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Symptoms of schizophrenia and regularity in treatment: a stochastic analysis

Abstract

Background: The alarming rise of mental disorders worldwide stimulates the need to study them from a statistical viewpoint. Schizophrenia is one of the most prevalent mental illness which is characterised by various symptoms, the presence of a cluster of which leads to its diagnosis. Regular treatment leads to a remission of the illness which might relapse on discontinuity of medicines. There have been numerous epidemiological studies and clinical trials on the illness. However, schizophrenia also poses a challenge to statisticians in theorising and statistically modeling its different aspects. **Aim:** This is an attempt to study, by developing suitable stochastic models, the behaviour of the symptoms of schizophrenia manifested in a patient in relation to the successive visits to the doctor. **Methods:** The concepts of probability theory, structure functions, binomial distribution, Markov chain, and transition probabilities are the statistical tools used to model the medical facts regarding schizophrenia. **Results:** By developing probabilistic and stochastic models, a relationship between the number of symptoms at the time of diagnosis and the number of revisits to the doctor has been developed and thereby an important result regarding the expected number of symptoms present at a particular visit to the doctor has been established. A Markovian model studying the pattern of the symptoms in the course to recovery has been presented and its application in the behaviour of the symptoms of schizophrenia has been verified. **Conclusions:** It is expected that the above results might help doctors in planning out the treatment schedule in advance. It can also lead to a further study on cost benefit analysis of the treatment process.

Keywords: Revisits. Binomial Distribution. Markov Chain.

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1 INTRODUCTION

There has been an alarming rise in mental disorders throughout the world during the last decades and this has increased the need for the study and analysis of such disorders from the statistical point of view. Schizophrenia, a psychotic disorder, is by far one of the most prevalent among the mental illnesses. Schizophrenia is a disorder of unknown causes. It is characterised by symptoms that significantly impair functioning and that involve disturbances in feeling, thinking, and behaviour. It is a complex and intriguing major psychiatric disorder.[1]

Schizophrenia is characterised by various symptoms like sleeplessness, irritability, suspiciousness, irrelevant speech, sudden spells of laughing and crying, over religiousness, depression, presence of delusions and hallucinations, etc.[1,2] These symptoms in isolation are however not unique to schizophrenia. A cluster of symptoms with definite weightage lead to a diagnosis of schizophrenia.[2-4] In the early times, variability in diagnostic procedure existed in the different parts of the world. The diagnostic uncertainty and prevailing unreliability in diagnostic procedure made attempts at international comparison and compiling of data very difficult. This led to the concentrated international efforts at developing a standardised classificatory system regarding the symptoms of schizophrenia.[5] According to the Diagnostic Criteria for Research (DCR), which has been worked out by the World Health Organization (WHO),[6] the various symptoms that are observed in a patient with schizophrenia can be broadly classified, for diagnostic convenience, into three types A, B and C. For the diagnosis of schizophrenia, at least one of the symptoms listed under type A or at least two of the symptoms listed under type B should be present for most of the time during an episode of psychotic illness. All additional symptoms, some of which always accompany a type A or type B symptom and are observable in patients with schizophrenia but are not particularly required for diagnosis of schizophrenia, are included in type C.[2,4,7]

It is to be noted that schizophrenia cannot be cured completely.[4] It remains under control only if medicines are taken regularly. On subsequent visits to the doctor, it is expected that the number of symptoms, i.e. the severity of the disease will go on decreasing till ultimately all the symptoms will be kept under control. This state is the state of complete response or complete remission. This state will continue only on regular intake of medicines and regular follow-up with the doctor, otherwise there is a possibility of relapse of the illness.[4,5,8] This fact has also been verified by studying the data sheets of 200 patients with schizophrenia collected from the Department of Psychiatry, Gauhati Medical College

Hospital, Assam, India. A patient's condition and behaviour at a particular time can be studied for recovery only by a psychiatrist. Hence, regularity is a very important requirement in the treatment of schizophrenia.[4,5,8]

Objective of this work

This paper is an attempt to study, by developing suitable stochastic models, the behaviour of the symptoms of schizophrenia in relation to the successive visits to the doctor. The paper is organised as follows: In section 2, under materials and methods, a basic model of schizophrenia, with regards to symptoms present and its structure function, is defined and the relationship between the number of revisits to the doctor and the corresponding symptoms present is worked out. The analysis and results are presented in sections 3, 4, and 5. In section 3, on the basis of medical facts pertaining to schizophrenia, a result is obtained regarding the expected number of symptoms remaining at the rth revisit to the doctor when the number of symptoms present at the time of initial diagnosis is known. Section 4 presents a stochastic analysis of the symptoms of schizophrenia with respect to subsequent visits to the doctor. A Markovian model is defined and the probabilities of going to the states of remission from the state of active schizophrenia have been ascertained. In section 5, the model developed in section 4 is applied to the different types of symptoms of schizophrenia specifically and found to be justified. Discussion on the work done is given in section 6.

2 MATERIALS AND METHODS

Let N denote the total number of symptoms that can be manifested in case of schizophrenia. As mentioned earlier, all of these symptoms are not unique to schizophrenia. Out of the set of N symptoms, let n symptoms be sufficient to give a diagnosis of schizophrenia.

Define:

Y_j = 1, if the jth symptom is present
= 0, otherwise, j = 1, 2, 3,……,N

Y_j's are i.i.d (independently and identically distributed)
with $P(Y_j = 1) = w$, $0 < w < 1$
and $P(Y_j = 0) = 1 - w$
where P(x) denotes probability of x.

2.1 Structure function

Let ϕ(y) be the structure function of schizophrenia where

$$\phi(y) = 1, \text{ if } \sum_{j=1}^{N} Y_j \geq n \qquad \text{(i.e. when the number of manifested symptoms is} \geq n)$$

$$= 0, \text{ if } \sum_{j=1}^{N} Y_j < n$$

$$\text{Now, } P[\phi(y) = 1] = \sum_{i=n}^{N} {}^{N}C_i w^i (1-w)^{N-i} \qquad (2.1.1)$$

which is the probability that a person is in the state of complete schizophrenia. By definition, the respective probabilities are given by the binomial distribution.

2.2 Relationship between the Number of Revisits and the Number of Symptoms

Let us keep a record of a patient of schizophrenia as follows:

S_0 = Number of symptoms present at the time of diagnosis, i.e. at the initial visit.

$$\therefore S_0 = \sum_{j=1}^{N} Y_j, \qquad S_0 = n, n+1, \ldots, N$$

S_0 is the sum of independent Bernoulli variates and can take values from n to N.

Therefore the distribution of S_0 will be truncated binomial.[9]

$$P(S_0) = \frac{{}^{N}C_{S_0} w^{S_0} (1-w)^{N-S_0}}{\sum_{S_0=0}^{n-1} {}^{N}C_{S_0} w^{S_0} (1-w)^{N-S_0}}$$

$$= \frac{{}^{N}C_{S_0} w^{S_0} (1-w)^{N-S_0}}{B_0} \qquad (2.2.1)$$

where B_0 is available from binomial tables with known N, n and w

ANALYSIS AND RESULTS

3 Probabilistic analysis of symptoms of schizophrenia

3.1 Medical fact

On administration of medicines, the number of symptoms gradually goes on diminishing. Normally, if a person recovers from a symptom once, that symptom will not recur during the course of treatment. Also, a new symptom, not seen at the time of diagnosis, will not appear at subsequent visits during treatment. Hence, as the symptoms are brought under control in the subsequent visits to the doctor, it is expected that at a certain visit, all the symptoms will disappear and the patient will then be said to show complete response to medication and be in the state of complete remission. If however, a state is reached when the patient has symptoms less than n, then he would be said to be in the state of partial remission. This is a state when the patient is functionally normal but still has certain symptoms of schizophrenia.[4,7]

Consider S_0 defined in section 2.2

Let S_1 = number of symptoms remaining of the S_0 symptoms at the first revisit

$$= \sum_{j=0}^{S_0} Y_j, \qquad S_1 = 0, 1, 2, \ldots, S_0$$

Hence S_i = number of symptoms remaining at the i^{th} revisit $= \sum_{j=0}^{S_{i-1}} Y_j$, $S_i = 0, 1, 2, \ldots, S_{i-1}$

If we consider r visits, we shall have

S_r = number of symptoms remaining at the r^{th} revisit where

$N \geq S_0 \geq S_1 \geq S_2 \geq \ldots\ldots\ldots \geq S_{r-1} \geq S_r \geq 0$

It is desirable that $S_r = 0$

Now, S_0 is a random variable. It is necessary to know S_0 as the number of symptoms in the first revisit would come from these S_0 symptoms.

$\therefore$ We can find the expected number of symptoms in the initial visit, i.e. $E(S_0)$ as follows:

$$E(S_0) = \frac{\sum_{S_0=n}^{N} S_0 \, {}^{N}C_{S_0} w^{S_0} (1-w)^{N-S_0}}{B_0}$$

$$= \frac{Nw}{B_0} \sum {}^{N-1}C_{S_0-1} w^{S_0-1} (1-w)^{N-S_0}$$

$$= \frac{NwB_0'}{B_0} = Nwk \text{ (say)} = N_0 \text{ (say)} \qquad (3.1.1)$$

where $k = \frac{B_0'}{B_0}$ and B_0' is available from binomial tables with known N, n and w

and B_0 is defined in 2.2.1

Now, S_1 is the sum of Bernoulli variates and $0 < S_1 < S_0$

S_0 being random, it is substituted by $E(S_0) = N_0$.

Thus, $0 < S_1 < N_0$

$\therefore S_1 \sim B(N_0, w)$

Hence, $S_r \sim B(N_{r-1}, w)$ where $N_{r-1} = E(S_{r-1})$, $0 < S_r < N_{r-1}$

In general, $S_i \sim B(N_{i-1}, w)$, $i = 1, 2, 3, \ldots.$ where $N_{i-1} = E(S_{i-1})$, $0 < S_i < N_{i-1}$

3.2 Result

If S_0 be the number of symptoms present in a schizophrenic patient at the time of initial diagnosis, then the expected number of symptoms remaining at the r^{th} visit to the doctor is given by

$$E(S_r) = N_0 (w)^r \qquad (3.2.1)$$

where $N_0 = E(S_0) = N\,k\,w$ where N, k, w are as defined in section 2 and in (3.1)

Proof:

Given $E(S_0) = N_0 = Nkw$

where k is available from binomial tables

Now, $P(S_r) = {}^{N_{r-1}}C_{S_r} w^{S_r} (1-w)^{N_{r-1}-S_r}$, $S_r = 0,1,2,\ldots\ldots,N_{r-1}$

$\therefore E(S_r) = N_{r-1} w$, $r = 1,2,3,\ldots.$

It is seen that

$E(S_r) = N_r = N_{r-1}w = (N_{r-2}w)w = N_{r-2}w^2 = (N_{r-3}w)\,w^2 = N_{r-3}\,w^3 = \ldots.. = N_0\,w^r = E(S_0)\,w^r$ (hence proved)

Thus, if the expected number of symptoms at the initial visit is known, the doctor can estimate the expected number of symptoms likely to be present at the r^{th} visit, ($r = 1,2,3,\ldots.$), provided w is known.

A doctor can thus ascertain the approximate number of visits that will be required to take the patient to the state of remission.

4 Stochastic Analysis of Symptoms of Schizophrenia with Respect to Subsequent Revisits to the Doctor

As mentioned in section 3, it is a medically accepted fact that the number of symptoms present initially in a patient with schizophrenia gradually diminishes during the subsequent visits to the doctor in the course of treatment. Hence, the number of symptoms at a particular visit depends on the symptoms appearing at the immediately previous visit. We can therefore suspect the presence of a Markov chain[10] with respect to the number of symptoms present in a visit.

Let $S_r = i$, $i = 0,1,2,\ldots,N$ be the total number of symptoms present in a patient in the r^{th} visit to the doctor, $r = 1, 2, 3,\ldots\ldots$

$\therefore \{S_r, r \geq 1\}$ is a Markov chain with state space $\$ = \{1, 2, 3,\ldots., N\}$ and transition probability matrix **P** given by[9]

P $= (p_{ij})$, i, j $= N, N\text{-}1,\ldots\ldots,0$;

where p_{ij} is the probability of going from state i to state j, i.e. from the state of having i symptoms to that of having j symptoms, j being less than i as it is expected that the number of symptoms would go on decreasing with time.

Here $(p_{ij}) = {}^{i}C_j w^j (1-w)^{i-j}$, i, j $= N, N\text{-}1,\ldots\ldots,0$ and $p_{ij} = 0\ \forall\ i < j$; $p_{00} = 1$ (4.1)

Now, for a diagnosis of schizophrenia, a person has to have a minimum of n symptoms out of a total of N symptoms. It is desirable that all the symptoms disappear in the course of treatment. This state is called the state of complete remission. If however, a state is reached when the patient has symptoms less than n, then he would be said to be in the state of partial remission. This is a state when the patient is functionally normal but still has certain symptoms. Nevertheless, he is still a patient of schizophrenia, but can be in states of complete or partial remission. However, from the medical point of view, it is desirable to take a patient to the state of partial remission, if not complete remission, as he will then be able to function normally.

To study this aspect we partition our transition probability matrix **P** in the following way:

$$\begin{array}{c} \\ N \\ N\text{-}1 \\ . \\ n \\ n\text{-}1 \\ . \\ 0 \end{array}
\begin{array}{c} \begin{array}{ccccccc} N & N\text{-}1 & \ldots\ldots & n & n\text{-}1 & \ldots\ldots & 0 \end{array} \\
\left[\begin{array}{cccc:ccc}
p_{NN} & p_{N,N-1} & \ldots\ldots & p_{N,n} & p_{N,n-1} & \ldots\ldots & p_{N,0} \\
0 & p_{N-1,N-1} & \ldots.. & p_{N-1,n} & p_{N-1,n-1} & \ldots\ldots & p_{N-1,0} \\
. & .. & \ldots\ldots & .. & .. & \ldots.. & .. \\
0 & 0 & \ldots.. & p_{n,n} & p_{n,n-1} & \ldots\ldots & p_{n,0} \\ \hdashline
0 & 0 & \ldots\ldots & 0 & p_{n-1,n-1} & \ldots\ldots & p_{n-1,0} \\
. & . & \ldots\ldots. & . & .. & \ldots\ldots. & .. \\
0 & 0 & \ldots\ldots & 0 & 0 & \ldots\ldots & 1
\end{array}\right] \end{array}$$

$$\textbf{i.e. P} = \left[\begin{array}{c|c} S & R \\ \hline O & NS \end{array}\right] \tag{4.2}$$

0

where

S = confirmed schizophrenia
R = schizophrenia in state of remission
NS = not schizophrenia but mentally ill
O = no mental illness

The partial sum: [9,10]

$$p_{N,n-1} + p_{N,n-2} + \ldots\ldots + p_{N,0} = \sum_{j=n-1}^{0} p_{N,j} \tag{4.3}$$

gives the probability of going to R (state of remission) from the state of highest schizophrenia with N symptoms.

And, the probability of going from the state of complete schizophrenia to the state of remission is given by

$$\sum_{i=N}^{n}\sum_{j=n-1}^{0} p_{i,j} = \sum_{j=n-1}^{0} p_{N,j} + \sum_{j=n-1}^{0} p_{N-1,j} + \sum_{j=n-1}^{0} p_{N-2,j} + \ldots\ldots + \sum_{j=n-1}^{0} p_{n,j} \tag{4.4}$$

= Pr [going from S to R]

= Pr ($W < n \mid W \geq n$) where W is the number of symptoms present.

P gives the transition probabilities for the first visit after initial diagnosis. The transition probabilities for the k^{th} visit can be obtained from $\mathbf{P}^k$ [10,11] where

$$\boldsymbol{P^k} = \left[\begin{array}{c|c} \mathbf{S}^k & \mathbf{R}_k \\ \hline \mathbf{O} & (\mathbf{NS})^k \end{array}\right] \tag{4.5}$$

where $\mathbf{R}_k = \mathbf{R}[\mathbf{S}^{k-1} + \mathbf{S}^{k-2}(\mathbf{NS}) + \mathbf{S}^{k-3}(\mathbf{NS})^2 + \ldots + (\mathbf{NS})^{k-1}]$

$$= RS^{K-1}\left[1 + \frac{NS}{S} + \left(\frac{NS}{S}\right)^2 + \ldots\ldots + \left(\frac{NS}{S}\right)^{K-1}\right]$$

$$= RS^{K-1}\left[\frac{\left(\frac{NS}{S}\right)^K - 1}{\left(\frac{NS}{S}\right) - 1}\right] \tag{4.6}$$

5 Application of the Markovian Model Defined in Section 4

As mentioned in Section 1, a patient with schizophrenia can have different combinations of symptoms of types A, B, and C. Let us consider the situations of a patient having symptoms of category A, B, AB, AC, BC, ABC, C, and O as the different states to which a patient with schizophrenia can belong. Here, A refers to the state when the patient has only type A symptoms, AB refers to the state when the patient has both type A and type B symptoms, and so on. C refers to the state when the patient has only type C symptoms and thus, can be said to be in partial remission whereas O refers to the state when there are no symptoms observable and hence, can be considered as complete remission. The states C and O together form the state of remission. Let us consider eight states as follows:

Patient with symptoms of type A, B, and C together
= state 1 (ABC)
Patient with symptoms of two types A and B together
= state 2 (AB)
Patient with symptoms of two types A and C together
= state 3 (AC)
Patient with symptoms of two types B and C together
= state 4 (BC)
Patient with symptoms of type A alone
= state 5 (A)
Patient with symptoms of type B alone
= state 6 (B)
Patient with symptoms of type C alone
= state 7 (C)
Patient with no symptoms, i.e. of type O
= state 8 (O)

(5.1)

In other words, the states from 1 to 6 constitute the states of active schizophrenia whereas states 7 and 8 constitute the states of remission. The endeavour of any treatment process is to take a patient to state 8 or at least to state 7.

Let, $X_k = i \quad \forall\ i = 1, 2, \ldots, 8$, represent the states of a patient with schizophrenia at the time of the k^{th} visit, $k = 0, 1, 2, \ldots$

Then $\{X_k, k = 0, 1, 2, \ldots\}$ will follow a markov chain with state space \$ = {1, 2,……, 8} and transition probability matrix (t. p. m.)

$\mathbf{P}_1$ = (pij)(i, j =1, 2,….,8) (5.2)

since the medical facts stated is sections 1 and 3 assure that transition from one state to another is in accordance with Markovian property.

It has been mentioned that on administration of medicines, the number of symptoms gradually goes on diminishing. Normally, if a symptom disappears once, it will not recur during the course of treatment. Also, a new symptom, not seen at the time of diagnosis, will not appear at subsequent visits during treatment. Thus, if a patient does not show the presence of 'aggression' (say) at the time of diagnosis, he will not develop the symptom later during the course of treatment, provided he is regular in the treatment process. In our case therefore, a patient with type A symptoms (state 5) can remain in state 5 or go to state 8 only whereas, a patient with symptoms of type ABC (state 1) can remain in state 1 or go to all the other states while a patient in state 2, with symptoms of type A and B together can remain in 2 or go to state 5 in which the type B symptoms have disappeared but type A symptoms remain or to state 6 in which the type A symptoms have disappeared but type B symptoms remain or go to state 8 in which the patient recovers from all the symptoms. Similar situations can be observed for the other states.

Thus $\mathbf{P}_1$ will take the following form:

$$\mathbf{P}_1 = \begin{bmatrix} p_{11} & p_{12} & p_{13} & p_{14} & p_{15} & p_{16} & p_{17} & p_{18} \\ 0 & p_{22} & 0 & 0 & p_{25} & p_{26} & 0 & p_{28} \\ 0 & 0 & p_{33} & 0 & p_{35} & 0 & p_{37} & p_{38} \\ 0 & 0 & 0 & p_{44} & 0 & p_{46} & p_{47} & p_{48} \\ 0 & 0 & 0 & 0 & p_{55} & 0 & 0 & p_{58} \\ 0 & 0 & 0 & 0 & 0 & p_{66} & 0 & p_{68} \\ 0 & 0 & 0 & 0 & 0 & 0 & p_{77} & p_{78} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \quad (5.3)$$

As mentioned earlier, states 1,2,….,6 constitute the states of active schizophrenia while states 7 and 8 constitute the states of schizophrenia in partial and complete remission. Hence, the matrix P_1 in (5.3) can be partitioned in accordance to (4.2) as follows:

$$\mathbf{P}_1 = \left[\begin{array}{cccccc|cc} p_{11} & p_{12} & p_{13} & p_{14} & p_{15} & p_{16} & p_{17} & p_{18} \\ 0 & p_{22} & 0 & 0 & p_{25} & p_{26} & 0 & p_{28} \\ 0 & 0 & p_{33} & 0 & p_{35} & 0 & p_{37} & p_{38} \\ 0 & 0 & 0 & p_{44} & 0 & p_{46} & p_{47} & p_{48} \\ 0 & 0 & 0 & 0 & p_{55} & 0 & 0 & p_{58} \\ 0 & 0 & 0 & 0 & 0 & p_{66} & 0 & p_{68} \\ \hline 0 & 0 & 0 & 0 & 0 & 0 & p_{77} & p_{78} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right]$$

$$= \left[\begin{array}{c|c} S & R \\ \hline O & NS \end{array}\right] \quad (5.4)$$

Hence, the probabilities defined in (4.3), (4.4) and (4.6) can be calculated in case of schizophrenia.

The various transitions that are possible from each state are separately shown in Figure 1.

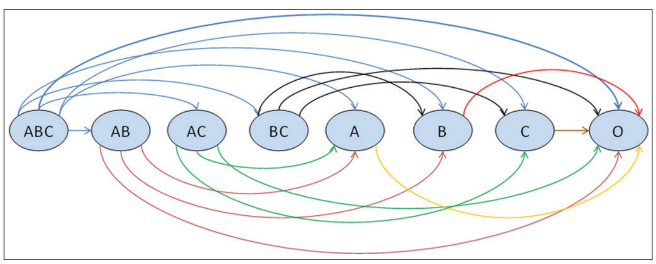

Figure 1: Digraph showing possible transitions from the various states of schizophrenia.

6 OBSERVATIONS

The mathematical modeling of the symptoms of schizophrenia, in conjunction with the concept of regularity of a patient in his visits to the psychiatrist, is found to be rare in literature. The stochastic models developed in this paper are expected to be of great help to doctors in framing their treatment strategies regarding patients with schizophrenia. The estimation of the expected number of visits required to take a patient to the state of remission with the knowledge of the number of symptoms manifested at the time of diagnosis might help doctors in planning out the treatment schedule in advance. It can also lead to a further study on cost benefit analysis as the treatment process necessarily involves expenditure.

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