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MULTILEVEL HIDDEN MARKOV MODELS FOR STUDYING TYPE-1 DIABETES

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Abstract

Type-1 diabetes, also known as insulin-dependent diabetes, is a chronic illness brought on by the body's inability to manufacture insulin. This study intends to comprehend the glucose levels of 12 patients from Chinese sources 572 times continuously throughout 143 hours, or once every 15 minutes. We used various Markov models, including the Markov model, hidden Markov model (HMM), and multilevel hidden Markov model, to comprehend the pattern in the data. Three states, hypoglycemia, normal blood sugar, and hyperglycemia, were used to create the probability mass function for the Markov model. For the HMM, emission states increase, decrease, and remain the same, whereas concealed states are hypoglycemia,

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normal, and hyperglycemia. We select data with a positively skewed distribution for the multilevel hidden Markov model, and the Akaike information criterion (AIC) score determines the hidden states. The models' respective AIC values are Markov 3138.475 and MHMM 290.689. According to AIC values, the multilevel hidden Markov model is the best.

1. Introduction

Type-1 diabetes, also called *insulin-dependent diabetes*, is a chronic medical condition caused by a lack of capability of the body to produce insulin. Insulin is a hormone produced by the pancreas called *beta cells*. Insulin helps regulate blood sugar levels and makes it easier for glucose to enter the cells, which can be used for energy. When the body does not produce and use enough insulin, glucose accumulates in the blood. High blood sugar levels can lead to serious health problems. Type-1 diabetes is a condition caused by an autoimmune reaction. The immune system mistakenly attacks and destroys the pancreas' insulin beta cells. Although there is no definitive explanation for this autoimmune reaction, environmental factors and genetic predispositions are believed to play a role.

Typically, Type-1 diabetes first appears in childhood or adolescence. Extreme thirst, frequent urination, unexplained weight loss, increased hunger, weariness, and blurred vision are just a few of the symptoms that might appear suddenly and severely. These symptoms are brought on by the body's inability to utilize glucose properly, which results in the breakdown of fats and proteins for energy. For Type-1 diabetes therapy, daily insulin delivery via injections or an insulin pump is necessary to control blood sugar levels. People with Type-1 diabetes must frequently check their blood sugar levels, usually several times daily, and adjust their insulin dosages as appropriate. Controlling the sickness requires a healthy lifestyle, regular exercise, and a proper diet. People with Type-1 diabetes must be watchful and constantly care for themselves to avoid complications, including cardiovascular disease, kidney issues, nerve damage, and eye issues. Continuous glucose monitoring devices and advancements in insulin delivery technology have significantly improved the quality of life for persons with Type-1 diabetes and allowed for more precise and helpful treatment.

The World Health Organization (WHO) reports that the number of persons with diabetes has continuously climbed from 108 million in 1980 to 422 million in 2014. Diabetes prevalence has risen more quickly in low- and middle-income nations than in high-income nations. A little over nine million individuals worldwide had Type-1 diabetes in 2017, with high-income nations housing the bulk of those affected. Type-1 diabetes has no recognized cause, and there is no known cure. About 2 million deaths were brought on by diabetes and renal disease in 2019.

These papers collectively suggest that Markov models can help study diabetes. Compare three Markov models for variations in blood sugar levels in diabetic individuals to find the best model (Dumitrescu and Popescu [5]). The Markov model is a suggested method for effectively managing and tracking the health of the equipment (Wang et al. [12]). Experiments show that the model has a low average absolute error and can predict the time until a preset event as well as the present state with accuracy (Cartella et al. [2]). Using separate classifiers on the same set of data could improve prediction accuracy (Gill and Mittal [6]). Aarts [1] suggested that multivariate data reduces the required sample size and increases the stability of the outcomes. Varshney et al. [11] used the hidden Markov model, which highlights the danger of problems for patients with high hemoglobin in A1c level; one may predict the probabilities of transition between various stages of diabetes. Ruiz-Suarez et al. [10] applied hidden Markov models, and their extensions are effective tools for categorizing observations resulting from temporal-dependent systems. Markov models are used to predict missing event types in diabetic patient data, enhancing the data quality (de Carvalho et al. [3]). The work of Kirchherr et al. [8] on long-term plasticity in neuronal populations would benefit greatly from a multilevel Bayesian HMM paradigm. Ginn et al. [7] concluded that the number of subjects strongly influences a model’s performance. Multivariate data typically reduces the required sample size and enhances the stability of the outcomes (Moraga and Aarts [9]).

2. Stochastic Modelling

Stochastic models are deterministic models that describe randomness over time. These models are used in many areas like Physics, bioinformatics, economics, engineering, etc. There are different models for diabetes. In this context, we are comparing three different models for Type-1 diabetes with stochastic properties.

Markov model

Markov models are stochastic models for sequential data where the future depends only on the previous immediate state. This model follows the memory-less property. The mathematical description of the model with a transition diagram is as follows:

$$a_{ij} = P(X_{n+1} = j \mid X_n = i).$$

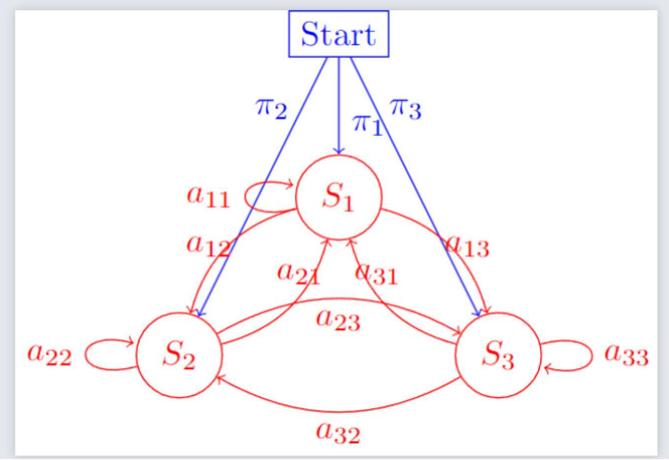


Figure 1. Schematic diagram of Markov model with three states, namely, S_1 means hypoglycemia, S_2 is normal and S_3 is hyperglycemia.

Probability mass function (PMF)

The probability mass function was formulated based on occurrences of the state for one-state, two-state and three-state emission sequences. The mathematical expressions are given.

PMF for one-state

Let us assume sample space = {Hypo, Normal, Hyper} and favorable space will be a count of states. Then for one emission state, we have three possibilities as shown in the given PMF:

$$P_{\omega}(hypo) = \begin{cases} \sum_{i=2}^{3} \pi_i & hypo = 0, \\ \pi_1 & hypo = 1, \end{cases} \quad P_{\omega}(normal) = \begin{cases} \pi_1 + \pi_3 & normal = 0, \\ \pi_2 & normal = 1 \end{cases}$$

and $P_{\omega}(hyper) = \begin{cases} \sum_{i=1}^{3} \pi_i & hyper = 0, \\ \pi_3 & hyper = 1. \end{cases}$

PMF for two-state sequence

Assume sample space = {Hypo, Normal, Hyper} and favorable space to be a count of states. Then, for two emission state, we have 8 possibilities as shown in the given PMF:

$$P_{\omega}(hypo) = \begin{cases} \sum_{i=2}^{3} (\pi_2 p_{2i} + \pi_3 p_{3i}) & hypo = 0, \\ \sum_{i=2}^{3} (\pi_1 p_{1i} + \pi_i p_{i1}) & hypo = 1, \\ \pi_1 p_{11} & hypo = 2, \end{cases}$$

$$P_{\omega}(normal) = \begin{cases} \sum_{\substack{i=1 \\ i \neq 2}}^{3} (\pi_1 p_{1i} + \pi_3 p_{3i}) & normal = 0, \\ \sum_{\substack{i=1 \\ i \neq 2}}^{3} (\pi_2 p_{2i} + \pi_i p_{i2}) & normal = 1, \\ \pi_2 p_{22} & normal = 2 \end{cases}$$

and

$$P_\omega(hyper) = \begin{cases} \sum_{i=1}^{2} (\pi_1 p_{1i} + \pi_2 p_{2i}) & hyper = 0, \\ \sum_{i=1}^{2} (\pi_3 p_{3i} + \pi_i p_{i3}) & hyper = 1, \\ \pi_3 p_{33} & hyper = 2. \end{cases}$$

PMF for three-state sequence

Let us assume sample space = {Hypo, Normal, Hyper} and favorable space will be a count of states. Then, for three emission state, we have 27 possibilities as shown in the given PMF:

$$P_\omega(hypo) = \begin{cases} \sum_{i=2}^{3} (\pi_2(p_{22}p_{2i} + p_{23}p_{3i}) + \pi_3(p_{33}p_{3i} + p_{32}p_{2i})) & hypo = 0, \\ \sum_{i=2}^{3} (\pi_1(p_{12}p_{2i} + p_{13}p_{3i}) + \pi_2(p_{21}p_{1i} + p_{2i}p_{i1}) & \\ \quad + \pi_3(p_{31}p_{1i} + p_{3i}p_{i1})) & hypo = 1, \\ \sum_{i=2}^{3} (\pi_1(p_{1i}p_{i1} + p_{11}p_{1i} + \pi_i p_{11}p_{i1})) & hypo = 2, \\ \pi_1 p_{11}^2 & hypo = 3, \end{cases}$$

$$P_{\omega}(normal) = \begin{cases} \sum\limits_{\substack{i=1 \\ i \neq 2}}^{3} (\pi_1(p_{11}p_{1i} + p_{13}p_{3i}) + \pi_3(p_{33}p_{3i} + p_{31}p_{1i})) & normal = 0, \\ \sum\limits_{\substack{i=1 \\ i \neq 2}}^{3} (\pi_1(p_{12}p_{2i} + p_{i1}p_{i2}) + \pi_2(p_{21}p_{1i} + p_{3i}p_{i3}) & \\ \qquad + \pi_3(p_{32}p_{2i} + p_{3i}p_{i2})) & normal = 1, \\ \sum\limits_{\substack{i=1 \\ i \neq 2}}^{3} (\pi_2(p_{2i}p_{i2} + p_{22}p_{2i} + \pi_i p_{22}p_{i2})) & normal = 2, \\ \pi_2 p_{22}^2 & normal = 3 \end{cases}$$

and

$$P_{\omega}(hyper) = \begin{cases} \sum\limits_{i=1}^{2} (\pi_1(p_{11}p_{1i} + p_{12}p_{2i}) + \pi_2(p_{22}p_{2i} + p_{21}p_{1i})) & hyper = 0, \\ \sum\limits_{i=1}^{2} (\pi_1(p_{12}p_{2i} + p_{13}p_{3i}) + \pi_2(p_{21}p_{1i} + p_{2i}p_{i1}) & \\ \qquad + \pi_3(p_{31}p_{1i} + p_{3i}p_{i3})) & hyper = 1, \\ \sum\limits_{i=1}^{2} (\pi_3(p_{3i}p_{i3} + p_{33}p_{3i} + \pi_i p_{33}p_{i3})) & hyper = 2, \\ \pi_3 p_{33}^2 & hyper = 3. \end{cases}$$

Hidden Markov model

Consider an observational series X_t that is recorded for $t = 1, ..., T$. Assume that the distribution of X_t is influenced by state, a latent (unobserved) variable. The sequence (S_t, X_t) forms a hidden Markov model (HMM) if S_t is a Markov chain of order 1 and for each $t \geq 1$, X_t and X_{t+1} are conditionally independent. Figure 2 provides a graphic illustration of the HMM structure. The parameters of an HMM include the state initial probabilities, the state transition probability matrix, and the emission distribution parameters, which describe the conditional distribution of observations given states. The sojourn time is the amount of time spent in a state. The sojourn time distribution is shown to be a geometric distribution in the HMM model:

$$\text{Initial probabilities} = \pi_i = P(\pi_i = 1),\ \forall i = 1, 2, \dots, n,$$

$$\text{Transition probabilities} = P(X_{t+1} \mid X_t, X_{t-1}, \dots, X_1) = P(X_{t+1} \mid X_t),$$

$$\begin{aligned}\text{Emission probabilities} &= P(E_t \mid E_{t-1}, E_{t-2}, \dots, E_1, X_t, X_{t-1}, \dots, X_1)\\ &= P(E_t \mid X_t).\end{aligned}$$

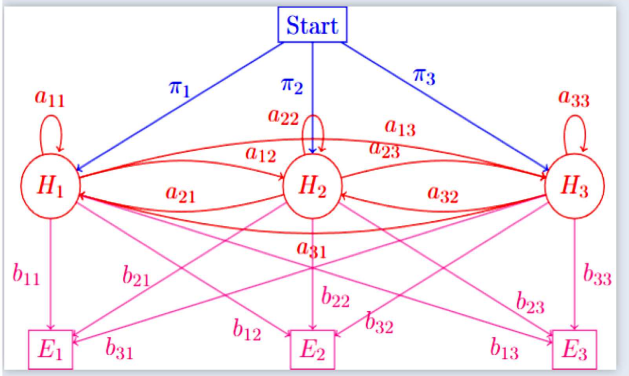


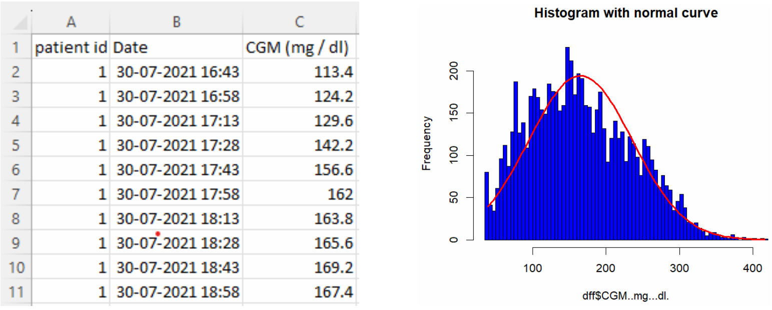
Figure 2. Schematic diagram for the HMM, the emission states are represented by the letters E_1, E_2, and E_3, which stand for increasing, decreasing, and remaining the same, respectively, and the hidden states are represented by the letters H_1, H_2, and H_3.

Multilevel hidden Markov model

An HMM is called a *multilayer hidden Markov model* (*MHMM*). Several HMMs can be executed simultaneously. States can represent higher-level concepts or behaviors in this way, helping to capture more intricate patterns and connections in the data. In this work, we studied a state sequence consisting of three hidden states and one dependent variable with three categories.

3. Numerical Study

Numerical illustrations are essential for modelling behaviours. This study focused on secondary data from Type-1 diabetes (ShanghaiT1DM) corresponding to 12 Type-1 diabetes patients. We combined 12 patent data with 1 column to apply various Markov models in this study. Modified data includes patient ID, Date, Time, and Glucose levels every 15 min 572 times with 143hr of data. Template of Excel data and data representation followed. Data analysis and simulation were performed using R studio and Excel.



	A	B	C
1	patient id	Date	CGM (mg / dl)
2	1	30-07-2021 16:43	113.4
3	1	30-07-2021 16:58	124.2
4	1	30-07-2021 17:13	129.6
5	1	30-07-2021 17:28	142.2
6	1	30-07-2021 17:43	156.6
7	1	30-07-2021 17:58	162
8	1	30-07-2021 18:13	163.8
9	1	30-07-2021 18:28	165.6
10	1	30-07-2021 18:43	169.2
11	1	30-07-2021 18:58	167.4

Figure 3. Data visualization of glucose levels.

From Figure 3, it is clear that data is sequential over a period of time. So here, the assumption of the stochastic model and Markov property is satisfied. So, we applied different Markov models to understand the trend in glucose levels.

Markov chain

To implement this Markov model for the given data set, glucose levels are divided into three categories: Hypoglycemia: glucose levels are less than 90mg/dl in the CGM (mg/dl). Normal: glucose levels between 90 and 130mg/dl. Hypertension: glucose levels above 130mg/dl are considered. Following the consideration of states, the state sequence was checked using a plot in Rstudio to confirm the Markov property. The *p*-value of this Markov property is approximately 0.3994, and the chi-square statistic is 14.69313 with a degree of freedom of 14. Here *p*-value exceeds 0.05. Data follows Markov property. Initial Probability Vector, Transition Probability, Standard Error and 95% Confidence Interval matrices are as follows:

$\pi = [0.15472030.19245340.6528263]$

$$\begin{bmatrix} 0.9134 & 0.0857 & 0.0009 \\ 0.0689 & 0.8456 & 0.0855 \\ 0.0002 & 0.0250 & 0.9748 \end{bmatrix}\begin{bmatrix} 0.0028 & 0.0023 & 0.0009 \\ 0.0028 & 0.0043 & 0.0026 \\ 0.0002 & 0.0013 & 0.0014 \end{bmatrix}$$

$$\begin{bmatrix} 0.9137 & 0.0762 & 0.0001 \\ 0.0653 & 0.8393 & 0.0792 \\ 0.0002 & 0.0226 & 0.9726 \end{bmatrix}\begin{bmatrix} 0.9231 & 0.0839 & 0.0030 \\ 0.0746 & 0.8536 & 0.0879 \\ 0.0007 & 0.0268 & 0.9771 \end{bmatrix}.$$

The transition probability matrix appears as the first matrix, followed by the standard error matrix and the two confidence intervals for the transition probability matrix. Given that the Markov chain is irreducible, it is evident from the preceding matrix that a periodic Markov that is persistent, ergodic, and has a stationary distribution, is $\pi = \{0.1540369, 0.2391579, 0.6068052\}$. It is evident from the stationary distribution that the likelihood of hyperglycemia glucose levels in the future is considerable. According to the Markov model, there are more opportunities as glucose levels move from hyperglycemia to hyperglycemia, and the change from hyperglycemia to normal has no bearing on the situation, much like it does with hypoglycemia. A normal patient is at a high risk of developing hyperglycemia or hypoglycemia. Patients with hypoglycemia have a good likelihood of returning to normal, but they also have a lower risk of developing hyperglycemia.

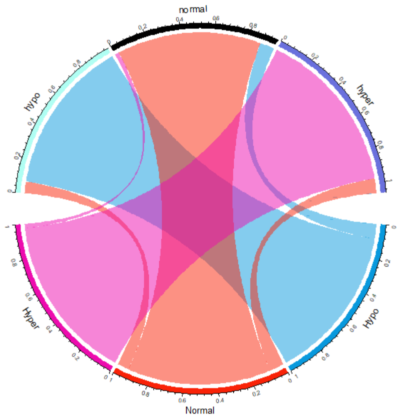


Figure 4. Transition probability matrix plot.

Algorithm for simulation in R

To forecast the glucose levels state by the Markov model, we applied Markov algorithm used by Dobrow [4] in R to simulate states. The algorithm and results are as follows:

Require: Initial probability vector (π), transition matrix (p), number of steps (N).

Output: $X_0, X_1, X_2, \ldots, X_n$

```
Algorithm. Choose $X_0$ from the initial probability vector.
For $i = 1, \ldots, n$
Assume that $X_{i-1} = J$
Set $p = j$th row of $p$
Generate $X_i$ according to $p$ end For
```

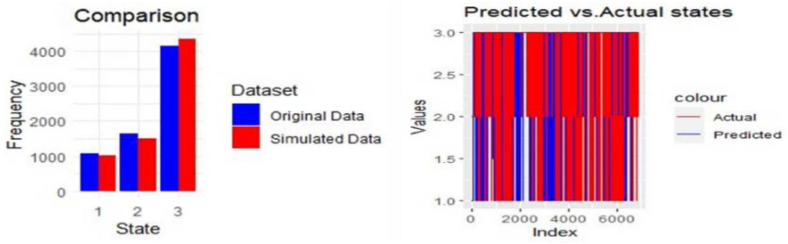


Figure 5. Simulated and actual states plot.

From the above-simulated states by prior transition probability matrix (TPM), states are coming accurately with less error. In future, we can estimate the next glucose level state by the simulation. The numerical probability mass functions are given below:

Table 1. Probability mass function for hypo state

Hypo	0	1	2	3
One	0.8452797	0.1547203	-	-
Two	0.8318764	0.02680656	0.141317	-
Three	0.8193962	0.0261313	0.02539765	0.1290749

Table 2. Probability mass function for normal state

Normal	0	1	2	3
One	0.8075466	0.1924534	-	-
Two	0.7779684	0.05929852	0.1627331	-
Three	0.7499342	0.06077464	0.05168871	0.1376025

Table 3. Probability mass function for hyper state

Hyper	0	1	2	3
One	0.3471737	0.6528263	-	-
Two	0.3305653	0.03307477	0.6363599	-
Three	0.3153653	0.02928244	0.03335255	0.6203089

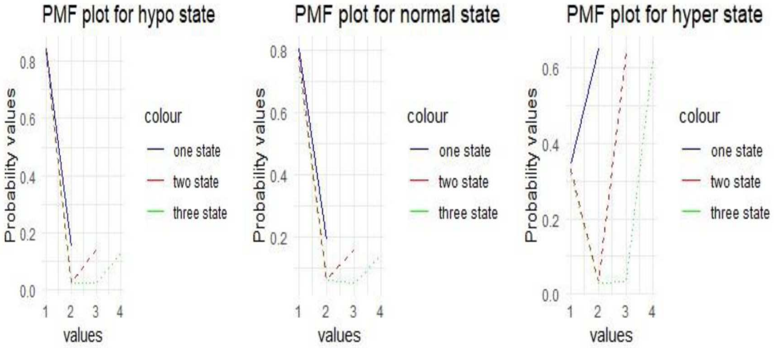


Figure 6. Three-state probability plot.

According to the tables and figures above, the likelihood of hyperglycemia is higher when it does not occur than when it does, but all other probability values except three are significant. While the non-occurrence of three from the usual condition is high, all likelihood estimates vary significantly. The likelihood of four hyperglycemia states occurring is higher than their non-occurrence, although all but two of the maximum probability values are significant. Based on the three tables above, the likelihood of hyperglycemia is high and significant.

Hidden Markov model

The hidden Markov model consists of transition probabilities with states names S = {Hypo, Normal, Hyper} and emission states E = {Increase, Decrease, Remain same}. The numerical matrix and graphical presentation are as follows:

$$\text{Emission probability} = \begin{bmatrix} 0.4002 & 0.4021 & 0.1977 \\ 0.3967 & 0.4822 & 0.1211 \\ 0.3998 & 0.4993 & 0.1009 \end{bmatrix}.$$

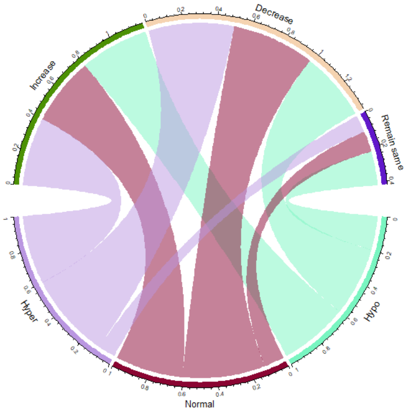


Figure 7. Emission probability matrix plot.

As we can see from the matrix and plot above, there is a significant risk of hyperglycemia when glucose levels rise or fall. When glucose levels fall, there is a good possibility that everything will return to normal; the significance likelihood will climb and stay the same. When there is both a reduction and a rise, hypoglycemia results.

Multilevel hidden Markov model

Using Bayesian estimation, the MHMM function fits a multilevel hidden Markov model to data from multiple subjects. One broad "population" HMM is estimated using a multilevel approach that considers subject heterogeneity. The function may manage covariates at the subject level and different subject-level observation times. A hybrid metropolis is used for estimation within the Gibbs sampler, and the forward-backwards algorithm is sequentially finished for each topic. Here, we performed MHMM for the data by patient ID 12 patients with glucose levels every 15 minutes. In this model, we used the technique of AIC to determine hidden states. We tested with 2, 3 and 4 hidden states. The three hidden states model got a low average AIC, i.e., 290.6883, and the average log-likelihood is –133.3441. So, we performed further analysis with three hidden states. The number of dependent variables in this model is one, i.e., glucose levels. In the model fit, we have done 1000 iterations used in the Markov chain Monte Carlo algorithm with a burn-in of 200 bootstrap samples. The transition and emission probabilities matrices are as follows:

$$\begin{bmatrix} 0.839 & 0.134 & 0.027 \\ 0.083 & 0.814 & 0.103 \\ 0.005 & 0.033 & 0.962 \end{bmatrix} \begin{bmatrix} 0.933 & 0.042 & 0.025 \\ 0.017 & 0.963 & 0.020 \\ 0.004 & 0.005 & 0.991 \end{bmatrix}.$$

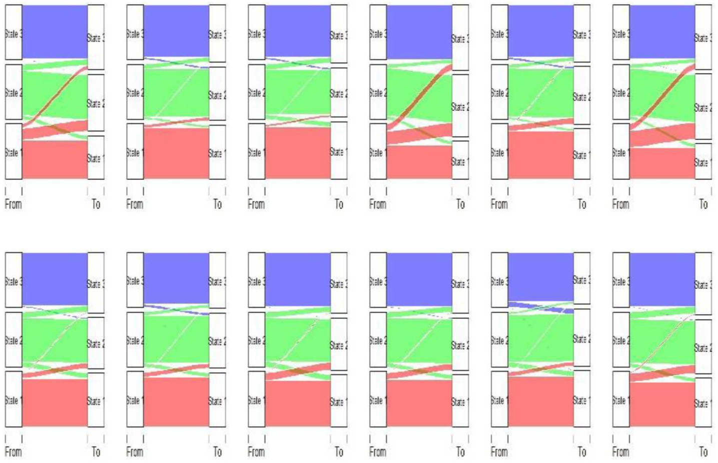


Figure 8. 12 patients transition probabilities matrix plot.

The above graph shows that the transition happening from the same state to the same state is high compared to the rest. The main advantage of MHMM was comparing more than one HMM at a time using bootstrap and MCMC algorithms. Based on the AIC value, MHMM fits the best model for this data.

4. Results and Discussion

This study primarily examined various Markov models for classifying diabetes. Here, we have three separate models: Markov models, hidden

Markov models and multilevel hidden Markov models. The MHMM Markov method was used to simultaneously comprehend several HMMs with various subjects. We separated the Markov model section into three states based on the glucose levels. The probability mass function of the Markov model - a persistent, ergodic, periodic, irreducible chain - was determined. The transition from hyperglycemia to hyperglycemia presents more opportunities, while the transition from hyperglycemia to normal is not as significant as the transition from hypoglycemia. It is reasonable to assume that a normal patient will experience either hyperglycemia or hypoglycemia.

A patient with hypoglycemia is less likely to experience hyperglycemia but has a fair probability of getting back to normal. Because of the simulation of the previous TPM and IPV states, states are arriving more accurately and with less mistake. We have the ability to forecast and influence the glucose level situation in the future. When glucose levels decrease or increase by HMM, hyperglycemia is very likely to happen. When blood glucose levels drop, there is a good chance they will rise back up to normal and a good chance they will stay the same. Hypoglycemia occurs when both a reduction and an increase take place. In comparison to the other two models, the three-state model for MHMM has the best AIC value. The primary benefit of MHMM was its ability to be used with the MCMC algorithm if we had data from 12 patients and applied HMM to each patient instead. Lastly, hyperglycemia is quite likely based on glucose levels. According to the data, hyperglycemia is the second most frequent occurrence, followed by normal. Using both real and simulated data, we apply the Markov model to blood glucose levels and find that it performs the best in predicting the next state.

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