



HAL
open science

Computational models in psychiatry: a toy-model to apprehend the dynamics of psychiatric disorders

Christophe Gauld, Damien Depannemaecker

► **To cite this version:**

Christophe Gauld, Damien Depannemaecker. Computational models in psychiatry: a toy-model to apprehend the dynamics of psychiatric disorders. 2022. hal-03753153v2

HAL Id: hal-03753153

<https://hal.science/hal-03753153v2>

Preprint submitted on 8 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Computational models in psychiatry: a toy-model to apprehend the dynamics of psychiatric disorders

Christophe Gauld^{1,2,*}, Damien Depannemaecker^{3,*}

¹ Child Psychiatry Department, University Hospital Lyon, 59 Bd Pinel, 69000 Lyon, France

² Institut des Sciences Cognitives Marc Jeannerod, UMR 5229 CNRS & Université Claude Bernard Lyon 1

³ Paris-Saclay University, Centre National de la Recherche Scientifique (CNRS), Institute of Neuroscience (NeuroPSI), 91198 Gif sur Yvette, France

* The two authors contributed equally to this work

Corresponding author: Christophe Gauld,
Department of Child Psychiatry, University of Lyon, 59 Bd Pinel, 69 000 Lyon, France
Phone: 00 33 785 516 497
e-mail: christophe.gauld@chu-lyon.fr

Figure: 3 **Table:** 2

Short title: A toy-model to apprehend the dynamics of psychiatric disorders

Funding source: None.

Ethical Conduct Confirmations: No data was used in this study, that did not involve humans subjects.

Abstract

Introduction: Given this research attention on the dynamical aspects of psychiatric disorders in recent years and their clinical significance, this article seeks to provide a computational model capturing the heterogeneous individual evolutions of psychiatric disorders.

Methods: We propose a 3+1 dimensional toy-model reproducing the clinical observations encountered in clinical psychiatry. This model is based on differential equations aggregating perceived environmental influence over time, internal and subjective patient specific factors, and their interaction with the apparent rate or intensity of symptoms.

Results: Constrained by clinical observation of case formulations, four main psychiatric conditions were modeled: i) a healthy situation, ii) a kind of psychiatric disorder evolving following an outbreak (i.e., schizophrenia spectrum), iii) a kind of psychiatric disorder evolving by kindling and bursts (e.g., bipolar and related disorders); iv) and a kind of psychiatric disorder evolving due to its susceptibility to the environment (e.g., persistent complex bereavement disorder). Moreover, still following the observational constraint of stereotyped case formulations, we simulate the action of treatments on different psychiatric disorders.

Conclusions: Dynamical systems allows to understand the interactions of psychiatric disorders with the environmental, descriptive, subjective and biological variables. Although this non-linear dynamical toy-model have limitations (e.g., explanatory scope or discriminant validity), simulations provide at least five main interests for clinical psychiatry, as a visualization of the potential different evolution of psychiatric disorders, sustaining case formulations, information about attracting states, or the possibility of a nosological refinement of psychiatric models (e.g., staging and symptom network models).

Keywords: biology; computational psychiatry; dynamical systems; environment; simulations.

1 Introduction

Contemporary psychiatric nosology is based on categorical and static taxonomic distinctions. Thanks to the International Classification of Diseases, Eleventh Edition (ICD-11) (1) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (2), the operationalization of psychiatric disorders within descriptive and categorical nosographies has been one of the most important advances in contemporary psychiatry (3). Partly related to these specificities, such classification systems have major limitations that substantially impede scientific progress (4; 5). In addition to the difficulty in “carving the nature at its joints”, i.e. clearly demarcated psychiatric disorder entities as discrete taxa (6), a large part of these limitations stems from the conception of psychiatric disorders as categorical kinds, aka separate entities stable over time (7; 8). In this way, categorical psychiatric disorders fail to provide: i) operational and clinically relevant modelizations of their inherent dependence on time, ii) their intrinsic non-linearity perceived in clinical practice, iii) and their intraindividual variability.

Psychiatric disorders are dynamical conditions. They are field-dynamic phenomena with temporal extension occurring in a context (9). They may be conceived as evolving entities, varying over time under the pressure of allostatic loads (i.e., accumulations of external factors over time), according to the evolution of symptoms (e.g., a delirium reinforcing the interpretative mechanisms) or according to the subjective perception of an individual’s life. Therefore, a flow of current research theoretically aims to show that psychiatric disorders can be modeled dynamically (10). Dynamical models aim to provide a precise outline accounting for the evolution of various psychiatric disorders or conditions over time, according to different types of temporal evolutions. For instance, Schizophrenia Spectrum (SS), Bipolar and related Disorders (BD), Major Depressive Disorders (MDD) evolve by outbreaks and oscillations. Attention Deficit/Hyperactivity Disorders (ADHD), Autism Spectrum Disorders (ASD) could be considered as more continuous. Others, as Obsessive-Compulsive Disorders (OCD), normal grief or Persistent Complex Bereavement Disorder (PCBD) raise the question of an evolution influenced by various contextual factors (2). However, despite a number of theoretical expectations on this subject (11), dynamical models were very little developed to model psychiatric disorders.

We identified the existence of at least four main types of non-modeled clinical theoretical

proposals in the psychiatric literature. The first one corresponds to the diathesis-stress and 3P models (12). Such models of case formulations propose to integrate predisposing, precipitating and perpetuating factors (13): i) predisposing factors makes the system sensitive to a stimulus, and depends on the prior state of the system states; ii) precipitating factors initiate the dynamics of the psychiatric disorder by kindling behavior; iii) perpetuating factors keep the system burnished despite the absence of stimuli. This non-mathematized formulation allows to follow the evolution of patients from the early stages of neurodevelopment, and to visualize their evolution over the life-course as a function of the influence of the three aforementioned factors. The second kind of clinical theoretical proposal corresponds to the kindling model. This clinical formulation, from the field of epilepsy, explains the manifestations of a relatively short stage of a psychiatric disorder. At a during fleeting moments of susceptibility (e.g., from a few hours to a few weeks), a triggering factor would lead to expressing the manifestations of this disorder. Then, this psychiatric disorder will deploy its acute manifestations in successive bursts, on a relatively short time scale (14). The kindling formulation brings together two parameters, when the system is above a certain threshold: an increase in the frequency of cycles of bursting, and a triggering of these cycles more and more independently of environmental factors (i.e., reflecting a phenomenon of sensitization). The third kind of clinical theoretical proposal corresponds to staging models. Staging formulations consider the different stages of evolution of psychiatric disorders (15) relying especially on longitudinal studies (16). However, this proposal remains based on a linear conception of psychiatric disorders (11). Finally, the fourth kind of clinical theoretical proposal corresponds to the conception of psychiatric disorders through the prism of dynamical systems, as we are going to explain, develop and use in this work.

In this article, we propose to use dynamical systems in order to build a computational model of psychiatric disorders. The main goal of the use of dynamical systems is to computationally validate empirical observations made by psychiatric clinicians and researchers. Like non-modeled clinical theoretical proposals, this computational model allows stereotyped case formulations, defined as tools that can help organize complex and contradictory information about a person (17). These stereotyped case formulations are those described in the textbook of clinical psychiatry and transmitted to any clinician in his/her elementary formulation, and as he/she can then observe it in his/her daily practice (corresponding to irrefutable and prototypical cases of dynamical evolutions

of psychiatric disorders).

Such dynamical model will allow to learn about non-linear phenomena and instability, major variations related to fluctuations in initial conditions, phenomena of resilience and fragility or the attainment of tipping points (transitions) and steady states, attractors and oscillations between multiple stability, in response to internal conditions or external stressors. It also incorporates the elements mentioned in the three previous kinds of clinical modeling, e.g., predisposing, precipitating and perpetuating factors, consideration of different time frames, sensitization and stages of psychiatric disorders.

More precisely, we propose here a model which reduces complexity by considering aggregates of non-linear relationships between a limited number of variables influencing psychiatric disorders: the environment, the subjective phenomenological experience, and symptoms. Indeed, such a model ignores the fine details of a system, such as the individual properties or specific events, and produces an abstract representation of complex system such as psychiatric disorders. Our computational model is called a toy-model. A toy-model does not voluntarily rely on any measurement (mechanism or biophysical element, or clinical data): rather, (abstract) values are forced on qualitative behaviors, empirically perceived in clinical practice. As we will discuss, such a toy-model could only serve to apprehend, understand, or support discussions of the possible dynamics of psychiatric disorders, by reproducing certain phenomenological aspects. In the same way that it has already been proposed in the context of epilepsy (18), under the name of *epileptor* (19), which accounts for electrophysiological brain activity, this dynamical modeling of psychiatric symptoms, subjectivity, biology and environment could thus be qualified as *psychiator*.

2 Methods

We propose a model based on dynamical system for psychiatric disorders. The model captures the temporal evolution of a phenomenon using mathematical differential equations. Differential equations allow to calculate next states given a current state, depending on time. In a first-order differential system, the state of a variable at a time t is calculated based on its variation with respect to time t . The rate of amplitude changes over time will determine the time scale. Each equation composing the system can vary according to its own time scale. This notion of time scales is an

important consideration in psychiatric disorders because psychiatric acute events occur on a much slower scale (minutes, hour, day, weeks) than that of the global development and consequences of a psychiatric disorder itself (months, years, decades). Thus, to model psychiatric disorders, a fast sub-system switch from a basic (healthy or already pathologically latent) state to a state with high level of symptoms. A slower system is needed to drive the transition between these states. A slow-fast system should be proposed, including these different time scales, in which an external input drives the transition between states. This dynamical-based model presents i) a stereotypical description ii) and a qualitative description of the temporal evolution of psychiatric disorders.

First, the stereotypical description of the temporal evolution of psychiatric disorders phenomenologically reproduces the empirical dynamics of psychiatric disorders (e.g., the clinically observed relationships between the psychiatric variables), as described in the empirical and historical descriptions of clinicians and researchers. Secondly, the qualitative description of the temporal evolution of psychiatric disorders is based on the description and the labeling of variables and parameters of the dynamical evolution of these disorders, by clinicians and researchers. We seek to infer the dynamical relationships that exist between the variables producing a psychiatric phenomenon. Then, we describe the expected temporal trajectory of the variables, by including different relevant psychiatric aspects into the equations to obtain the desired phenomenological characteristics.

The psychiatrist is designed in a contingent way to exemplify the phenotype of psychiatric disorders. The parameters are identified in order that the simulation dynamics correspond to clinical observations. The modeling of psychiatric disorders could have been carried out in other ways. Our primary goal is to computationally match clinical observations. Thus, we voluntarily do not start from DSM, nor from empirical patient trajectories, to determine the equations of the model (20). As its name indicates, a toy-model is deliberately used to explain and make practical a behavioral function (like a box containing balls, which is considered as a toy-model allowing to understand, in a simplified way, both the solar system and the interactions between atoms).

As schematized in Fig. 1, the set of elements which should be integrated into the model, in order to account for the observed evolution of the psychiatric disorders modeled, should be: 1) a first variable x , which corresponds to the intensity (or "rate", or "apparent level") of symptoms; 2) a second variable y , which aggregates the intrinsic elements of a patient interacting with the

intensity of symptoms, i.e., referring to his/her "subjective state", or "phenomenological state". This variable is thus called a "potentiation variable", because it potentializes the intensity of symptoms; 3) and a third variable z , which correspond the external environment as it is perceived, i.e., filtered by the patient. We seek to model the interactions between variables x, y, z (see Results for details of the effects of these interactions). In addition to these variables, we add a variable f , corresponding to the slow temporal fluctuations. This variable depends on y because the onset of symptoms depends primarily on the "subjective state" of the patient, i.e., its potentiation. In other words, there can be temporal fluctuations only if the patient describes subjective states, which are themselves at the origin of a potentiation of the symptomatology. In this computational model, we hypothesize that a slow accumulation in f allow a (slow) transition towards the pathological state.

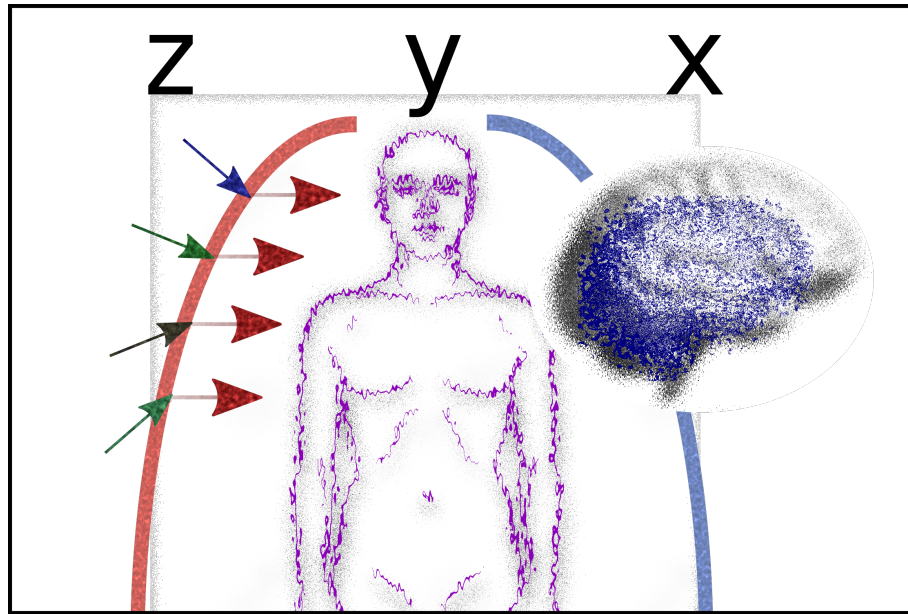


Figure 1: Toy-model representing computational dynamic model of psychiatric disorders. Observable variables from psychiatric disorders are represented into numerical variables. The variable x represents a symptomatic rate, the variable y represents the aggregation of intrinsic elements representing the patient subjectivity, and the variable z represents the effect of the external environment as perceived by the patient. Concrete and non-measurable or non-quantifiable elements are "included" in these abstract variables (i.e., their precise identification does not change the model and its dynamic).

The computational toy-model is thus described by the following equations:

$$\tau_x \frac{dx}{dt} = \frac{S_{max}}{1 + \exp(\frac{R_s - y}{\lambda_s})} - x \quad (1)$$

$$\tau_y \frac{dy}{dt} = \frac{P}{1 + \exp(\frac{R_b - y}{\lambda_b})} + L - xy + z \quad (2)$$

$$\tau_z \frac{dz}{dt} = S(\alpha x + \beta y)\zeta(t) - z \quad (3)$$

The first equation 1 can be understood as: "The intensity of symptoms increases due to subjective state y of the patient, and saturate to a maximal value S_{max} " (i.e., referring to a model with sigmoidal function) If nothing participate to maintain high intensity of symptoms, the intensity of symptoms decreases over time (modeled with the exponential decay $-x$). The evolution of the intensity of symptoms occurs with the time scale of τ_x . The R_s parameter corresponds to a more difficult triggering of the system, the sensitivity is less in terms of potentiation (i.e. if R_s is high, the appearance of symptoms occurs only for a very high value of the variable y). It can be seen as a form of sensitivity or propensity to develop symptoms depending on its internal state. The Λ_S parameter corresponds to the increase in the intensity of symptoms x as a function of the subjective state of the patient y (or potentiation), which is therefore almost linear in the middle of the curve (Λ_S is the slope of the symptom curve, where the sigmoid is centered).

The second equation 2 refers to the intrinsic elements specific to the patient, referring to the subjective state of the patient. The variable y (subjective state, or potentiation variable), evolves on the time scale τ_y , and depends on the elements described below. The first term ($\frac{P}{1 + \exp(\frac{R_b - y}{\lambda_b})}$) may be seen as the effect of the aggregate of subjective underlying elements which have a dynamical effect depending on the state of the patient. Fixed level of potentiation P corresponds to the subjective level of a patient allowing the existence of symptoms (in terms of the Cambridge model, it could be seen as the "primordial soup", i.e., the making of the semantic configuration from a set of biological signals) (21). In other words, P , refers to the influence of the initial context on the expression of symptoms through the variable y . The R_b and Λ_b parameter are interpreted as for the intensity of symptoms but in terms of potentiation. The parameter L corresponds to the level of predisposing factors that contribute as a permanent shift in the potentiation. This parameter

gives the baseline level of sensitivity of the disorder. It corresponds to the basic level towards which the system tends when the intensity of symptoms diminished. The decay in time of this state potentiation being faster soon after paroxysmal symptomatic period, the decay is model by $(-xy)$. Finally, the variable y is influenced by the perceived environment through z .

Indeed, the third equation refers to the external world perceived by a patient, modeled by the variable z (equation 4). It depends on the global sensitivity level S , and the joint effects of symptoms x and potentiation y respectively pondered by factor α and β . The factors α and β maybe positive or negative depending on the type of psychiatric disease considered. The external activity entered the equation as external noise $\zeta(t)$, set between -1 and 1 with Gaussian distribution. The release occurs with an exponential decay $(-z)$ and z evolve with a time constant τ_z .

A fourth equation can be added to modeled slower processes of psychiatric disorders. This equation is equivalent to a change of a parameter over time to capture elements on a much longer timescale, especially at the scale of a lifetime:

$$\tau_f \frac{df}{dt} = y - \lambda_f f \quad (4)$$

This equation could be adapted considering that the fluctuations are interpreted as protective or risk factors (depending on the value of parameters λ_f). These fluctuations can create slow evolution or oscillations of other variables, over the long term. This is a variable of slowness, which interacts at a longer time with the other three variables evolving more rapidly. The variable depends on the internal potentiation y , and affect the latter as a multiplicative factor of L . Thus the differential equation of y become:

$$\tau_y \frac{dy}{dt} = \frac{P}{1 + \exp(\frac{R_b - y}{\lambda_b})} + fL - xy + z \quad (5)$$

Due to the structure of these equations, we have to consider a set of six constraints. First, we are looking for a system to represent several states, in order to account for the phase transitions: 1) of the psychiatric state below a first threshold delimiting a state of health and a state of entry into the disorder; 2) of the psychiatric state above the threshold of psychiatric disorder; 3) of the psychiatric state corresponding to the maximum intensity of symptoms, i.e., the most intense state of crisis describable for a disorder. Secondly, configurations containing negative x (the intensity

of symptoms) and y (the "subjective state" of the patient, a variable of potentiation) are not considered, as they are not (patho)physiologically plausible. Thirdly, the rate of the noise $\zeta(t)$ is chosen at 0.01, meaning that the perceived environment variable z changes every 0.01 days (noise will be generated every 14.4 minutes). It is a compromise between the duration of variability of the symptoms of psychiatric disorders and their environment (i.e., considering a state change every 14.4 minutes).

Fourthly, the S_{max} parameter is fixed on a Likert scale (steps from 0 to 10). In the simulations, we saturate the scale to 10, to challenge the system to design maximum symptom intensity. Conversely, the other parameters cannot be quantified or bounded, because they depend on each patient specifically.

Finally, we propose a model with 3+1 differential equations, composed of 13 parameters. The simulations presented here use an Euler integration method with $dt = 0.01$.

In the following section, we will perform four simulations of this model to verify that they correspond to stereotypical dynamics of psychiatric conditions: a healthy condition, a schizophrenia spectrum disorder, a rapidly cycling bipolar disorder, and a persistent complex bereavement disorder. From the observed dynamics of simulations of these four different stereotyped formulations of psychiatric conditions, and based on this set of equations, we will propose to identify contingent relative threshold values (maximum and minimum) for each of the 13 parameters of the model. These values will be identified empirically in order to be consistent with clinical observations. We will add for each of these simulations an external event that acts as an environmental trigger, not related to the patient. Finally, in addition to these four simulations, we will propose a fifth simulation in which we visualize the effect of a therapy according to knowledge and stereotyped clinical observations.

3 Results

The modeling of psychiatric disorders through a toy-model built on 3+1 differential equations could be used on stereotypical psychiatric disorders and conditions, named here case formulations. Depending on the variability of the parameters handled in this toy-model, various dynamics of different psychiatric disorder could be modeled. Each of these conditions tends to be as stereotyped

as possible relative to empirical observations of clinical practice, but each could be dynamically different (these are therefore contingent results). Thus, in each of the following case formulations, based on observation of stereotypical cases, we can identify that each dynamic could be observed when the value of a parameter increases or decreases.

3.1 Identification of contingent and relative parameter values for the simulations

Constrained by clinical observations, simulations of four psychiatric conditions (2.a, 2.b, 2.c, 2.d) provide us contingent and relative parameter values, which correspond to the maximum and minimum thresholds found empirically in order to obtain variable behavior in the simulations which are consistent with the clinical observation (Table 1). For all simulations $\lambda_f = 1$ and $\tau_f = 720$.

	S_{max}	R_s	λ_s	τ_x	P	R_b	λ_b	L	τ_y	S	α	β	τ_z
Fig.2 a.	10	1	0.1	14	10	1.04	0.05	0.2	14	4	0.5	0.5	1
Fig.2 b.	10	1	0.1	14	10	0.904	0.05	0.2	14	4	0.5	0.5	1
Fig.2 c.	10	1	0.1	14	10	1.04	0.05	1.01	14	10	0.5	0.5	1
Fig.2 d.	10	1	0.1	14	10	1	0.05	0.6	14	4.5	0.5	0.5	1

Table 1: **Parameters:** Values of parameters for the different patterns shown in the figures

3.2 Dynamics of psychiatric disorders: simulation results

3.2.1 Healthy situation

In this case formulation, described in the panel (a) of the **Figure 2**, the patient modeled through the toy-model is in one possible healthy state. The corresponding parameters are given in Table 1, which thus provide the basic relative and contingent threshold values from which other psychiatric conditions will evolve.

At a random time of 5,500 days (about 15 years), a potentially destabilizing life event occurs. It could be, for instance, the death of a loved one. However, given the healthy characteristics of the modeled patient, this event causes at most a normal grief, with a brief resolution of the symptoms. After the effect of the perturbation, all variables come back to their (healthy) initial level.

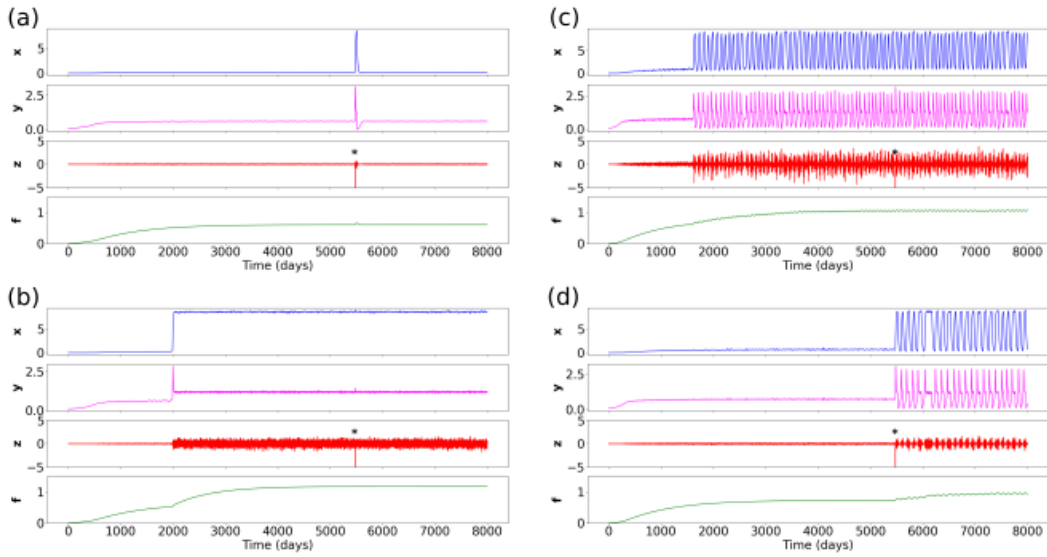


Figure 2: Simulation for different set of parameter, with a negative event from the environment (variable z) label with an asterisk. (a) Healthy situation, the negative event create transient symptoms, potentiation and sensibility to environment, and then come back to the basal healthy level. (b) Constant symptoms pathology (e.g., schizophrenia spectrum), the symptoms appear at some point in the life time as the potentiation has increase due to the slow evolution of the accumulating variable f , together with predisposition (reflect by in set of parameters), the pathology is strongly express when the negative event occurs which weakly affect the other variables. (c) Oscillating symptoms pathology (rapid cycles in bipolar disorder), the symptoms appear at some point in the life time as the potentiation has increase due to the slow evolution of the accumulating variable f , together with predisposition (reflect by in set of parameters), the pathology is strongly express when the negative event occurs which weakly affect the other variables. (d) Oscillating symptoms pathology (persistent complex bereavement disorder) is triggered by the negative event and remains present despite the disappearance of this event.

3.2.2 Schizophrenia spectrum

In this case formulation, described in the panel (b) of the **Figure 2**, the psychiatric patient would be diagnosed with a schizophrenia spectrum. This psychiatric disorder could be found, for instance:

Based on clinical constraints, we can identify that this dynamic could be observed when the R_b decreases (i.e. less resistant to potentiation and thus to develop symptoms)

At the random time of 5,500 days, in the absence of any intervention, a potentially destabilizing life event occurs. After this event, the symptoms persist. Moreover, there is no longer any reactivity to environmental stimuli.

3.2.3 Rapid cycles in bipolar disorder

In this case formulation, described in the panel (c) of the **Figure 2**, the psychiatric patient would be diagnosed with a rapidly cycling bipolar disorder. Here, the R_b (i.e., resistance) is different from the formulation box (b), but identical to (a). However, the P (i.e., base level of potentiation) is much higher in this formulation box. It is this difference that leads to the occurrence of rapid cycles. Moreover, the S (global amplitude with which one perceives his environment) is very high, the individual perceives his environment in a very important way.

Each complete cycle lasts approximately 100 days, with a symptom plateau lasting approximately 15 days, similar to what can be found in clinical practice. Finally, we retrieve that despite the presence of an intense life event, there is no change in the patient's sensitivity to his environment or in the intensity of the symptoms.

3.2.4 Persistent Complex Bereavement Disorder

In this case formulation, described in the panel (d) of the **Figure 2**, the psychiatric patient would be diagnosed with a Persistent Complex Bereavement Disorder (PCBD).

In the PCBD, it is precisely the onset of an intense life event that causes this disorder. However, unlike the situation (a) in which the rate of symptoms and sensitivity to the environment returns to normal after a certain time, the patient modeled in this case continues to have fluctuations in mood.

This case formulation is thus close to the healthy situation, except for the P which is slightly higher, with a slightly lower resistance R_b : this slight shift leads to the non-return to the healthy state of this formulation box.

3.2.5 Action of psychiatric therapeutics on different psychiatric disorders

In the **Figure 3**, (a), (b) correspond to the panel (b) of the **Figure 2**, aka to the schizophrenia spectrum. In the panel (a) (**Figure 3**), the given treatment is relatively good, but its effect is transient, after oscillation. This is the stereotypical case of antipsychotic treatments in schizophrenia, which take effect after several weeks and require adjustments related to early relapses.

In the panel (b) (**Figure 3**), the treatment does not work well, as can be seen in schizophrenia.

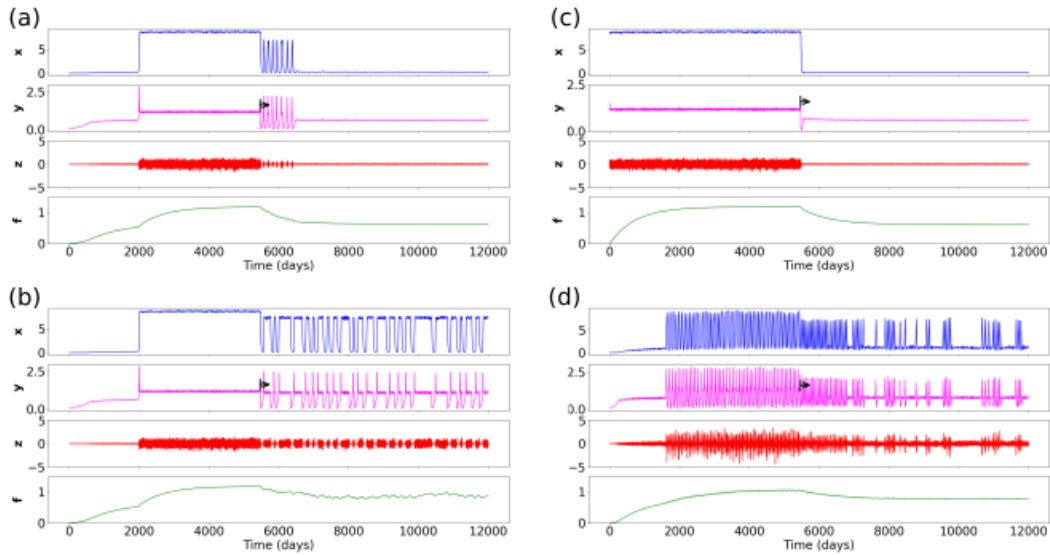


Figure 3: Action of psychiatric therapeutics on different psychiatric disorders. The black arrow corresponds to the beginning of the treatment. (a) and (b) Schizophrenia spectrum, subjected to effective treatment (a), or subjected to insufficient treatment (b). (c) Childhood-onset disorder (e.g., neurodevelopmental) treated with a rapidly acting drug (e.g., methylphenidate) or other therapy. (d) Rapid cycling bipolar disorder, with ineffective treatment but changes in the frequency, regularity and intensity of cycles.

In the panel (c) (**Figure 3**), the symptom diminution is immediate (on/off). Note that we have defined a dynamic for this case formulation for which the symptomatology appears from birth, as is the case with neurodevelopmental disorders. It could then be a treatment with methylphenidate, classically given in attention deficit disorders with or without hyperactivity and having a good and rapid efficacy.

In the (**Figure 3**), panel (d) corresponds to panel (c) in Figure 2, i.e., rapid cycling bipolar disorder. We then find increasingly rare cycles over the years, with more frequent healthy states. Note that the treatment is ineffective, but it still changes the frequency, regularity and intensity of cycles.

4 Discussion

In this work, we proposed a toy-model, the "psychiator", that can phenomenologically reproduce the time evolution of the intensity of psychiatric symptoms, interacting with the internal individual

state and his/her perceived external inputs, while considering different time scale. This computational model enables to understand the effects of non-linear relations between different psychiatric disorders' determinants. It has a set of limitations and strengths that we will detail.

4.1 Main interests

We retrieve at least five main interests of such a computational toy-model.

First, as we have seen in this study by varying the values of the parameters, such a model allows visualization of simulations of different psychiatric disorders. Such visualizations allow to find potentially new endpoints for clinical and research purposes, which in themselves enables a new model to be refined. This model allows to show that the interactions between three relatively simplified variables lead to behaviors that are very difficult to intuitively interpret. This complexity thus demonstrates the need to consider non-linear relationships rather than single variable-phenotype relationships at the clinical level. For instance, for psychotherapy, such non-linear formalization of the patient behaviors could help case formulations. It can also constitute a didactic and pedagogical tool to help the patients to understand the (non-linear) factors at the origin of their distress (22; 23).

Secondly, this model provides a high flexibility, allowing a large number of concepts to be discussed and made practical. Indeed, its interest lies in the possibility of using a large number of different data, with different actions on the parameters, in order to observe in particular the inter- and intra-individual differences of psychiatric disorders. For instance, the model is sufficiently generic to be interpreted for different type of symptoms. Moreover, the versatility of this model (i.e., the fact that the model can be adapted to many different psychiatric disorders and conditions) allows to compare the differential evolutions of these disorders. This comparison could help to specify their phenotypes and refine their precision. Psychiatry is struggling with the issues of differential diagnoses (i.e., distinguishing two disorders whose symptoms overlap) and with the issues of comorbidity (i.e., assessing whether to designate two distinct disorders or if a single disorder has characteristics of another disorder). In recent decades, no diagnostic biomarker, neither predictive nor endotype have been identified to clearly define the boundaries of psychiatric disorders: in this way, hopes lies in the differential evolution of psychiatric disorders themselves, potentially evaluable with such a computational model. Thus, the very large number of possible

combinations refers to the infinite number of phenotypic variations in psychiatry. In other words, such a model provides access to the variability of psychiatric phenotypes for the same disorder. Indeed, we consider a practical model which includes variations between its limit cycles and its fixed points, with an influence of the noise varying the characteristics of the system, and potentially several bifurcations.

Thirdly, on the therapeutic level, such a toy-model provides information on the attracting states (i.e., the states to which the system gravitates). This result allows to understand what stabilizes the patient in a given (healthy) state. The warning signals leading to this attracting state can thus be detected upstream (24). However, contrary the naïve affirmation of many theoretical papers in the scientific literature, the level of complexity considered in our 4-dimensional model impedes us to provide a metaphor that simplistically represents psychiatric disorders –like a "bullet in the valley", i.e., the attraction of a state towards a minimum, at the "bottom of the valley" (25).

Fourthly, this model proposes a dynamically theoretical framework allowing to constitute longitudinal studies and the use of assessment tools in daily life. Indeed, the absence of large cohorts of longitudinal data in psychiatry is due to numerous economic or organizational factors. However, they also relate to a lack of methodological tools. This model provides a flexible framework allowing to accommodate a large number of heterogeneous data, distinguishing between factors depending on the patient, her/his subjective experience and the environment. In other words, such a framework constitutes a prerequisite for the collection of longitudinal data in psychiatry (e.g., neurodevelopmental data). Such methods may be integrated into moment-to-moment ecological macro- or micro-level assessment (depending on the period), and especially a widely used methods such as ecological momentary assessment or joint modeling of time-to- event outcome with time-dependent predictors (i.e., considering the time-to-event nature of predicting the onset of disorder) (15). In return, data offered by such techniques would allow to confirm and validate this model in terms of predictivity. Based on repeated evaluations (in ecological daily life), such individual predictions allow a patient to be informed of her/his level of risk and of the (natural or under treatment) course of her/his psychiatric disorder.

Fifthly, such a model could refine at least two kinds of nosological psychiatric models: staging models (15) and symptom network models of psychopathology (26). Concerning staging models, one of the criticisms of these proposals is that stable and static clinical pictures at any given time

could not be predicted on the basis of a sampling of cross-sectional data (15). While it is true that a visualization of cross-sectional data at a single point in time cannot provide predictions about the future emergence of a particular psychiatric disorder, having multiple sets of cross-sectional data allows this kind of inference, as is done in the studies using ecological momentary assessment (27; 28). Thus, a set of snapshots of clinical states can be integrated in our model to provide information on the dynamic course of psychiatric disorders, in a non-linear manner. Symptoms networks could also be modeled based on our computational dynamical model. More precisely, interactions between heterogeneous variables (objective, subjective or environmental) can be considered in such a model, and their evolution can thus be explained (in the manner of temporal networks, e.g., multi-level vector autoregression model on time-series data) (29). More precisely, at a theoretical level, in symptom network models, a psychiatric disorder is defined as the steady frozen state of a strongly connected network. A dynamic component could be added to this definition, especially by providing a notion of threshold corresponding to a bifurcation of the model. Finally, given that there are neither clinical data nor biophysical elements implemented in this model, on the nosological level, such a ubiquitous toy-model, in future works, would allow to propose new classifications of psychiatric disorders according to their dynamics. Indeed, we would find some disorders particularly sensitive to the environment (e.g., OCD), others presenting a rapid rhythmic activity (e.g., rapid cycles in bipolarity), and others with abrupt bifurcations in their trajectory.

4.2 Limitations

This toy-model also has several limitations.

First, the explanatory scope of this model remains limited. There could have been an infinity of models, impeding this model from being considered as predictive. The absolute values of parameters are not representative of any physically measurable elements. Comparable dynamics could be found with completely different set of parameters, or even with different ordinary equations. The interest of this toy-formulation refers to that qualitative interpretations of parts of the equation for psychiatry. To be predictive for a given patient, the model should incorporate her/his specific collected longitudinal values. Unlike digital twins (i.e., data-driven mathematical models of patients that allow for more precise and effective medical interventions) (Bruynseels et

al., 2018), this toy-model is not built to be personalized. For instance, it cannot be excluded that the values of some random patients can induce, for instance, limit cycles or oscillations, potentially difficult to interpret in clinical practice. However, the objective of this study is not to select the best model (in terms of structuration of the equations), but to propose a systematic formulation of an observed phenotypic behavior, based on the clinically relevant variables and parameters.

Secondly, this model is reductionist regarding clinical practice. However, it integrates in an original way non-linear relations between qualitatively and clinically interpretable equations. Indeed, we have proposed a phenomenological model, in which it is not the mechanistic structures that are important, but the behavior of the whole system (30).

Thirdly, it turns out that this model should be tested with experimental data to ensure its discriminative, construct and/or predictive validity. We hypothesize that research in psychiatry waited for such a robust model to collect empirical data, and that no robust model could be built for lack of empirical data. The absence of measurements of such values is largely due to the absence of a model as we propose it. We are thus seeking to break this vicious circle with such a phenomenological model. Indeed, after empirical validation, the structure of this computational model could serve as a basis for simulating behavior and predicting the course of disorders (in certain contexts and depending on the subjectivity parameters of the subjects), with the possibility of an optimization. In order to choose whether certain other methods could allow to model psychiatric disorders in the same way, a set of models similar to this one should be constructed, with a sorting of these models by an analysis of the choice of the best model (in terms of choice of the free parameters). Future studies will aim to identify the values of the (13) parameters described in the Table 1.

Fourthly, to actually model different psychiatric diagnoses, it could be necessary to refine the model which would have different symptom regimes, or symptoms of a different nature. Indeed, in this model, only the symptom rate is discussed, but not the nature of symptoms forming the dynamics (e.g., it is not possible to distinguish the effect of delirium versus acoustico-verbal hallucinations in schizophrenia). Note that in the simulations, the representation of x corresponds to the intensity of the symptoms, and that the model corresponds to an abstract representation of psychiatric disorders: the fluctuations do not allow to affirm whether these are depressive or maniac episodes. However, this computational model aims to model the characteristics of specific

individuals (e.g., “an individual with an autism spectrum disorder”), and not a psychiatric category (e.g., “autism spectrum disorders”). Thus, even if psychiatric disorders should necessarily be characterized as a various set of different systems, this approach remains idiographic: for some individuals, the dynamic model will evolve towards a characteristic psychotic break, and for others, it will evolve towards a return to the previous state, according to the individual characteristics of the different variables.

Fifthly, a last limit concerns the difficulty to interpret the dynamics of the models. Indeed, the variables incorporated account for non-linear phenomena which are not intuitively explainable to a clinician. More precisely, it could be difficult to know why some stressors and triggers evolve in the system (e.g., inducing a dissociation), why certain nonlinear effects occur at particular times (e.g., fluctuations of affective states), how interactions between certain symptoms occur (e.g., low mood and overeating or anorexia) or what the way self-reinforcing cascades take place (e.g., rapid-cycling mood episodes). Clinical inference from this kind of model (predictive or not) should be very careful. By extension, it will be necessary to ensure that these individual-level models are not naively transferred to group-level models.

5 Conclusion

Predicting the onset of psychiatric disorders has focused on the evaluation of a spectrum of variables ranging from genetics to the environment, including neurocognitive measurements and subjective feelings. The conditions for the emergence, maintenance and recurrence of a psychiatric disorder remain unknown, and this lack stems in large part from the lack of dynamic modeling of psychiatric conditions and disorders, despite a growing literature advancing such promises for at least several decades (31). In order to shift from this research, we propose with this “psychiator” to dynamically modelize human behaviors in a non-linear way, while maintaining clinical, phenomenological and biological plausibility useful to the clinician. Although this model is only a toy-model, it offers a conceptual basis for data acquisition, and can serve as a starting point for establishing a theoretical definition of psychiatric disorders based on dynamic systems.

6 Acknowledgments

Any.

7 Disclosure statement

We report no conflicts of interest related to this work.

8 Authors' contributions

Christophe Gauld and Damien Depannemaecker were the principal investigators and study supervisors. Christophe Gauld conceptualized and supervised the analysis. Damien Depannemaecker made the mathematical equation formalization and run the simulations. Christophe Gauld and Damien Depannemaecker interpreted the results and wrote the manuscript. The two authors approved the final version.

References

- [1] International Classification of Diseases, Eleventh Revision (ICD-11). World Health Organization (WHO); 2019. Available from: <https://icd.who.int/>.
- [2] Association AP. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; 2013. Available from: <https://doi.org/10.1176%2Fappi.books.9780890425596>.
- [3] Kendler KS. DSM disorders and their criteria: how should they inter-relate?;47(12):2054-60.
- [4] Hyman SE. The Diagnosis of Mental Disorders: The Problem of Reification;6(1):155-79. eprint: <https://doi.org/10.1146/annurev.clinpsy.3.022806.091532>. Available from: <https://doi.org/10.1146/annurev.clinpsy.3.022806.091532>.
- [5] Krueger RF, Bezdjian S. Enhancing research and treatment of mental disorders with dimensional concepts: toward DSM-V and ICD-11. *World Psychiatry*. 2009 Feb;8(1):3-6.
- [6] Kendler KS. The nature of psychiatric disorders. *World Psychiatry*. 2016 Feb;15(1):5-12. Available from: <https://doi.org/10.1002/wps.20292>.
- [7] Haslam N, Ernst D. Essentialist Beliefs About Mental Disorders;21:628-44.
- [8] Zachar P. Psychiatric Disorders Are Not Natural Kinds. *Philosophy, Psychiatry, Psychology*. 2000 September;7(3).
- [9] Demic S, Cheng S. Modeling the Dynamics of Disease States in Depression. *PLoS ONE*. 2014 oct;9(10):e110358. Available from: <https://doi.org/10.1371%2Fjournal.pone.0110358>.
- [10] Kelso S. In: *Dynamic Patterns: The Self-Organization of Brain and Behavior*; 1995. .
- [11] Nelson B, McGorry PD, Wichers M, Wigman JTW, Hartmann JA. Moving From Static to Dynamic Models of the Onset of Mental Disorder: A Review;74(5):528-34. Available from: <https://doi.org/10.1001/jamapsychiatry.2017.0001>.
- [12] Wright CD, Tian AG, Billingsley AL, Steinman SA, Larkin KT, McNeil DW. A Framework for Understanding the Role of Psychological Processes in Disease Development, Maintenance,

- and Treatment: The 3P-Disease Model;10. Available from: <https://www.frontiersin.org/article/10.3389/fpsyg.2019.02498>.
- [13] Spielman A. Assessment of insomnia. *Clinical Psychology Review*. 1986;6(1):11-25. Available from: <https://doi.org/10.1016%2F0272-7358%2886%2990015-2>.
- [14] Adamec RE. Does kindling model anything clinically relevant? *Biological Psychiatry*. 1990 feb;27(3):249-79. Available from: <https://doi.org/10.1016%2F0006-3223%2890%2990001-i>.
- [15] McGorry P, Keshavan M, Goldstone S, Amminger P, Allott K, Berk M, et al. Biomarkers and clinical staging in psychiatry. *World Psychiatry*. 2014 oct;13(3):211-23. Available from: <https://doi.org/10.1002%2Fwps.20144>.
- [16] de la Fuente-Tomás L, Sierra P, Sanchez-Autet M, Arranz B, García-Blanco A, Safont G, et al. A clinical staging model for bipolar disorder: longitudinal approach. *Translational Psychiatry*. 2020 jan;10(1). Available from: <https://doi.org/10.1038%2Fs41398-020-0718-9>.
- [17] Eells TD, Kendjelic EM, Lucas CP. What's in a case formulation? Development and use of a content coding manual. *J Psychother Pract Res*. 1998;7(2):144-53.
- [18] Depannemaecker D, Destexhe A, Jirsa V, Bernard C. Modeling seizures: From single neurons to networks. *Seizure*. 2021 aug;90:4-8. Available from: <https://doi.org/10.1016%2Fj.seizure.2021.06.015>.
- [19] Jirsa VK, Stacey WC, Quilichini PP, Ivanov AI, Bernard C. On the nature of seizure dynamics. *Brain : a journal of neurology*. 2014 8;137(Pt 8):2210-30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24919973><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4107736>.
- [20] Hilborn R, Mangel M. *The Ecological Detective*; 1997.
- [21] Berrios GE, Chen EYH. Recognising Psychiatric Symptoms. *British Journal of Psychiatry*. 1993 sep;163(3):308-14. Available from: <https://doi.org/10.1192%2Fbjp.163.3.308>.

- [22] Fried EI, Robinaugh DJ. Systems all the way down: embracing complexity in mental health research. *BMC Medicine*. 2020 jul;18(1). Available from: <https://doi.org/10.1186%2Fs12916-020-01668-w>.
- [23] Burger J, van der Veen DC, Robinaugh DJ, Quax R, Riese H, Schoevers RA, et al. Bridging the gap between complexity science and clinical practice by formalizing idiographic theories: a computational model of functional analysis. *BMC Medicine*. 2020 apr;18(1). Available from: <https://doi.org/10.1186%2Fs12916-020-01558-1>.
- [24] Hayes AM, Andrews LA. A complex systems approach to the study of change in psychotherapy. *BMC Medicine*. 2020 jul;18(1). Available from: <https://doi.org/10.1186%2Fs12916-020-01662-2>.
- [25] Nelson B, McGorry PD, Wichers M, Wigman JTW, Hartmann JA. Moving From Static to Dynamic Models of the Onset of Mental Disorder. *JAMA Psychiatry*. 2017 may;74(5):528. Available from: <https://doi.org/10.1001%2Fjamapsychiatry.2017.0001>.
- [26] Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017 jan;16(1):5-13. Available from: <https://doi.org/10.1002%2Fwps.20375>.
- [27] van Os J. The Dynamics of Subthreshold Psychopathology: Implications for Diagnosis and Treatment. *American Journal of Psychiatry*. 2013 jul;170(7):695-8. Available from: <https://doi.org/10.1176%2Fappi.ajp.2013.13040474>.
- [28] McGorry P, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity. *The Lancet*. 2013 jan;381(9863):343-5. Available from: <https://doi.org/10.1016%2Fs0140-6736%2812%2961268-9>.
- [29] Haslbeck JMB, Bringmann LF, Waldorp LJ. A Tutorial on Estimating Time-Varying Vector Autoregressive Models. *Multivariate Behavioral Research*. 2021;56(1):120-49. PMID: 32324066. Available from: <https://doi.org/10.1080/00273171.2020.1743630>.
- [30] Marr D. *Vision*; 2010.
- [31] Nelson B, McGorry PD, Fernandez AV. Integrating clinical staging and phenomenological psychopathology to add depth, nuance, and utility to clinical phenotyping: a heuristic chal-

lenge. The Lancet Psychiatry. 2021 feb;8(2):162-8. Available from: <https://doi.org/10.1016%2Fs2215-0366%2820%2930316-3>.