The Cortisol Awakening Response for Using Fuzzy Time Series and Genetic Algorithms

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Abstract- A growing body of data suggests that a significantly enhanced salivary cortisol response to waking may indicate an enduring tendency to abnormal cortisol regulation. More methods have been proposed to deal with forecasting problems using fuzzy time series. In this paper, our objective was to apply the response test to a population already known to have long-term hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation. We hypothesized that the free cortisol response to waking, believed to be genetically influenced, would be elevated in a significant percent age of cases, regard less of the afternoon Dexamethasone Suppression Test (DST) value based on fuzzy time series and genetic algorithms. The proposed method adjusts the length of each interval in the universe of discourse for forecasting the Longitudinal Dexamethasone Suppression Test (DST) data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout the experimental results show that the proposed method gets good forecasting results.

Index Terms- Fuzzy Time Series, Genetic Algorithms, Fuzzy Logical Relationship, Fuzzy Logical Relationship Groups, Mean Square Error, glucocorticoids, salivary cortisol, bipolar disorder, lithium, Dexamethasone Suppression Test, DST.

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I. INTRODUCTION

A growing body of literature points to hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation as a critical factor in the development of mood disorders. Long-term enhanced cortisol secretion may have important health ramifications in addition to its contribution to mood syndromes. The free cortisol response to waking is a promising series of salivary tests that may provide a useful and non-invasive measure of HPA functioning in high-risk studies. The small sample size limits generalizability of our findings. Because interrupted sleep may interfere with the waking cortisol rise, we may have underestimated the proportion of our population with enhanced cortisol secretion. Highly cooperative participants are required [**1**].

Forecasting activities play an important role in our daily life. In order to solve the forecasting problems, many researchers have proposed many different forecasting methods [**2**], [**3**], [**4**], [5]. In [**6**], Song et al. proposed the definition of fuzzy time series. They also proposed the time-invariant model [**7**] and the time-variant model [**8**] of fuzzy time series to forecast enrolments of the University of Alabama. Both the time-invariant model and time-variant model used Max-Min Composition operations. In [**2**], Chen presented a method to forecast enrolments of the University of Alabama using simple arithmetic operations to get good forecasting results. In [**9**], Huarng pointed out that the length of intervals affects forecasting results in fuzzy time series, and he proposed the distribution-based length method and the average-based length method for handling the forecasting problems. In [**4**], Chen used the high-order fuzzy time series model to forecast the enrolments of the University of Alabama. In [**10**], Sullivan et al. proposed the Markov model, which used linguistic labels with probability distributions to forecast the medical data.

II. FUZZY TIME SERIES

In this session, we briey review the concept of fuzzy time series from [**6**], [**7**], [**8**]. The main difference of fuzzy time series and traditional time series is that the values of fuzzy time series are represented by fuzzy sets [**11**] rather than real values.

Let D be the universe of discourse, where $D=\{d_i\}_{i=1}^{n}$. A fuzzy set A_i in the universe of discourse D is defined as follows:

$$D=\{d_i\}_{i=1}^{n}\ A_i=\sum_{i=1}^{n}\frac{f_{A_i}(d_i)}{d_i},$$

where f_{A_i} is the membership function of the fuzzy set A_i, $f_{A_i}: D\rightarrow[0,1]$, $f_{A_i}(d_j)$ is the degree of membership of d_j in the fuzzy set A_i, $f_{A_i}(d_j)\in[0,1]$ and $1\le j\le n$.

Recently, interest has turned to more refined testing and the probability that HPA dysregulation may even predate the onset of clinical illness [**12**]. Preliminary data suggest that this dysregulation may be concentrated within the families of individuals with mood disorders [**13**], suggesting the hypothesis that early abnormalities in cortisol regulation may confer a risk for the future development of mood disorders. To understand the temporal relation between HPA dysregulation and the onset of bipolar disorder (BD), it is essential to have a reliable and non-invasive test that can be repeatedly administered prospectively and is acceptable to high-risk populations. Promising candidates for such a test include the salivary free cortisol response to waking and the short day time profile, a test that adds afternoon and evening measurements to the waking values[12].

Let $Y(t)\,(t=....,0,1,2.....)$ be the universe of discourse in which fuzzy sets $f_i(t)\,(i=1,2......)$ are defined in the universe of discourse $Y(t)$. Assume that $F(t)$ is a collection of $f_i(t)\,(i=1,2......)$, then $F(t)$ is called a fuzzy time series of $Y(t)\,(t=....,0,1,2.....)$.

Assume that there is a fuzzy relationship $R(t-1,t)$, such that $F(t)=F(t-1)\,o\,R(t-1,t)$, where the symbol "o" represents the max-min composition operator, then $F(t)$ is called caused by $F(t-1)$.

Let $F(t-1)=A_i$ and let $F(t)=A_j$, where A_i and A_j are fuzzy sets, then the fuzzy logical relationship (FLR) between $F(t-1)$ and $F(t)$ can be denoted by $A_i \to A_j$, where A_i and A_j are called the left-hand side(LHS) and the right hand side (RHS) of the fuzzy logical relationship, respectively.

Fuzzy logical relationships having the same left-hand side can be grouped into a fuzzy logical relationship group(FLRG). For example, assume that the following fuzzy logical relationships exist:

$A_i \to A_{ja}$,

$A_i \to A_{jb}$,

$A_i \to A_{jc}$,

.

.

.

$A_i \to A_{jm}$,

Then these fuzzy logical relationships can be grouped into a fuzzy logical relationship group, shown as follows:

$A_i \to A_{ja}, A_{jb}, A_{jc}, ...A_{jm}$.

III. A NEW METHOD TO FORECAST ENROLLMENTS BASED ON FUZZY TIME SERIES AND GENETIC ALGORITHMS

In this session, we present a new method to forecast the Longitudinal Dexamethasone Suppression Test (DST)[13] data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout, based on fuzzy time series and genetic algorithms.

Step 1: Let D_{min} and D_{max} be the minimum and the maximum known data. Based on D_{min} and D_{max}, define the universe of discourse D as $[D_{min} - D_1, D_{max}+D_2]$, where D_1 and D_2 are two proper positive integers. From Table 1,

Step 2: We can see that $D_{min} = 90$ and $D_{max} = 430$. Thus, we let $D_1 = 40$ and $D_2 = 20$. Therefore, the universe of the discourse D = [50, 450]. Firstly, divide the universe of discourse D into Eight intervals d_1, d_2, d_3, d_4, d_5, d_6, d_7 and d_8, where $d_1 = [50, x_1]$, $d_2 = [x_1, x_2]$, $d_3 = [x_2, x_3]$, $d_4 = [x_3, x_4]$, $d_5 = [x_4, x_5]$, $d_6 = [x_5, x_6]$, $d_7 = [x_6, x_7]$ and $d_8 = [x_7; 450]$; x_1, x_2, x_3, x_4, x_5, x_6 and x_7 are integer variables and $x_1 < x_2 < x_3 < x_4 < x_5 < x_6 < x_7$. We can see that the universe discourse D = [50, 450] into Eight intervals d_1, d_2, d_3, d_4, d_5, d_6, d_7 and u_8, where $d_1 = [50, 100]$, $d_2 = [100, 150]$, $d_3 = [150, 200]$, $d_4 = [200, 250]$, $d_5 = [250, 300]$, $d_6 = [300, 350]$, $d_7 = [350, 400]$ and $d_8 = [400; 450]$;

Define the linguistic terms A_i represented by fuzzy sets, shown as follows:

$$A_1 = {}^{1}\!/_{d_1} + {}^{0.5}\!/_{d_2} + {}^{0}\!/_{d_3} + {}^{0}\!/_{d_4} + {}^{0}\!/_{d_5} + {}^{0}\!/_{d_6} + {}^{0}\!/_{d_7} + {}^{0}\!/_{d_8},$$

$$A_2 = {}^{0.5}\!/_{d_1} + {}^{1}\!/_{d_2} + {}^{0.5}\!/_{d_3} + {}^{0}\!/_{d_4} + {}^{0}\!/_{d_5} + {}^{0}\!/_{d_6} + {}^{0}\!/_{d_7} + {}^{0}\!/_{d_8},$$

$$A_3 = {}^{0}\!/_{d_1} + {}^{0.5}\!/_{d_2} + {}^{1}\!/_{d_3} + {}^{0.5}\!/_{d_4} + {}^{0}\!/_{d_5} + {}^{0}\!/_{d_6} + {}^{0}\!/_{d_7} + {}^{0}\!/_{d_8},$$

$$A_4 = {}^{0}\!/_{d_1} + {}^{0}\!/_{d_2} + {}^{0.5}\!/_{d_3} + {}^{1}\!/_{d_4} + {}^{0.5}\!/_{d_5} + {}^{0}\!/_{d_6} + {}^{0}\!/_{d_7} + {}^{0}\!/_{d_8},$$

$$A_5 = {}^{0}\!/_{d_1} + {}^{0}\!/_{d_2} + {}^{0}\!/_{d_3} + {}^{0.5}\!/_{d_4} + {}^{1}\!/_{d_5} + {}^{0.5}\!/_{d_6} + {}^{0}\!/_{d_7} + {}^{0}\!/_{d_8}$$

$$A_6 = {}^{0}\!/_{d_1} + {}^{0}\!/_{d_2} + {}^{0}\!/_{d_3} + {}^{0}\!/_{d_4} + {}^{0.5}\!/_{d_5} + {}^{1}\!/_{d_6} + {}^{0.5}\!/_{d_7} + {}^{0}\!/_{d_8},$$

$$A_7 = {0}/{d_1} + {0}/{d_2} + {0}/{d_3} + {0}/{d_4} + {0}/{d_5} + {0.5}/{d_6} + {1}/{d_7} + {0.5}/{d_8},$$
$$A_8 = {0}/{d_1} + {0}/{d_2} + {0}/{d_3} + {0}/{d_4} + {0}/{d_5} + {0}/{d_6} + {0.5}/{d_7} + {1}/{d_8},$$

where $A_1, A_2, ...andA_n$ are linguistic terms represented by fuzzy sets. Then, we can fuzzify the Longitudinal Dexamethasone Suppression Test (DST)[**13**] data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout, shown in Table 1. Furthermore, we can get the fuzzy logical relationship groups as shown in Table 2, where the ith fuzzy logical relationship group contains fuzzy logical relationships whose current state is A_i, where $1 \le i \le 8$. Then, apply the following forecasting method to forecast the data [**2**]:

Case 1: Assume that the fuzzified data of the ith year is A_j and assume that there is only one fuzzy logical relationship in the fuzzy logical relationship groups in which the current state of the fuzzy logical relationship is A_j , shown as follows:

"$A_j \rightarrow A_k$"

where A_j and A_k are fuzzy sets and the maximum membership value of A_k occurs at interval d_k, then the forecasted data of the i + 1th year is the midpoint m_k of the interval d_k.

Case 2: Assume that the fuzzified data of the ith year is A_j and assume that there are the following fuzzy logical relationships in the fuzzy logical relationship groups in which the current states of the fuzzy logical relationships are A_j, respectively, shown as follows:

$A_j \rightarrow A_{k1}$; $Aj \rightarrow A_{k2}$; .... $Aj \rightarrow A_{kp}$;

where A_j, A_{k1}, A_{k2}, ... , and A_{kp} are fuzzy sets and the maximum membership values of A_{k1}, A_{k2}, ... , and A_{kp} occur at intervals d_1, d_2, ... , and d_p, respectively, and the midpoints of the interval d_1, d_2, ... , and d_p are m_1, m_2, ... , and m_p, respectively, then the forecasted enrollment the i + 1th year is equal to $(m_1+m_2+ ..... +m_p)/p$.

Case 3: Assume that the fuzzified data of the ith year is A_j and assume that there are no fuzzy logical relationship groups whose current state of the fuzzy logical relationship is A_j, where the maximum membership value of Aj occurs at interval d_j, then the forecasted data of the i+1th year is the midpoint m_j of the interval d_j. By applying the above forecasting method, we can get the forecasted data as shown in Table 4.

EXAMPLE 3.1

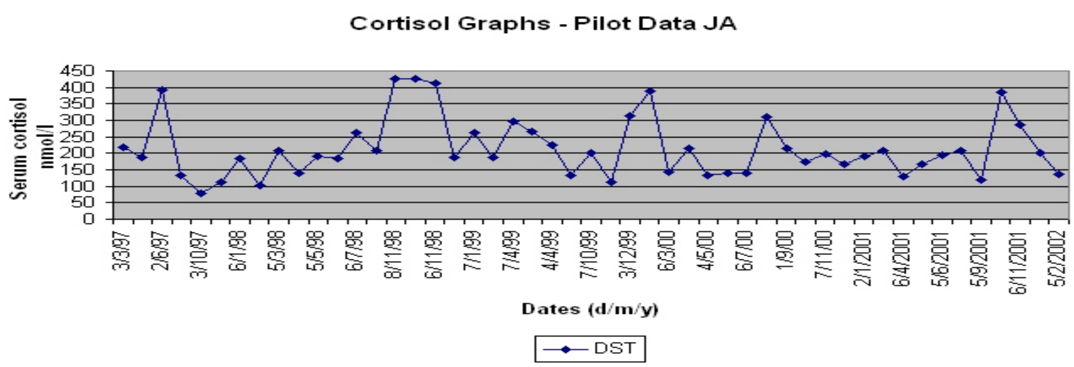

Figure 1: The Longitudinal Dexamethasone Suppression Test (DST) data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout.

We apply the proposed method to forecast the Longitudinal Dexamethasone Suppression Test (DST)[**13**] data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout based on high order fuzzy logical relationships. d_1 = [50, 100], d_2 = [100, 150], d_3 = [150, 200], d_4 = [200, 250], d_5 = [250, 300], d_6 = [300, 350], d_7 = [350, 400], d_8 = [400, 450]

Table 1: Corresponding Medical Data

S. No.	Actual Value	S. No.	Actual Value
1	225	26	120
2	190	27	315
3	395	28	390
4	140	29	145
5	90	30	210
6	120	31	135

7	180	32	140
8	110	33	140
9	210	34	310
10	145	35	210
11	190	36	180
12	185	37	195
13	260	39	175
14	210	39	190
15	430	40	210
16	430	41	135
17	420	42	175
18	190	43	195
19	260	44	210
20	190	45	120
21	295	46	385
22	270	47	290
23	230	48	195
24	140	49	140
25	199		

Table 2: Fuzzified value and Fuzzy logical relationships for Medical data

S. No	Actual Value	Fuzzy set	Fuzzy logical relationships
1	225	A_4	-
2	190	A_3	$A_4 \rightarrow A_3$
3	395	A_7	$A_3 \rightarrow A_7$
4	140	A_2	$A_7 \rightarrow A_2$
5	90	A_1	$A_2 \rightarrow A_1$
6	120	A_2	$A_1 \rightarrow A_2$
7	180	A_3	$A_2 \rightarrow A_3$
8	110	A_2	$A_3 \rightarrow A_2$
9	210	A_4	$A_2 \rightarrow A_4$
10	145	A_2	$A_4 \rightarrow A_2$
11	190	A_3	$A_2 \rightarrow A_3$
12	185	A_3	$A_3 \rightarrow A_3$
13	260	A_5	$A_3 \rightarrow A_5$
14	210	A_4	$A_5 \rightarrow A_4$
15	430	A_8	$A_4 \rightarrow A_8$
16	430	A_8	$A_8 \rightarrow A_8$
17	420	A_8	$A_8 \rightarrow A_8$
18	190	A_3	$A_8 \rightarrow A_3$
19	260	A_5	$A_3 \rightarrow A_5$
20	190	A_3	$A_5 \rightarrow A_3$
21	295	A_5	$A_3 \rightarrow A_5$
22	270	A_5	$A_5 \rightarrow A_5$
23	230	A_4	$A_5 \rightarrow A_4$
24	140	A_2	$A_4 \rightarrow A_2$
25	199	A_2	$A_2 \rightarrow A_2$
26	120	A_2	$A_2 \rightarrow A_2$
27	315	A_6	$A_2 \rightarrow A_6$
28	390	A_7	$A_6 \rightarrow A_7$
29	145	A_2	$A_7 \rightarrow A_2$
30	210	A_4	$A_2 \rightarrow A_4$
31	135	A_2	$A_4 \rightarrow A_2$

32	140	A_2	$A_2 \rightarrow A_2$
33	140	A_2	$A_2 \rightarrow A_2$
34	310	A_6	$A_2 \rightarrow A_6$
35	210	A_4	$A_6 \rightarrow A_4$
36	180	A_3	$A_4 \rightarrow A_3$
37	195	A_3	$A_3 \rightarrow A_3$
38	175	A_3	$A_3 \rightarrow A_3$
39	190	A_3	$A_3 \rightarrow A_3$
40	210	A_4	$A_3 \rightarrow A_4$
41	135	A_2	$A_4 \rightarrow A_2$
42	175	A_3	$A_2 \rightarrow A_3$
43	195	A_3	$A_3 \rightarrow A_3$
44	210	A_4	$A_3 \rightarrow A_4$
45	120	A_2	$A_4 \rightarrow A_2$
46	385	A_7	$A_2 \rightarrow A_7$
47	290	A_5	$A_7 \rightarrow A_5$
48	195	A_3	$A_5 \rightarrow A_3$
49	140	A_2	$A_3 \rightarrow A_2$

Table 3: Fuzzy logical relationship groups

Groups	Transformed second order fuzzy logical relationship
Group 1	$A_1 \rightarrow A_2$
Group 2	$A_2 \rightarrow A_1$, $A_2 \rightarrow A_2$, $A_2 \rightarrow A_3$, $A_2 \rightarrow A_4$, $A_2 \rightarrow A_6$, $A_2 \rightarrow A_7$
Group 3	$A_3 \rightarrow A_2$, $A_3 \rightarrow A_3$, $A_3 \rightarrow A_5$, $A_3 \rightarrow A_7$
Group 4	$A_4 \rightarrow A_2$, $A_4 \rightarrow A_3$, $A_4 \rightarrow A_8$
Group 5	$A_5 \rightarrow A_3$, $A_5 \rightarrow A_4$, $A_5 \rightarrow A_5$
Group 6	$A_6 \rightarrow A_4$, $A_6 \rightarrow A_7$
Group 7	$A_7 \rightarrow A_2$, $A_7 \rightarrow A_5$
Group 8	$A_8 \rightarrow A_3$, $A_8 \rightarrow A_8$

Then, based on the corresponding intervals of each medical data in Figure 1 shown in Table 1 and the forecasting method described above, we can calculate the forecasted data and calculate the mean square error (MSE) of each medical data, where the value of MSE is used as the fitness value of a data. If the MSE is higher, then the forecasted error is larger and the medical will not fit the environment enough. On the other hand, if the MSE is lower, then the forecasted error is lower and the medical data will better fit the environment, where the definition of MSE is shown as follows:

$$\mathrm{MSE} = \frac{\left(\dfrac{|\,\text{forecasted value}_i - \mathit{acutual\ value}_i\,|^2}{n} \right)}{\text{forecasted value}_i}$$

where “Forecasted value$_i$” denotes the forecasted data of the ith value, and “Actual value$_i$” denotes the actual data of the ith value.

Table 4: Forecasted Value and MSE

S. No	Actual Value	Forecasted Value	MSE
1	225	-	-
2	190	242	0.0390
3	395	235	0.0578
4	140	200	0.0612
5	90	237	0.2333
6	120	125	0.0059
7	180	237	0.0452
8	110	235	0.1623
9	210	237	0.0183

10	145	242	0.0955
11	190	237	0.0353
12	185	235	0.0386
13	260	235	0.0137
14	210	225	0.0102
15	430	242	0.0624
16	430	300	0.0431
17	420	300	0.0408
18	190	300	0.0827
19	260	235	0.0137
20	190	225	0.0263
21	295	235	0.0290
22	270	225	0.0238
23	230	225	0.0031
24	140	242	0.1040
25	199	237	0.0272
26	120	237	0.1392
27	315	237	0.0353
28	390	300	0.0329
29	145	200	0.0541
30	210	237	0.0183
31	135	242	0.1132
32	140	237	0.0989
33	140	237	0.0989
34	310	237	0.0336
35	210	300	0.0612
36	180	242	0.0492
37	195	235	0.0293
38	175	235	0.0489
39	190	235	0.0338
40	210	235	0.0170
41	135	242	0.1132
42	175	237	0.0506
43	195	235	0.0293
44	210	235	0.0170
45	120	242	0.1452
46	385	237	0.0549
47	290	200	0.0443
48	195	225	0.0219
49	140	235	0.0969

Based on the corresponding intervals of each medical data shown in Table 1, and the forecasting method described above, we can calculate the forecasted value as shown in Table 4. Based on the actual data shown in Table 1, we can compute the MSE of the medical data shown in Table 4, which is equal to 76.5

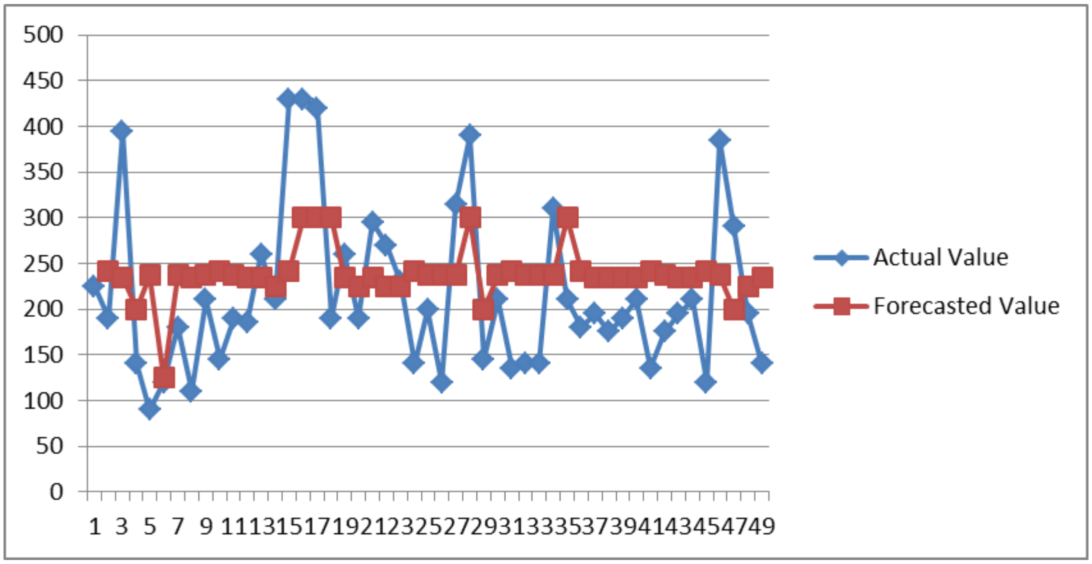

Figure 2: Actual value and Forecasted value for the Longitudinal Dexamethasone Suppression Test (DST)[10] data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout.

IV. EXPERIMENTAL RESULTS

There was a significant difference between BD patients and our control subjects in the maximum percentage rise of salivary cortisol response to awakening. Those showing a waking response also had significantly higher mean cortisol values at 30 minutes after waking, compared with 509 normal subjects described in Wust's and others study [**1**]. Base line values at time zero, immediately upon waking, did not differ significantly between our sample and Wust's control subjects [**1**]. Patients and our 5 control subjects did not differ significantly in the percent age decline from the peak morning value to the evening values. In this section we apply the proposed for forecasting the Longitudinal Dexamethasone Suppression Test (DST) data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout.
It means that the proposed method gets a higher average forecasting accuracy rate than other existing methods to forecast the maximum percentage rise of salivary cortisol response to awakening. we can see that the proposed method get the smallest RMSE than Huarng's method and Huarng's and Yu's method for forecasting the medical data.

V. CONCLUSION

In this paper, Our dysregulation, even when lithium-responsive BD patients are clinically well and their DSTs are observations support the hypothesis that the free cortisol response to waking can reflect relatively enduring HPA normal. Because the test is easy to administer, the free cortisol response to waking may hold promise as a marker in studies of high-risk families predisposed to, or at risk for, mood disorders, we have presented a new method for forecasting the Longitudinal Dexamethasone Suppression Test (DST) data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout based on fuzzy time series and genetic algorithms. We also make a comparison of the MSE of the forecasted medical data for different methods. In this paper, we use the MSE to compare the performance of prediction of salivary cortisol response to awakening. However, how to narrow the maximum deviation of predicted value from the actual one is more important than the MSE. Therefore, in the future, we will develop a new method to deal with a more accurate prediction by narrowing the maximum deviation of predicted value from the actual one. In this case, a more accurate prediction can provide the school authority to make right decision.

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