

# Using stochastic differential equations to model the ups and downs of patients with bipolar disorder for clinical purposes

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## Introduction

Bipolar disorder, often called manic-depression, is characterized by abnormal brain functioning that results in severe changes in mood, energy, and performance [1]. In 2006, the World Health Organization identified bipolar disorder as the sixth most disabling disease worldwide [2]. One in four untreated cases ends in suicide [3], while the economic effects of the disease range from lost employment and productivity to health and social care services [4]. While there is no current cure, bipolar disorder can be managed with a combination of pharmacological treatments and psychological interventions [5]. Nevertheless, treatment for bipolar disorder varies from patient to patient, and currently there are no methods to pre-select treatment or to monitor timely the success of medicine and therapy [5]. Similarly, both patients and doctors struggle to predict the occurrence of a patient's next extreme manic or depressive episode. Such trial-and-error practices consume much money and grief.

Several barriers impede the study of bipolar disorder, including the heterogeneity of the disease among patients as well as its episodic nature and the lack of an objective method of quantifying the severity and characteristics of bipolar disorder from patient to patient [6]. However, scales have been developed to track the progress of patients receiving treatment. The Young Mania Rating Scale (YMRS) was developed by clinicians in 1978 to assess the severity of manic states, with a score of 60 being the most manic [7]. It is comprised of eleven questions chosen to reflect the core symptoms of the manic phase of bipolar disorder. Both patient and

clinician answer the YMRS questions, allowing the quantification and tracking of the extreme ups and downs of the disorder. Conversely, the Hamilton Depression Rating Scale (HAM-D) measures the severity of depressed states, with a score of 53 being the most depressed [8]. A clinician's answers to twenty-one questions about the patient determine the HAM-D score. As both the YMRS and HAM-D scales have been employed for over twenty-five years, much patient information over time has been recorded in these relatively simple formats.

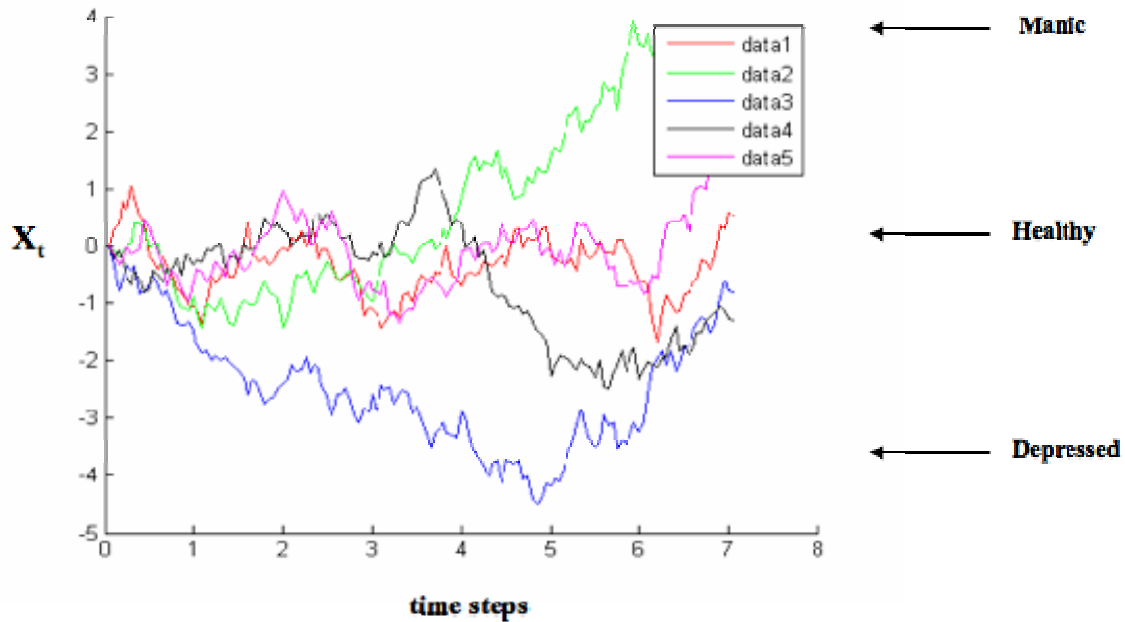
### **General methodology**

We predict that using stochastic differential equations to model the ups and downs of patients with bipolar disorder will develop a quantitative understanding of the illness that addresses clinical questions and includes predictors for a patient's outcome. We plan to construct a mathematical model using MATLAB with two patient-dependent parameters that describes the time evolution of a patient's illness-index, or deviation from normal mood and behavior. The model will be constructed to answer specific clinical questions by translating them into mathematical problems. Examples of such clinical questions include determining in an optimal way, using as little data as possible, whether a given treatment is effective or if the patient is doing worse; if a treatment is working, how long will it take for remission; what is the expected time for the next big episode for a patient in remission; and quantification of the effects of treatment, both choice and dose, for a patient. Fifteen years of clinical data supplied by our collaborators at Western Psychiatric Institute and Clinic (WPIC) will be used to estimate the model's parameters, all of which are patient-dependent.

More specifically, the mathematical framework will incorporate random noise,  $dZ_t$ , and patient parameters,  $\mu$  and  $\sigma$ , through the stochastic differential equation below, which is characterized as a generalized Ornstein-Uhlenbeck equation

$$(1) \quad dX_t = -\mu X_t dt + \sigma dZ_t$$

where  $X_t$  represents the illness-index, calculated using a combination of YMRS and HAM-D scores. The two constant, patient-dependent parameters  $\mu$  and  $\sigma$  are the homing towards healthy and noise constants, respectively. We will construct the illness-index,  $X_t$ , so that positive and high values indicate manic states while negative and high values indicate depressed states, with small values, positive or negative, being normal (see Fig. 1 below). The stochastic model can predict a patient's stability, range of manic and depressed fluctuations, expected time to recurrence or remission, and treatment effectiveness. Limitations of the model include predicting exact paths and exact times.



**Figure 1. The simulated ups and downs of five bipolar patients, generated by artificial data.** Equation 1 with  $\mu = 0.025$  and  $\sigma = 1.0$  as white noise was used. Large positive  $X_t$  values indicate manic states, while large negative values indicate depression, with normal being near zero.

## Specific aims

We plan to determine the minimum amount of data points of the illness-index,  $X_t$ , needed to estimate the patient-dependent parameters  $\mu$  and  $\sigma$ . This will allow accurate but efficient prediction of patient mood and behavior. In particular, we can examine the accuracy of the estimates as a function of the amount of data used by employing standard estimation formulas from stochastic analysis. Similarly, the amount of accuracy required to use the model clinically will be determined.

Furthermore, we will test our assumption that the two patient-dependent parameters are constants. If the model does not correctly predict patient behavior, we will reevaluate these parameters and test their accuracy as slowly changing parameters, piecewise constant parameters, and random parameters. Another assumption that will be tested is the selection of white noise. White noise has a Gaussian distribution that may not accurately reflect the mood shifts of bipolar patients, which are often characterized by jumps in mood rather than by smooth curves.

Characterizing the type of noise, whether it be white, Cauchy, pink, or another type, will be a top priority. Noise types can be determined by looking at the distribution of the points of the illness-index,  $X_t$ . White noise displays a bell-shaped distribution whereas Cauchy noise displays a steple-shaped distribution and so on. In relation, if different types of patients, for example say male and female, have different types of noise, we will want to recognize these patterns and classify the noise types for the purpose of assigning patients to appropriate categories for prediction and treatment.

We aim to construct the illness-index,  $X_t$ , from the YRMS and HAM-D scores to accurately represent patient mood. A straightforward approach is to subtract the scaled HAM-D score from that of the YRMS score

$$(2) \quad X_t = YRMS - HAM-D^*$$

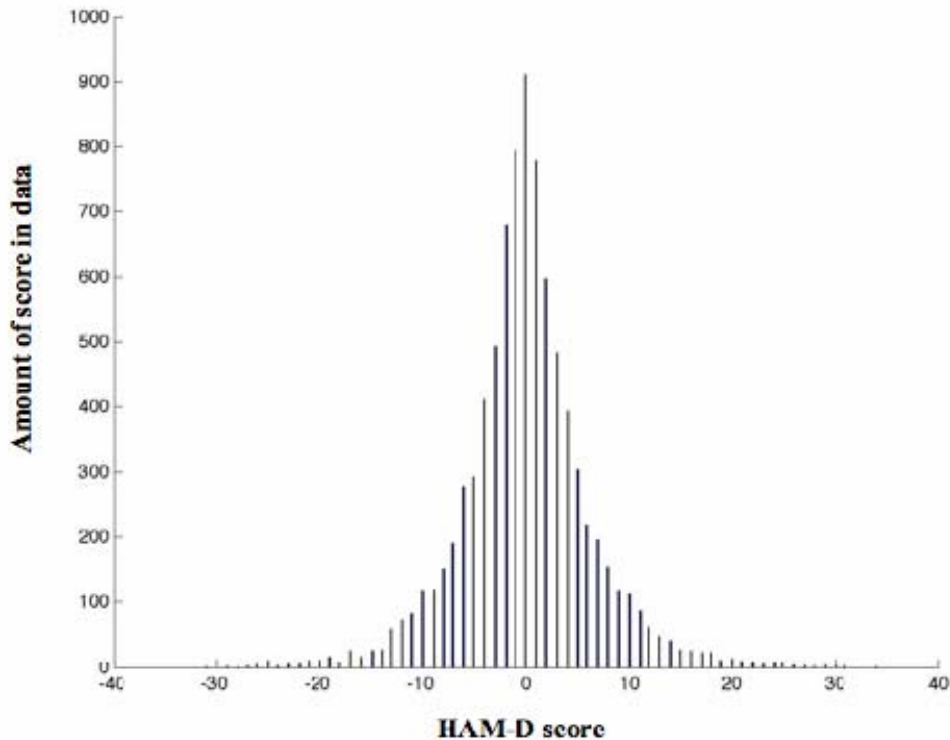
where  $HAM-D^*$  indicates the scaled HAM-D score. However, a portion of patients with bipolar disorder experience what is termed mixed state, in which they have the characteristics and feelings of both manic and depressed states at the same time [1]. Consequently, these types of patients may require a different approach to calculating their illness-index,  $X_t$ .

### **Proposed findings**

Preliminary analysis of the distribution of HAM-D scores in WPIC patients indicates that the most common noise type among bipolar patients is Cauchy noise (see Figure 2 on next page). As Cauchy noise is in part characterized by jumps, which reflect the severe mood shifts of bipolar patients, we also expect the YRMS and therefore illness-index distributions to have similar steeple-shaped distributions. Nevertheless, we will analyze different groupings of patients to determine whether dissimilar types of patients are best modeled by different types of noise or illness-indices. For example, women are in depressed states three times as often as men [3]. Therefore it is possible that their illness-indices or noise type may be different from that of men. Less obvious groupings are also possible and may yield clinically relevant results.

When the specifics of the model have been determined, its application may be used to pre-select the most effective treatment for a patient, to monitor the success or failure of treatment, to predict extreme episodes, and much more. Such practical clinical application will

save health care costs and time, while increasing quality of life and productivity of bipolar patients.



**Figure 2. Preliminary distribution curve of HAM-D scores from WPIC patients. The steple-shaped distribution indicates Cauchy noise. Cauchy noise contains jumps that are more representative of patients' severe shifts in mood.**

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