if BG is high, and keep insulin the same if BG is normal. This is a short-term adjustment that some motivated patients can make themselves using a "sliding scale" formula. These patients use previous BG level to calculate how much to increase or decrease their insulin by. Other patients may follow a set regimen and consult a nurse or doctor if problems arise. In such a case, a nurse may make adjustments to the overall schedule. Both regular and NPH insulin dosages may be changed.

Thus, it is important to know what type of therapy a patient is using. Are they making short term adjustments, or following a fixed therapy and making occasional changes to their insulin regimen? In the absence of any patient information, further methods are needed to evaluate policies. Other methods include matching them to clinical data to see what percentage of patients followed them. Furthermore, the number of patients who followed each action in a policy can be used as a confidence measure of that particular action.

## 4.2 Policies

Having discussed methods for evaluating policies, we now come to the policies themselves. For the first model, a list of actions recommended is shown in Table 3:

This policy does not seem to follow the rule of thumb suggested earlier. This can be due to either the model or the data. The model does not fully capture the effects of NPH insulin. In addition, some of the actions chosen had transition probabilities that were based on very few cases. For example, there were three instances where a patient was in a (pre-lunch, high BG) state and took the action of (less regular, less NPH). Normally, a patient should increase insulin when BG is high. It turned out that in two of the instances, the patient ended up with normal pre-supper BG, while in the remaining case, he ended up



with high BG. The probability of ending up with normal pre-supper BG is 2/3. Since all the other actions resulted in normal BG with lower probability, the action of (less regular, less NPH) was chosen as the recommended action even though it did not make clinical sense. It seems that placing a filter or some sort of error-checking mechanism on the transition probabilities may be able to improve the system.

State	Policy
pre-breakfast low	same regular, less NPH
pre-breakfast normal	same regular, same NPH
pre-breakfast high	more regular, less NPH
pre-lunch low	same regular, same NPH
pre-lunch normal	same regular, same NPH
pre-lunch high	less regular, less NPH
pre-supper low	same regular, same NPH
pre-supper normal	same regular, same NPH
pre-supper high	more regular, less NPH

**Table 3:** Optimal policy for the first model

#### 4.2.1 Improvements to the Probability Generator

Several methods were tried to improve the system. Actions with fewer than 10 observed cases were ruled out to filter out unusual actions. The new recommended policy followed the rule of thumb more closely. A final improvement was to rule out gaps in the data. Since unrecorded (or missed) dosages at meal times are treated as zero dosages, a whole series of these can be interpreted as a series of {Same Reg, Same NPH} actions. The new policies generated after implementing these improvements are shown below in Table 4.

The final results do seem reasonable according to the rule of thumb. The fact that most of the actions are to keep insulin the same may be because patients are already on a pre-

determined insulin therapy and are unlikely to change it.

State	Policy (after filtering)	(after eliminating gaps)
pre-breakfast low	same regular, same NPH	less regular, same NPH
pre-breakfast normal	same regular, same NPH	same regular, same NPH
pre-breakfast high	more regular, same NPH	same regular, same NPH
pre-lunch low	same regular, same NPH	same regular, same NPH
pre-lunch normal	same regular, same NPH	same regular, same NPH
pre-lunch high	same regular, same NPH	same regular, same NPH
pre-supper low	same regular, same NPH	less regular, same NPH
pre-supper normal	same regular, same NPH	same regular, same NPH
pre-supper high	more regular, more NPH	more regular, same NPH

**Table 4:** Improved Policies

#### 4.2.2 Results of Alternate Model

Policies were also generated for the alternate model. Unfortunately, using an additional state variable in the alternate model did not improve the recommendations. The main difficulty is in using dosage values instead of changes in dosage. Insulin regimens differed so much in the 80 patients studied that it was difficult to categorize them with only three intervals of dosage values. Also, if the difference in insulin dosage is small, two different dosages may be treated as the same action. After applying the same improvements as before, the results are as show in Table 5.

Again, the results are reasonable. The recommended regular insulin dosages do not follow the rule of thumb exactly because NPH is now factored in. However, the policy now reflects NPH dosage adjustments. NPH tends to be taken twice a day. When NPH is taken in the previous meal, less insulin is taken than if NPH is not taken because of NPH's long duration of action. This makes clinical sense. The actions for pre-supper when NPH was taken earlier seem unusual at first. Low regular insulin was taken for all three pre-supper states. This may be because the NPH taken at lunch is reaching its peak of action.

Thus, it is not necessary to take very much regular insulin. The actions for pre-supper and no NPH taken earlier were unexpected. Normally, NPH is taken in the evening to counteract increased glucose output in the early morning hours. An examination of the data indicated that patients were either not taking or recording NPH taken before supper. This was probably due to either an omission by the patient or Ultralente insulin, which has the longest duration of action, taken earlier.

Previous Meal's NPH	State BG and time slice	Action
no NPH	pre-breakfast low	Med Reg, Med NPH
	pre-breakfast normal	Med Reg, Med NPH
	pre-breakfast high	High Reg, Med NPH
	pre-lunch low	Med Reg, Low NPH
	pre-lunch normal	Med Reg, Low NPH
	pre-lunch high	Low Reg, Low NPH
	pre-supper low	Med Reg, Low NPH
	pre-supper normal	Low Reg, Low NPH
	pre-supper high	High Reg, Med NPH
NPH	pre-breakfast low	Med Reg, Low NPH
	pre-breakfast normal	Low Reg, Low NPH
	pre-breakfast high	Med Reg, Med. NPH
	pre-lunch low	Med Reg, Low NPH
	pre-lunch normal	Med Reg, Low NPH
	pre-lunch high	High Reg, Low NPH
	pre-supper low	Low Reg, Med NPH
	pre-supper normal	Low Reg, Med NPH
	pre-supper high	Low Reg, Med NPH

**Table 5:** Policy for alternate model

### 4.3 Simulator Tests

The policies can now be evaluated through the simulator. The simulator generates a sequence of states and actions and an average utility value indicating the desirability of the state sequence. In addition to re-deriving transition probabilities, the simulator can give some indication of whether there has been an improvement in the probabilities or policy.

Utility values were calculated for varying numbers of patient data sets. Forty data sets were used initially, and incremented by ten up to eighty. The average utilities increased with the number of data sets and stabilized at 70, suggesting better control as the probabilities and optimal policy became more accurate. Similarly, the recommended policies began following the rule of thumb more closely as the number of data sets were increased. They also stabilized after 70 data sets.

After the policies were improved by filtering probabilities substantiated by only few cases and eliminating gaps, new utilities were calculated through the simulator. There was no improvement in utilities, in fact, there was even a slight decrease. This was because filtering removed certain actions which had the highest probability of bringing BG to normal, even though those probabilities might have been inaccurate. If there was no filtering but gaps were eliminated, then the utilities were about the same as the original.

The simulator utilities for the alternate model were slightly lower than the improved policies described earlier. Since it was difficult to make this model fit all the data sets, the policy and probabilities might have been inaccurate. Also, since there were twice as many transition probabilities, fewer cases were available to substantiate each probability.

### 4.4 Confidence Measures

While the simulator is unable to compare the different models and policies, confidence measures may be used. The policy can be matched to clinical data to see if patients indeed followed this policy. These measures are calculated by merging the data from all patients

and counting all the cases where the patients followed the recommended action. An action taken 95% of the time is more reliable than 5%. Similarly, an action taken in 300 out of 400 patients has a higher confidence level than one taken in 3 out of 4 cases. The tables below show the confidence levels for the original policy, the improved policy, and the policy of the alternate model.

State	Policy	Percentage of cases	Number of cases out of total
pre-breakfast low	same R, less N	1.4	4/296
pre-breakfast normal	same R, same N	63.8	359/563
pre-breakfast high	more R, less N	0.4	8/1974
pre-lunch low	same R, same N	70.4	391/560
pre-lunch normal	same R, same N	71.3	420/589
pre-lunch high	less R, less N	0.2	3/1528
pre-supper low	same R, same N	50.8	247/286
pre-supper normal	same R, same N	67.2	462/689
pre-supper high	more R, less N	0.4	8/2098

**Table 6:** Confidence measures for the original policy

R = regular insulin

N = NPH

The original policy was determined using no error-checking mechanisms (filtering out isolated cases and eliminating gaps). Thus, some of the actions may be incorrect. Indeed, several of the recommended actions had low confidence measures. The new policy obtained after implementing error-checking mechanisms showed higher confidence measures.

Finally, confidence measures for policy of the alternate model are shown in Table 8. Several actions are highlighted in bold. These are actions which were followed by either a small percentage (< 10%) or a small number (< 20) of the patients. If these actions are replaced by ones which were taken by a majority of the patients, the new actions are as

shown in Table 9.

State	Policy	Percentage of cases	Number of cases out of total
pre-breakfast low	less R, same N	34.1	87/255
pre-breakfast normal	same R, same N	64.0	313/489
pre-breakfast high	same R, same N	26.1	487/1866
pre-lunch low	same R, same N	62.5	175/280
pre-lunch normal	same R, same N	68.8	284/413
pre-lunch high	same R, same N	58.6	754/1287
pre-supper low	less R, same N	36.2	111/307
pre-supper normal	same R, same N	65.7	328/499
pre-supper high	more R, same N	41.2	511/1261

**Table 7:** Confidence measures for policy recommended by first model

R = regular insulin

N = NPH

Previous Meal's NPH	State BG and time slice	Action	Percentage of cases	Number of cases out of total
no NPH	pre-breakfast low	Med R, Med N	37.4	46/123
	pre-breakfast normal	Med R, Med N	68.4	249/364
	pre-breakfast high	High R, Med N	4.3	57/1340
	pre-lunch low	Med R, Low N	26.6	30/113
	pre-lunch normal	Med R, Low N	72.2	125/173
	pre-lunch high	Low R, Low N	3.4	16/477
	pre-supper low	Med R, Low N	55.4	170/307
	pre-supper normal	Low R, Low N	3.5	15/434
	pre-supper high	High R, Med N	22.2	257/1156
NPH	pre-breakfast low	Med R, Low N	24.0	33/138
	pre-breakfast normal	Low R, Low N	7.3	18/246
	pre-breakfast high	Med R, Med N	38.0	201/529
	pre-lunch low	Med R, Low N	78.7	137/174
	pre-lunch normal	Med R, Low N	88.0	235/267
	pre-lunch high	High R, Low N	8.5	69/812
	pre-supper low	Low R, Med N	40.2	39/97
	pre-supper normal	Low R, Med N	30.3	59/99
	pre-supper high	Low R, Med N	14.1	10/417

**Table 8:** Confidence measures for policy recommended by the alternative model

R = regular insulin

N = NPH insulin

State	Original Policy	New Policy	%
pre-breakfast high, no NPH	High R, Med N	Med R, Med N	59.1
pre-lunch high, no NPH	Low R, Low N	Med. R, Low N	78.6
pre-supper normal, no NPH	Low R, Low N	Med R, Med N	55.4
pre-breakfast normal, NPH	Low R, Low N	Med R, Low N	55.1
pre-lunch high, NPH	High R, Low N	Med R, Low N	86.5
pre-supper high, NPH	Med R, Low N	Med R, Med N	34.1%

**Table 9:** New Policy

Did substituting the actions improve the policy? Let's examine the cases in Table 9. Where BG is high before supper (rows 2 and 6), more insulin is taken in each case. In addition, NPH was taken before supper. In rows 3 and 4, where BG is normal, a medium level of regular insulin is taken instead of low. This also makes sense. Finally, in rows 1 and 5, where BG is high, regular insulin is reduced from high to medium. This may be because patients tend to keep their insulin the same.

Analyzed in terms of confidence measures, filtering and eliminating gaps did improve the policy. The actions selected were taken by a large number of patients. The effect of an alternate model was ambiguous. The new model had twice as many probabilities, and there were few cases to substantiate each probability. Furthermore, the model did not fit all the patients well, so patients might take different actions under the same circumstances. Thus, the actions for the alternate model had lower confidence measures. Nonetheless, most of the actions were reasonable. From this analysis, confidence measures seem to provide a useful way of evaluating a policy and even replacing low-confidence actions.



# Chapter 5

## Discussion

Despite the simplified models used, the system was able to recommend reasonable policies. Furthermore, it did highlight some of the issues in constructing Markov models, calculating transition probabilities, working with clinical data, and evaluating the results.

### 5.1 Constructing Decision Models

The first issue is constructing decision models. The decision problem has to be simplified considerably so that the model is tractable. Insulin dosage adjustments depend on a large number of factors, such as insulin sensitivity, diet, patient physiology, etc. Previous history is also important. Rules for insulin adjustment usually take into account insulin dosages and glucose levels for the previous 2-4 days. Increasing model complexity, however, may be difficult. The current model used several thousand records of BG measurements and insulin dosages. A more complex model may require tens of thousands of such records. It may be difficult to obtain that much data for any one patient, as it will have to cover over ten years of data. In addition, such a model may be difficult to design and analyze.

This does not mean that Markov modeling is useless for the treatment of diabetes. First, the system was able to generate reasonable results despite many simplifications. The primary limitation of the model is a lack of memory. This problem can be solved by modeling quantities other than BG measurements and insulin dosages. Instead, the

model can use indirect quantities such as the running average of BG and the amount of insulin in the body. Running averages can be calculated directly from the data, while the amount of insulin in the body can be calculated from pharmacodynamic models. Further, cleaner data may allow us to reject fewer data points so that excessive amounts of data will not be required.

## **5.2 Calculating Transition Probabilities**

Another issue is how to calculate transition probabilities. The method of counting transitions is a method that is direct, easy to implement, and free from biases. While it is sufficient for calculating transition probabilities, it is data-intensive and sensitive to errors in the data. The program will count transitions that are indicated by the data, whether they make sense or not. These errors can be quite significant if there are few cases to dilute the erroneous case. Patients tend to favor certain actions over others when in a particular state, while there may be few cases of the other actions. A patient may deviate from his usual actions because of a change in diet, recording error, miscalculation of insulin dosage, or some special situation not indicated by the data. Therefore, some transition probabilities can not be calculated or worse, are unreliable. Some sort of filtering or selective rejection of outlying data points can deal with this problem.

It was initially feared that there were insufficient data to derive all the probabilities. But the problem turned out not to be insufficient data, but a limitation in that the data contained only positive actions--actions that tend to produce good outcomes. Thus, actions that tend to have negative effects are rarely taken, and it is difficult to determine transition probabilities for them. This is not a problem if the goal of building the Markov model is to determine optimal actions. However, the model cannot be used to predict BG levels because the complete set of transition probabilities is unavailable.

### 5.3 Working with Clinical Data

Working with the clinical data given further complicates the calculation of transition probabilities because of errors, missing data, and a lack of patient information. The clinical data used are logs kept by patients. The completeness and consistency of the logs differ across patients. A patient may record only BG measurements or insulin dosages, in which case the log is useless. Unspecified BG measurements are ignored since it is not clear whether they were taken before or after a meal. There may also be gaps in the data, where the patient either did not take insulin between meals or did not record it. The system treats such gaps as zero insulin dosages. If there are only a few of these gaps in the data, the error may be insignificant. If there are a large number of these gaps, however, the error can be quite significant. Ignoring these gaps assumes that patients taken insulin at every meal. While this is not always true, it applied to most patients in the data sets.

If many data sets are available, it is possible to select certain “good” training sets to learn transition probabilities from. Good data sets should have few gaps and errors. One may also select data sets which exhibit the best BG control, lowest average BG, or a coherent insulin regimen. Different characteristics may be selected for different goals. For example, if the goal is to learn short-term insulin adjustments, one should select data sets where patients are in stable condition and are only making small adjustments to their dosages. Patient information is very important for this purpose. Juvenile patients may have different responses to insulin over a number of years. Patients who develop serious health complications over a number of years may indicate that their insulin regimen was not effective. These would not make good training sets! It should be noted, however, that using pre-selected data sets may introduce biases and assumptions into the calculation.

In the lack of patient information, working with only one patient’s data may be easier. The patient’s insulin regimen and recording habits can be learned, and errors or gaps can be more easily detected. Deviations from the normal routine or overall changes to therapy

can be detected. Trends and distinguishing characteristics in the data can also be identified.

Finally, I have learned from this project that it is important to study the data. Until there is a consistent way of recording patient logs (and having patients follow it), unexpected problems may complicate the analysis of the data. The two heuristics used to improve the accuracy of the probabilities, eliminating gaps and filtering out probabilities based on a few actions, were discovered by finding the cases in the data that generated the erroneous policy. Other heuristics may be discovered by working with and studying additional clinical data.

## **5.4 Evaluating Policies**

Finding methods for evaluating a policy is a difficult problem. Several methods are used: comparing the policy with actual practice, simulation, and matching the policy with clinical data.

To compare a policy with actual practice, one must identify the goal of therapy. Is it a short term solution to prevent hypoglycemic episodes? Or is it to make adjustments in insulin therapy to lower average BG levels and keep BG within a narrow target range? If the goal is a short term solution, then the policy generated by the system fulfilled that goal. The general rule of thumb is to increase regular insulin when BG is high and decrease insulin when BG is low. However, it is unclear what is a suitable policy if the goal is to maintain stable BG levels over a period of time. The model simply does not contain enough information to make decisions about adjusting insulin therapy.

Once the goal of therapy is determined, one should analyze whether patients follow the same goal. Again, patient information is important. How are patients adjusting their insulin dosages, if at all? Some may use a sliding scale which calculates changes in regular insulin dosage based on the difference between measured glucose levels and the norm.

Such a formula is similar to a short term solution in that it would probably decrease insulin when BG is low and raise it when BG is high. Others may follow a fixed therapy and consult a doctor or nurse when they have problems.

Finally, confidence measures were a useful method for evaluating policies. They confirmed that the policies made clinical sense because a majority of patients followed them. They can also indicate whether the data sets are good training sets. If low-confidence actions are obtained, then perhaps the data sets selected are not appropriate for the decision model.

# Chapter 6

## Conclusion

### 6.1 Summary

Insulin therapy for Type I diabetes patients is a difficult control problem complicated by numerous factors. There is a trade-off between making the decision model as realistic as possible while keeping the model simple. Using clinical data to derive transition probabilities introduces additional difficulties. Despite simplification of the decision model and imperfect data, I was able to obtain reasonable results in terms of a policy of actions. Furthermore, I discovered some heuristics for dealing with clinical data and evaluating my results. Filtering, selective rejection of outliers, and other error-checking mechanisms are useful measures for dealing with imperfect data. For evaluating results, both expert opinion and confidence measures are effective measures.

### 6.2 Further Work

There are many ways to improve the decision models. One limitation of the current decision models is that previous glucose levels and insulin dosages are not remembered. However, the states can be modified such that they reflect previous history. For example, running averages of glucose levels represent past glucose measurements, while serum insulin levels reflect previous insulin injections and insulin absorption. Additional state variables may be added to include diet and exercise.

Careful selection of training data can also improve the results. While the data used yield reasonably correct results, better or cleaner data can make the transition probabili-

ties more accurate. Patient information is very important for classifying and selecting good data sets. Furthermore, working with data from only patient may yield probabilities and policies which closely fit the patient.

These ideas can address many of the problems encountered in this project. With a model which can address previous history and data sets which are carefully selected, it may be possible to use Markov modeling to advise patients on insulin adjustment.

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