CentraleSupélec
Université Paris-Saclay

Projet de 3A
Rapport

Dynamical Systems for Computational Psychiatry

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April 15, 2023

Contents

1 Introduction

1.1 Context

Psychiatric disorders are mental health conditions that affect a person's thoughts, emotions, and behaviors. They can range from mild to severe and can disrupt daily life activities. Examples of psychiatric disorders include major depressive disorders, anxiety disorders, schizophrenia spectrum, bipolar disorder, or eating disorders. These disorders are typically diagnosed based on symptoms, behaviors, subjective experiences, and patterns of thoughts, and are treated with a combination of therapy, medication, and lifestyle changes. Although a large number of biomarkers and endophenotypes have been identified in the research, none are currently usable in clinical practice.

A specific characteristic of psychiatric disorders is that their symptoms can fluctuate over time. These fluctuations of psychiatric symptoms refer to interactions between different aspects of a person's mental state, e.g., changes in mood, behavior, thoughts, or physiological processes. External and environmental factors also mediate these interactions.
For instance, in a person with bipolar disorder, we can observe fluctuations between manic and depressive episodes, and these episodes are influenced by stress, sleep patterns, and other environmental factors. In individuals with depression, we can observe the persistence or worsening of symptoms over time, despite treatment, and this may be related to changes in brain function and other physiological processes.

The main objective of this project is to better understand the dynamics of psychiatric disorder symptoms, an objective that could have the purpose of finding better treatments. However, there was no computational model to study these dynamics while considering symptoms, internal factors, environment, and temporality. Damien Depannemaecker, theoretical neuroscientist, and Christophe Gauld, clinical psychiatrist, proposed such a model in a recent article (Gauld and Depannemaecker 2023).

2 State of the art

2.1 Theoretical proposals

There are three main types of non-mathematical clinical theoretical proposals for diseases temporal evolution in the psychiatric literature:

The first one corresponds to the 3P model (Wright et al. 2019). The 3P model is defined as a model considering 3 factors: predisposing, precipitating and perpetuating (Spielman 1986). Predisposing factors make the system sensitive to a stimulus and depend on the prior state of the system states. Precipitating factors initiate the dynamics of psychiatric disorders under the action of a trigger (named "kindling", see below). The interaction between the first two factors (the predisposing and precipitating factors) is sometimes called a "stress-diathesis" model. Perpetuating factors keep the system burnished despite the absence of stimuli. The 3P model allows us to understand 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. It is not typically described with equations, but rather is a conceptual framework for understanding the neurobiological mechanisms underlying the development and progression of psychiatric disorders. 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. This psychiatric disorder bursts by successive acute manifestations on a relatively short time scale (Adamec 1990). When the system is above a certain threshold, the kindling formulation brings together two parameters: an increase in the frequency of cycles of bursting, and a triggering of these cycles more and more independently of environmental factors.

The third kind of clinical theoretical proposal corresponds to staging models. Staging models are defined as psychiatric models aimed at distinguishing subgroups evolving by (successive) stages (McGorry et al. 2014).

However, these three proposals remain theoretical, they have never been formalized in such a way as to have a framework independent of the person who implements it. Mathematical formalization allows us to free ourselves from this subjectivity. One of the objectives of this project is to propose such a frame. In this way, another kind of clinical theoretical proposal corresponds to the conception of psychiatric disorders through the prism of dynamical systems. This conception is the subject of this study.

2.2 Computational theoretical proposals

Current computational models found in the literature integrate biological factors. They can be predictive. They can involve different time scales. However, rare are the models that allow the common integration of all these variables. Studies are restricted to parameters such as noise from the environment (e.g., psychosocial stress) (Huber, Braun, and Krieg 2000) or monovariable approaches (Demic and Cheng 2014). Monovariable approaches have a limited dynamic and cannot account for complex effects, as the system's behavior at a given time only depends on the current state and does not depend on previous states. Moreover, current computational psychiatry models also rarely integrate symptoms.

Complex dynamical systems theories have been used to metaphorically explore psychiatric disorders (e.g., depression which can be understood as a metaphorical "stuck state" of emotional processing) (Sulis 2021); (Boldrini, Placidi, and Marazziti 1998); (Bystritsky et al. 2012); (King et al. 1983). However, this metaphor has largely remained highly theoretical and has only marginally resulted in a manipulable model based on the dynamical system (Durstewitz, Huys, and Koppe 2021).

2.3 Model of Depannemeacker & Gauld

Damien Depannemaecker and Christophe Gauld proposed such a model in a recent article (Gauld and Depannemaecker 2023), build on stereotypical case formulations defined in the clinical reference literature. This model is a toy model that produces an abstract rep-

resentation of patients. It is made to reproduce qualitatively the dynamics of psychiatric symptoms across time, but not to predict anything so far, as no comparison with real data was made. As it is not built on empirical data, it could only serve to apprehend, understand, or support debates on the possible dynamics of psychiatric disorders. It also provides a framework for moving away from the "standard" classification of pathology.

2.3.1 Equations

The dynamic of the model is governed by a set of differential equations between 4 variables.

- **x** accounts for the apparent intensity of symptoms
- **y** correspond to patients'"subjective state", or "phenomenological state", but also to biological elements (e.g., genetic data or brain morphological data). It is thus called a "potentiation variable" because it potentializes the intensity of symptoms
- **z** correspond to the external environment as it is perceived and filtered by the patient
- **f** is made to model slow temporal fluctuations. It is a more abstract variable that can be considered as a scaling parameter for the influence of predisposing factors on y (equation (2))

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

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

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

$$\tau_f \frac{df}{dt} = y - \lambda_f f \tag{4}$$

We consider that x and y must always be positive for clinical interpretation. Parameter values and descriptions are given in Table 1. The value ranges for L and Rb were chosen this way because it is around these values that the model presents a dynamic that resembles a clinically relevant case formulation. With higher or lower values it is possible that the dynamics of the variables no longer correspond to the patient dynamics seen in tonic practice. However, the model has not been tested for these extreme ranges, so to truly validate the value range, it will be necessary to map these value ranges to actual data value range.

Table 1: Description and value of the parameters

Symbol	Value or value range	Description
τ_x τ_y τ_z τ_f	14 days 14 days 1 day 720 days	Time scales of each equation
S_{max}	10	Maximal level of symptoms
R_s R_b	1 $[0.904, 1.15]$	Sensitivity: the difficulty in triggering the system. Rs refers to sensitivity in terms of symptoms. Rb refers to sensitivity in terms of internal elements (or potentiation).
λ_s λ_b	0.1 0.05	Slope of the symptom and internal elements (or potentiation) curves. λ_s corresponds to the increase in the intensity of symptoms x as a function of the subjective state of the patient y. λ_b corresponds to the increase in the internal elements (or potentiation) y as a function of the environment z.
P	10	Maximal rate of internal elements of the systems: the aggregation of biological, psychological, or subjective/phenomenological elements. It refers to the fabrication of the semantic configuration of a phenotype from a set of biological signals. It is an element of potentiation of symptoms.
L	$[0, 2.5]$	Level of predisposing factors: it contributes to a permanent shift in the internal elements (potentiation).
λ_f	1	Scaling factor of the slow evolution of the fluctuations affecting L
S	4	Overall sensitivity level to the environment
α β	0.5 0.5	Weight of the effect of the variable x and y on the perception of the environment
$\zeta(t)$	$\mathcal{N}(0,\ 1)$	gaussian noise whose value change every 14 min

2.3.2 Description

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}. If nothing participates to maintain the high intensity of symptoms, the intensity of symptoms decreases over time (modeled with the exponential decay -x).

In equation (2), the evolution of y depends on itself through P, the maximal fixed level of potentiation, and is influenced by fL, the level of predisposing factors. The decay in time of this state potentiation being faster soon after paroxysmal symptomatic period, the decay is modeled by (-xy). Finally, the variable y is influenced by the perceived environment through z.

Equation (3) refers to the influence of the environment, it depends on the overall sensitivity level S, and the joint effects of symptoms x and the potentiation y respectively pondered by factor α and β. It has been multiplied by a Gaussian noise $\zeta(t)$ to model the randomness of environmental events. The release occurs with an exponential decay (-z).

Equation (4) 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.

2.4 Reproduce case formulations

This model was built by Depannemeacker & Gauld to be able to capture specific dynamical behavior of different psychiatric conditions. They found, empirically, a set of parameters for which the system behavior can be associated with a healthy condition, a schizophrenia spectrum disorder, a rapidly cycling bipolar disorder, and a persistent complex bereavement disorder.

For all sets of parameters, the values of S_{max}, R_s, λ_s, τ_x, P λ_b, τ_y, α, β, τ_z, λ_f and τ_f are those given in Table 1. The values of R_b, L and S for each case are given in Table 2 (below)

Table 2: Values of parameters R_b, L and S for each clinical case

Clinical case	R_b	L	S
Healthy condition	1.04	0.2	4
Schizophrenia spectrum disorder	0.904	0.2	4
Rapidly cycling bipolar disorder	1.04	1.01	10
Persistent complex bereavement disorder	1	0.6	4.5

In figure 1 are the time series for each case, at a random time of 5,500 days (about 15 years, a clinically relevant scale for studying the development and dynamics of psychiatric disorders), a potentially destabilizing life event occurs. It could be, for instance, the death of a loved one. It is labeled with a black arrow marker on the z-time-series. We present in the Methods section the way those curves were computed.

- Figure 1a (Healthy situation): the negative event creates transient symptoms (x), potentiation of internal elements (y), and environmental sensitivity, and then the system returns to the baseline healthy level.

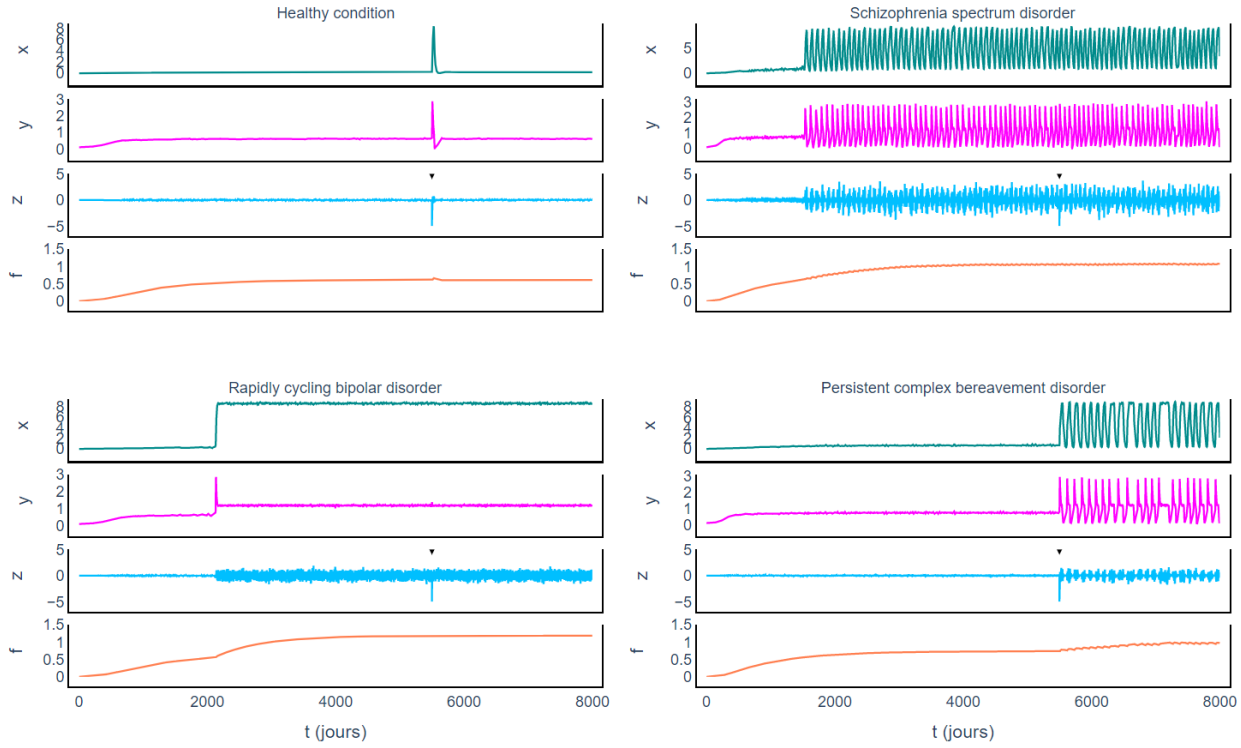


Figure 1: Times series for different sets of parameters corresponding to different cases a) (top-right) healthy condition, b) (top-left) schizophrenia spectrum disorder, c) (bottom-right) rapidly cycling bipolar disorder, d) (bottom-left) persistent complex bereavement disorder

- Figure 1b (schizophrenia spectrum): symptoms appear at some point in life when potentiation has increased due to slowly changing accumulation variable f. The pathology is strongly expressed when the negative event occurs and weakly affects the other variables.
- Figure 1c (rapid cycling in bipolar disorder): symptoms appear at some point in life when potentiation has increased due to a slow-changing accumulation variable f. The disorder is strongly expressed when a negative event occurs which weakly affects the other variables.
- Figure 1d (persistent complex grief disorder) a negative event triggers and stabilizes the oscillations despite the disappearance of this event.

This is how this model can reproduce qualitatively dynamical behaviors of some psychiatric conditions. Now, the objective of this work is to study the underlying dynamics of this model and to understand what is the influence of each parameter on these dynamics.

2.5 Objectives

Our objective is to better understand the dynamics of the model and to verify the following hypotheses :

1. The higher the level of predisposition (L) of a patient is, the higher will be the symptoms he develops.

2. If Rb (referring, in the model, to the resistance of the patient to the emergence of symptoms) is high enough, the patient will not face a high increase in symptoms during his life.

To this extent, we need to study the dynamics of x (the symptom rate) according to 2 parameters: L (the predisposition level) and Rb (the resistance of the patient to the development of symptoms). To do this, we choose to study the underlying dynamic structure rather than running multiple simulations. We will first focus on the dynamics of the 2d (x-y) subsystem, which provides the main dynamical behavior of our system, and see that f and z can be considered as perturbations of this 2d dynamics. Then we will analyze the impact of variables f and z, on the (x-y) dynamics, which will give us an overview of the dynamical behavior of the entire system and allow us to answer our hypotheses.

3 Methods

To answer our hypotheses, we chose to use the dynamical systems framework to characterize the dynamics of the model. We could have performed multiple simulations but it would have been computationally costful and less general. Here we also seek to propose an analysis that allows us to better understand the model and show what behaviors are intrinsically related to its dynamics, so doing a dynamical analysis is way more useful for us. Indeed this model was built to improve our understanding of psychiatric disorders dynamics.

In this analysis, we will only change the value of parameters L and Rb, and consider the other parameters as fixed. Therefore, our conclusion will only be valid for the chosen set of values of the other parameters. It would be difficult to study the effect of the 15 parameter values at the same time, and their value can be considered nominal for this context, allowing us to model most patient profiles with variations of L and Rb only.

3.1 Starting from the (x-y) subsystem

First, we justify why we started from the analysis of the (x-y) subsystem.

3.1.1 z can be considered as a perturbation noise

The variable z models the effect of the external environment on the patient. Its dynamics is described by equation (4), where the $S(\alpha x + \beta y)\zeta(t)$ term corresponds to a Gaussian noise of mean 0 and whose amplitude is proportional to the value of x and y. According to equation (4), the value of z thus corresponds to a low-frequencies-filtration of this Gaussian noise. Its time constant is 14 times smaller than that of x and y, so we can consider it will noise the evolution of x and y. In the following, we will study first the dynamics of the system for z set to 0, because the mean value of z is 0, and then see how it evolves if we take into account z. In figure 2 one can observe that z variations are way faster than for x and y.

3.1.2 f variations are way slower than the ones of x and y

The time scale of f is way bigger than the one of x and y ($\tau_f = 720$ days and $\tau_{x,y} = 14$ days). f was constructed as a slow variating scaling factor for the predisposing factor L. In figure 2 one can observe that f variations are way slower than for x and y. For this reason, studying the dynamics of x and y only is interesting because it will contain the short-time dynamics. Fixing the value of f will allow for a characterization of the short-time variations of the system dynamics. Indeed, we can consider that in the timescale of the variations of f, the (x-y) subsystem is always in a quasi-equilibrium. We can then study separately the dynamics of f and its effect on the 2D x-y dynamics.

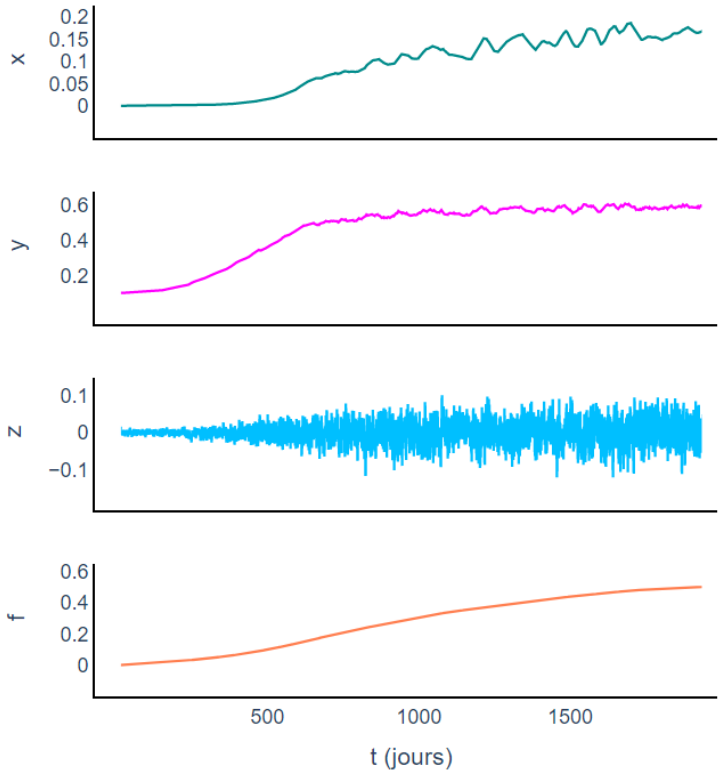


Figure 2: Example of time course for x, y, z and f

3.1.3 "f.L" factor

The L parameter corresponds to the level of predisposing factors. For a fixed L value, f evolves during the life of a patient, making the "f.L" term evolve in the $\frac{dy}{dt}$ equation (3). For this reason, studying the impact of the variations of the "f.L" term on the x-y dynamics can allow us to better understand how the global dynamics will evolve over a lifetime. To do this, we will only change the L value for a fixed value of f. We will then study the (x-y) subsystem with a fixed value of f at 1 because it allows a better correspondence between L when f is fixed and the f.L product when f is variable.

3.1.4 High and low symptoms area

In this model, low (resp. high) values of x and y correspond to low (resp. high) symptom levels and symptom development potential. In the following, we will name those areas as low and high symptoms areas.

In the following analysis, we will first focus on the dynamics of the 2D (x-y) system and consider the effect of z and f as respectively fast and slow perturbations to characterize the full dynamics.

3.2 Simulations

The equations of the model are non-linear and require to be solved numerically. I used an Euler method of time-step dt = 0.01 days, as used in Gauld and Depannemaecker 2023. This means that the perceived environment variable z changes every 0.01 days = 14.4 min. This is striking a balance between capturing useful clinical information like mood changes during the day and avoiding capturing environmental noise without clinical value like instantaneous emotions to any life event.

PyDSTool python library was used to compute the nature and the stability of the fixed points, by numerical approximations, and the bifurcation diagrams.

For all simulations and computations, we used Python 3.9.13, figures were plotted with Plotly, and I used PyDSTool 1.23.5 for specific dynamics computations.

In this section, we present the different simulations performed and the way we build the associated figures.

3.2.1 Time course

As we said above, I solved the equations with an Euler method of time-step dt = 0.01 days, and I used Plotly to print the figures. You have 4 examples of time courses in figure 1.

3.2.2 X-Y Phase plane

As seen in the previous section, we focused on the (x-y) subsystem dynamics. Therefore it is useful to visualize the (x-y) phase plane with the different dynamical objects it contains. To this extent, we developed a code using numpy, Plotly, and PyDSTool.

It is important to remember that the dynamical behavior of x and y depends on the value of the variables z and f. For that reason, this 2 dimensional (x-y) phase plane does not describe the full dynamics of the system, only that of the (x-y) subsystem. So the shape of this (x-y) phase plane also depends on the value of z and f and is always computed from a given value of z and f.

At each point, the vector field is given by equations (1) and (2). The null clines are the set of points (x,y) for which one of the derivatives is null. The x-nullcline (resp. y-nullcline) corresponds to the set of points for which $\frac{dx}{dt} = 0$ (resp. $\frac{dy}{dt} = 0$). They were found analytically :

$$\text{x-nullcline} = \left\{ (x, y) \,|\, x = \frac{S_{max}}{1 + exp(\frac{R_s - y}{\lambda_s})} \right\}$$

$$\text{y-nullcline} = \left\{ (x, y) \,|\, x = \frac{1}{y} \left(\frac{P}{1 + exp(\frac{Rb - y}{\lambda_b})} + f.L - z \right) \right\}$$

For the fixed points computation, we used PyDSTool. It gave automatically the position, the nature, and the stability of each fixed point

I also added the projection of the trajectory on the x-y plane for $t \in [0, 8000]$ days. It is important to remember that this trajectory evolves in a 4D space and does not exactly follow the vector field of the phase plane, it is just a projection of the (x-y) trajectory on a particular phase plane. Figure 3 is an example of such a figure.

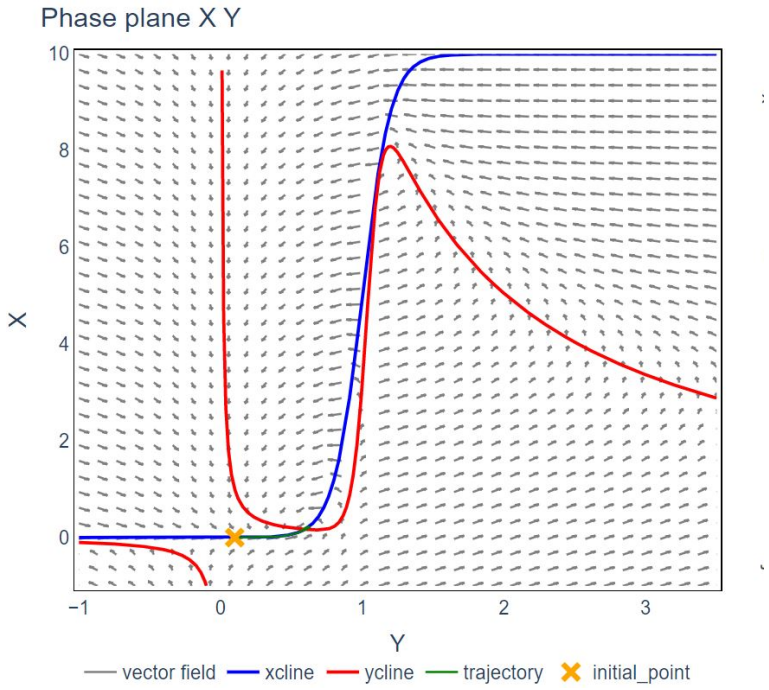


Figure 3: X-Y Phase plane for $L = 0.2$, $Rb = 1.04$, $z = 0$, $f = 0.5$, initial conditions $x = 0$, $y = 0.1$, $z = 0$, $f = 0$ and for different sets of parameters.

3.2.3 Visualisation app

To visualize both the time courses and the x-y phase diagram, I created a Python app from scratch using dash framework, showing variables time courses and the x-y phase diagram. As we said the X-Y phase plane depends on the value of z and f, so I added sliders to update the x-y phase plane according to z and f values. I also added sliders for some parameter values to easily visualize the effects of parameter changes on the system, as well as the possibility to remove noise, add a perturbation around 4,500 days, superpose the (x-y) trajectory and choose initial coordinates for the trajectory.

The code for this app is available and attached to this document. Figure 4 presents a screenshot of its interface

3.2.4 Bifurcation Diagrams

Bifurcation diagrams were computed using PyDSTool and printed using matlplotlib.

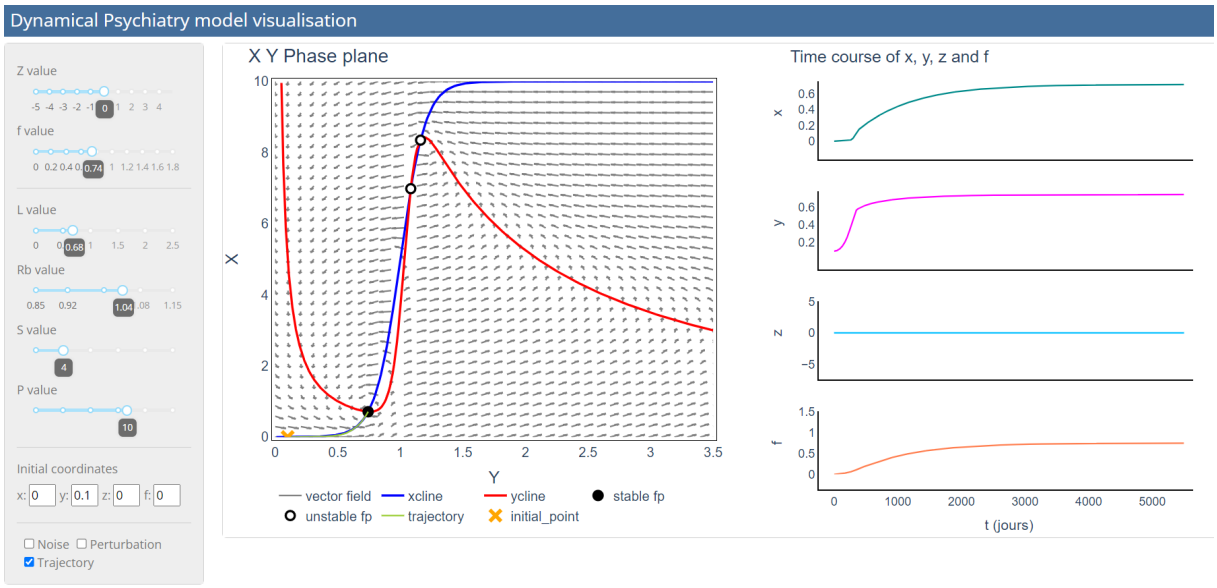


Figure 4: Screenshot of the visualization app

3.3 Presentation of the analysis

In the following section, we will first show that studying the 2 dimension (x-y) subsystem can provide us useful information about the global behavior of the system, as it contains the heart of the dynamics. Indeed, f and z can be seen as perturbations on the (x-y) subsystem.
Then, we will perform a bifurcation analysis on the (x-y) subsystem, for two parameters, L (the level of predisposition) and Rb (the sensitivity). Here we will see how these two parameters influence the dynamics of the system. From this analysis, we will see if our hypotheses are verified for the subsystem. In the following, We will then add the other variables to see if our conclusions remain true for the entire system.
We will see how the variations of f influence the system and what changes from the 2-dimensional analysis. As f is just a scaling factor for the value of L, we will see that taking into account the variations of f is equivalent to having a slowly increasing L value in the (x-y) subsystem.
Then we will study the impact of the perturbation caused by z on the (x-y) subsystem, and see that it can allow the subsystem to exit the domain of attraction of an object.
Knowing all of this, we can state our hypotheses for the entire system.

4 Results

4.1 Analysis of the (x-y) subsystem

For this analysis, we set z = 0 and f = 1. We want to study the dynamics of the 2D x-y subsystem according to the value of 2 parameters: L, Rb in order to state our hypotheses. In the entire subsection, a reference to L must be understood as $f.L$ with f fixed to 1.

4.1.1 Bifurcation analysis of L variable

We computed the bifurcation diagrams of L, for Rb set to 1.04. This value was chosen in the original article as relevant to reproduce clinical cases.
You can see the result in figure 5. The value of L in the following description is only valid for this specific value of Rb, but the general shape of this diagram remains the same for other values of Rb, as discussed in the next section. In figure 6, you can see a phase plane diagram corresponding to each described interval.

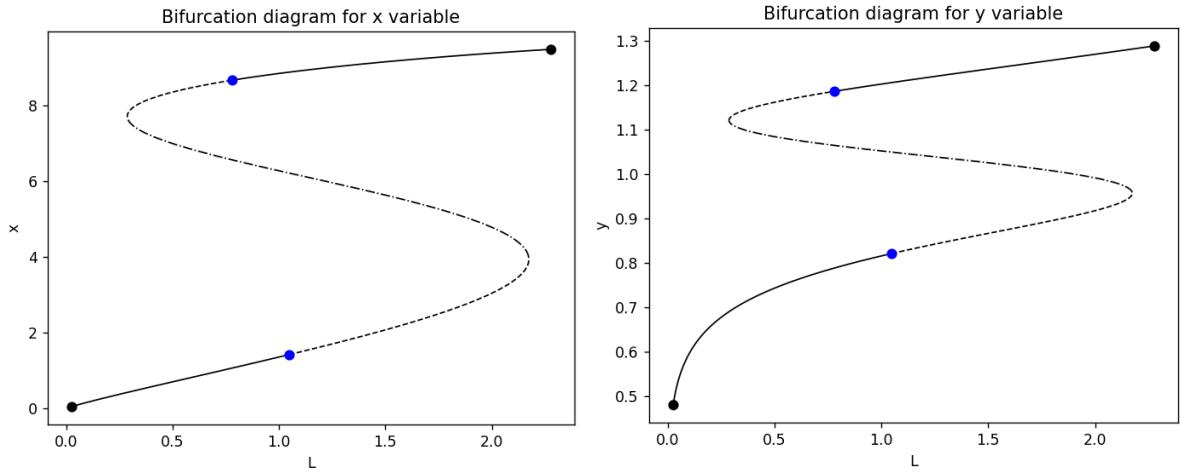


Figure 5: Bifurcation diagram for L parameter for parameter values of the table, with Rb=1.04, z=0, and f=1. Solid lines correspond to stable fixed points and dashed lines to unstable ones. Blue points correspond to Hopf bifurcations and black points to the extremities of the curve.

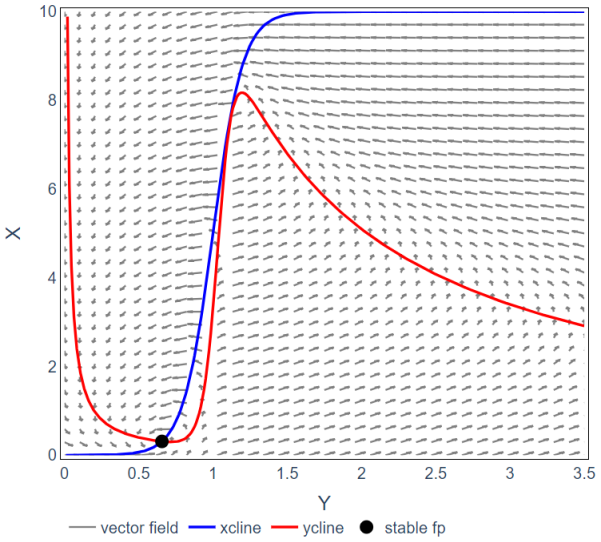
In figure 5, we can observe that there can exist 1, 2, or 3 fixed points. As a reminder, low (resp. high) values of x and y correspond to low (resp. high) symptom levels and symptom development potential. I will name those areas as low and high symptoms areas. The nature and the stability of the fixed points are given by PyDSTool.

For L<0.29, there is only one fixed point, which is a stable spiral, in the area of low symptoms and potential. This corresponds to a healthy patient profile; the system will remain in the low symptoms area.

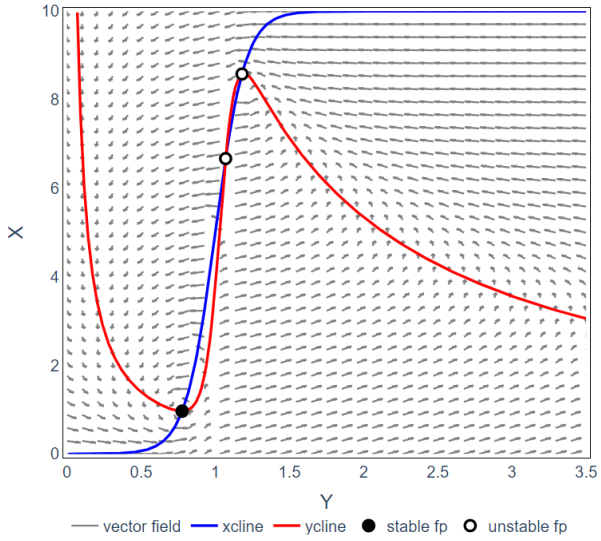
For L in [0.29, 0.78], there is the existence of 2 unstable points in the high symptoms area, a saddle, and a node, and there is still a stable spiral in the low symptom area.

At L = 0.78, a supercritical Hopf bifurcation occurs and the unstable spiral becomes a stable spiral. For L in [0.78, 1.04], one can observe two sable spirals, one in the high symptoms area and one in the low symptoms area, and an unstable saddle between the two areas. In this situation, it is possible for the patient to have a constant high level of symptoms, and to switch from one stable state to the other because of external input.

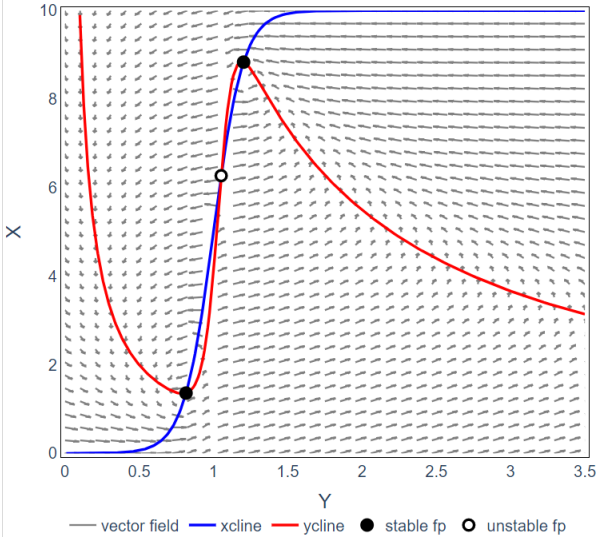
At L = 1.05, a subcritical Hopf bifurcation occurs and the low symptoms stable spiral becomes an unstable spiral. For L in [1.05, 2.17], we thus have an unstable spiral in the low symptoms area, a stable spiral in the high symptoms area, and a saddle in the intermediate area. In this situation, the patient can only be in a high symptoms state, and even an external output can not allow him to return to a stable low level of symptoms.



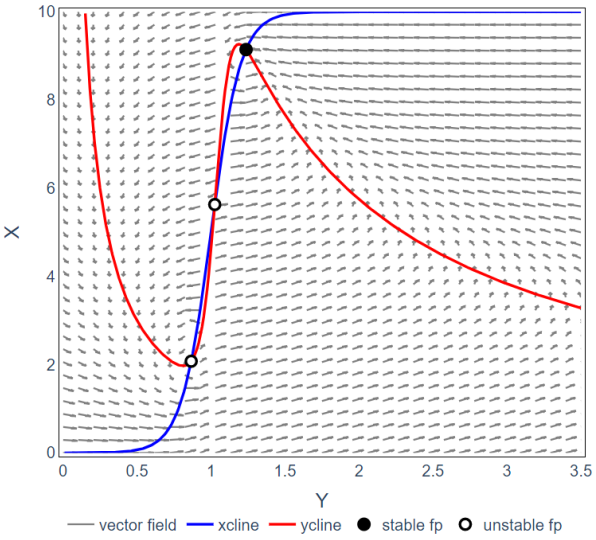
(a) $L = 0.2$



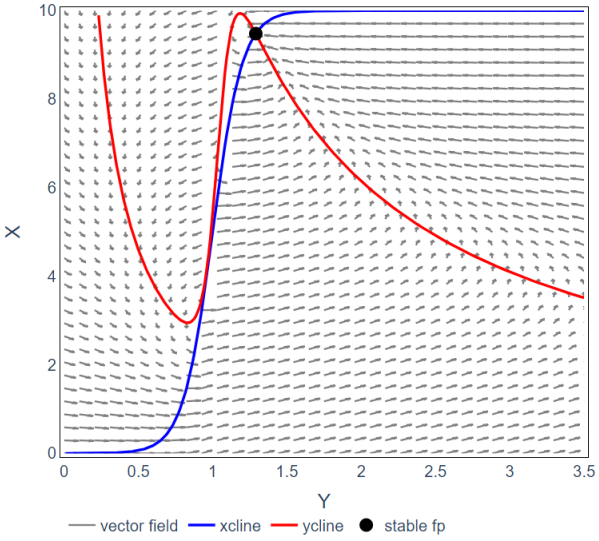
(b) $L = 0.7$



(c) $L = 1$



(d) $L = 1.5$



(e) $L = 2.3$

Figure 6: X-Y phase planes for different values of L, and z=0, f=1, Rb=1.04

For L > 2.17, there only is a stable spiral in the high symptom area. Equally, the patient can only remain in a high-symptom level state.

Globally, the more we increase L (meaning $f.L$ with f=1) and the higher the equilibrium of x and y will be, with a discontinuity at L = 1.05. This validates our first hypothesis for the (x-y) subsystem for this value of Rb. Now we want to determine if this result holds for other values of Rb.

4.1.2 Effect of Rb value on L-related bifurcations

To see the impact of the Rb value on the L bifurcation diagram, we computed this bifurcation diagram for different values of Rb. The result can be observed on figure 7.

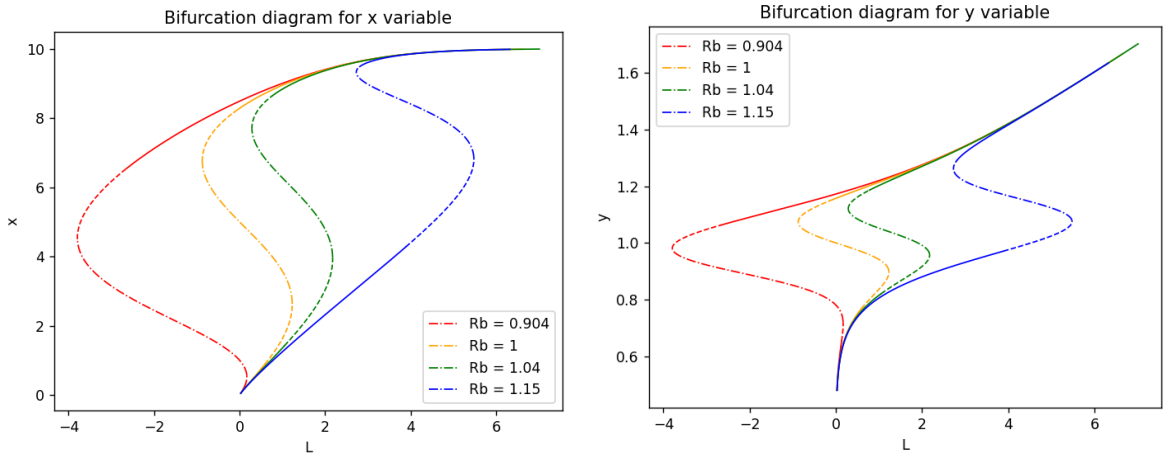


Figure 7: Bifurcation diagram for L parameter for z=0 and f=1 and different values of Rb. Solid lines correspond to stable fixed points, and dashed lines to unstable ones. The whole range of L values was shown but L is not supposed to take values outside the $[0, 2.5]$ interval

If we change the value of Rb, it will roughly result in a translation of the bifurcation diagram of L. Lower Rb values make the x-L and y-L bifurcation curves translate to the left. Globally, we observe that the higher the value of Rb is, the higher L must be for the subsystem to stabilize in a high symptoms area.

One can see that no matter the value of Rb in the chosen range, the coordinates of the stable equilibria are an increasing function of L ($f.L$ with f=1), with a discontinuity. This then validates our first hypothesis for the subsystem.

4.1.3 Bifurcation analysis of Rb variable

In figure 8, it can be observed that for small values of Rb, there is only one fixed point in the high symptoms area and that if we increase the value of Rb, the subsystem tends to stabilize to low symptom levels. It is not visible in the figure but there is no value of Rb for which no stable fixed point exists. This was for the specific value of $L = 1.01$, in the following we will see the effect of L value on this diagram.

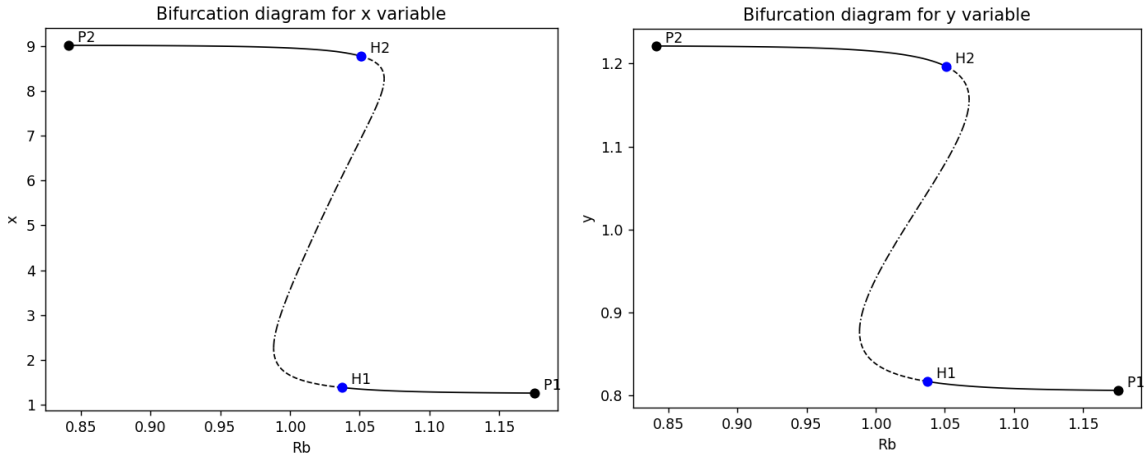


Figure 8: Bifurcation diagram for Rb parameter for L=1.01, z=0 and f=1. Solid lines correspond to stable fixed points, dashed lines to unstable ones. Blue points correspond to Hopf bifurcations, and black points to the extremities of the curve.

4.1.4 Effect of L value on Rb-related bifurcations

On figure 9 we represented the bifurcation curves of Rb for different values of L. We can see that no matter the value of L, there is a value of Rb such that the subsystem's only equilibrium corresponds to a low level of symptoms. However, this equilibrium is higher for higher values of L.

In the case of our subsystem, no change in the equilibria can occur across time, so there won't be any high increase in symptoms once it reached equilibrium. Therefore our second hypothesis is verified anyway, but this analysis will help us in the following when perturbations will be added to the subsystem.

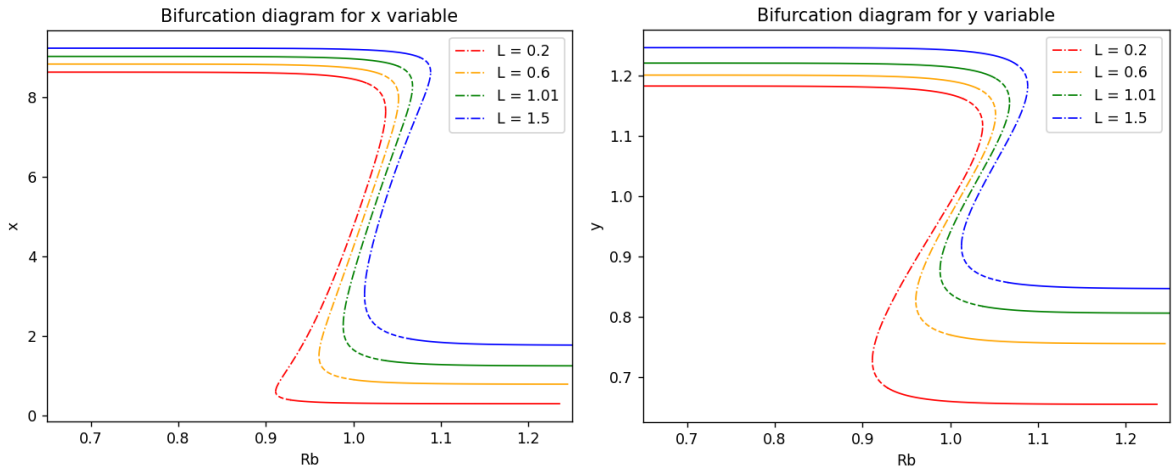


Figure 9: Bifurcation diagram of Rb parameter for z=0 and f=1 and different values of L. Solid lines correspond to stable fixed points, dashed lines to unstable ones.

4.2 Analysis of the (x-y-f) subsystem

We saw that our hypotheses are verified for the (x-y) subsystem, now we will show that they remain true if we take into account the variations of f.

4.2.1 Relation between f and y

Here we study the relation between y and f and show that every moment, f converges to the current value of $\frac{y}{\lambda_f}$.

As a reminder, the equation describing the evolution of f is :

$$\tau_f \frac{df}{dt} = y - \lambda_f f$$

So, for a fixed value of y, $f(t) = \frac{y}{\lambda_f} - (f_0 - \frac{y}{\lambda_f})e^{-\frac{t}{\tau_f}}$, i.e. $f \underset{t \to +\infty}{\longrightarrow} \frac{y}{\lambda_f}$ exponentially, with a time constant of $\tau_f = 720$ days.

So if y increases, f will increase as well.
In practice, it can be observed that y quickly reaches a first equilibrium and that f slowly converges to that value, we will see an illustration of that in the next figure.

4.2.2 Impact of the variations of f on the (x-y) subsystem

The slowly increasing value of f can induce a bifurcation of the (x-y) subsystem, here is an example of a situation where it occurs.

In figure 10 one can observe an example of a time course for L = 1.5. For t<3200 days, the (x-y) subsystem is stabilized in a low symptom state, but the increasing value of f makes the value of $f.L$ exceed the threshold of 1.05 (at t=3200, f = 0.71, so $f.L = 1.05$. This causes a bifurcation in the (x-y) subsystem, and the system will reach a high symptom state.

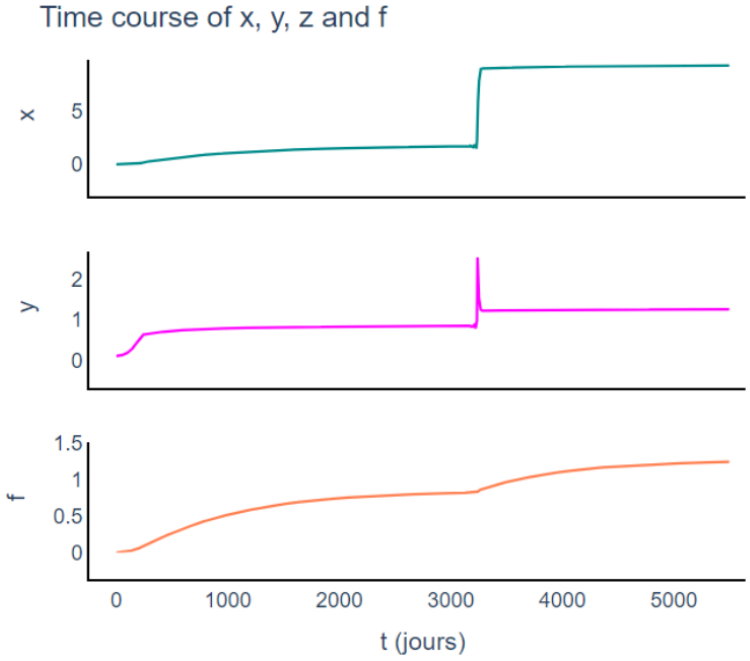
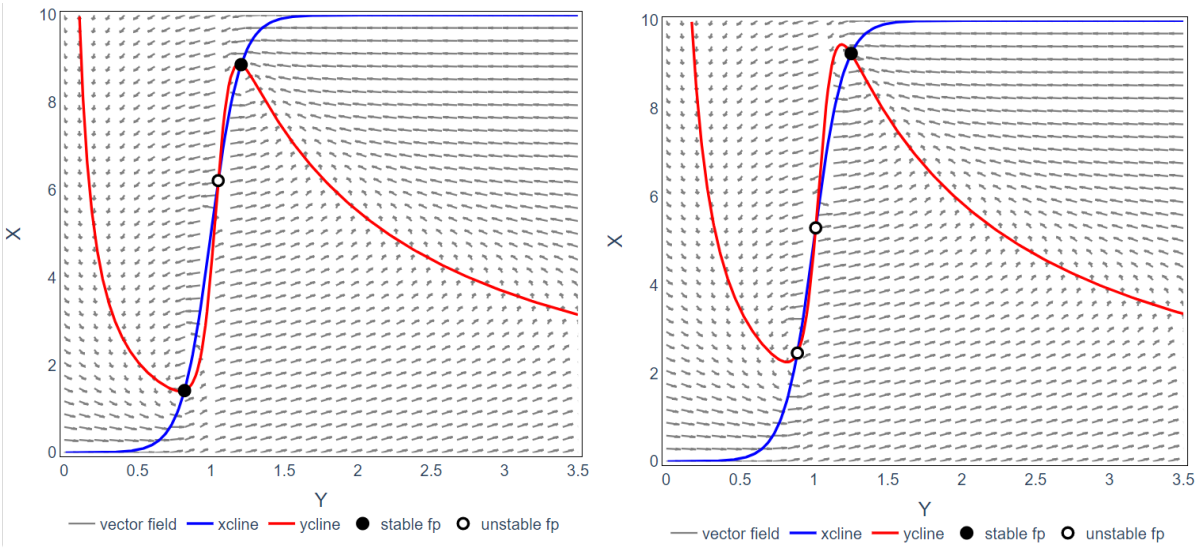


Figure 10: Time courses of x,y,f for L=1.5, Rb=1.04, z set to 0 and $x_0 = 0, y_0 = 0.1, f_0 = 0$

In figure 11a and 11b you can see the x-y phase plane for the (x-y) subsystem for t<3100

days and for t>3100 days. You can notice that for t<3100 days, there is a low symptom fixed point and that for t>3100 days this fixed point is unstable.



(a) $t = 1700$ (b) $t = 4500$

Figure 11: X-Y Phase planes for f=0.7 (corresponding to t=1700 days in the simulation of figure 10) and f=1.16 (corresponding to t=4500 days), L= 1.5, Rb=1.04 and z is set to 0

This could correspond to a case where a patient spontaneously develops a disease during his life, without environmental input. Our second hypothesis is about this type of event and states that for a resistance (Rb) that is high enough, this cannot happen.

When entering a high symptom area, y will take higher values and thus will f because f will tend toward y. But if f increases, the value of $f.L$ will increase even more, making it even more difficult to come back to the existence of a stable fixed point in the low symptoms area for the (x-y) subsystem.

4.2.3 Relation between L and the final value of f.L

In this section, we study the relationship between f and L, and see that f, and more generally f.L is an increasing function of L. As discussed in the methods section, we are more interested in the value of the $f.L$ term because it is easier to relate it to the analysis of the (x-y) subsystem we have made. In figure 12 you can see the final value taken by $f.L$ with respect to the value of L in the (x-y-f) subsystem, starting from $x_0 = 0, y_0 = 0.1, f_0 = 0, z_0 = 0$.

It can be observed that the higher the value of L is, the higher the final value of the final f.L product is. In particular, there is a brutal increase at L = 1.31. At this point the value of f is 0.82, the "effective value of L", the f.L products thus equals 1.05. It corresponds to the value of L with f set to 1 where a bifurcation occurs and the low symptoms stable spiral becomes unstable (see previous section, figure 5).

In conclusion, the higher L will be, the higher the $f.L$ product will be.

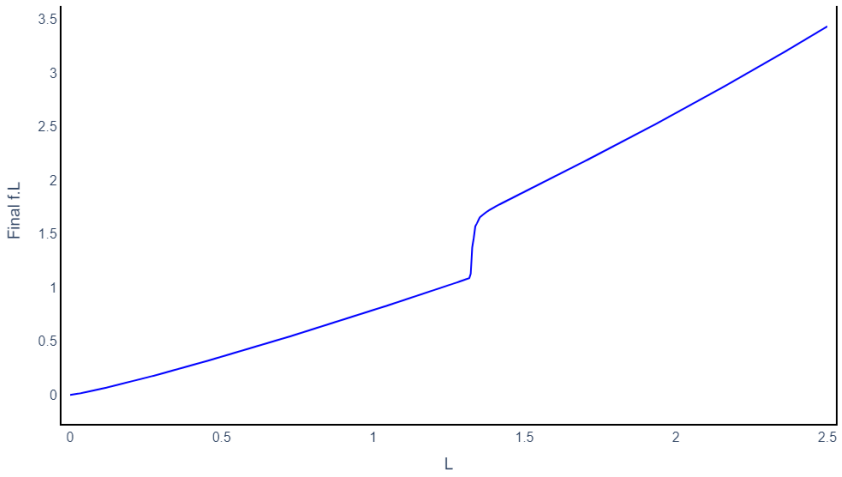


Figure 12: Final value of $f.L$ (after 8000 days) with respect to L value. For each value of L, time courses were computed, starting from $x = 0, y = 0.1, f = 0, z = 0$ for $Rb = 1.04$, and the final value of f was saved.

4.2.4 Conclusion for the (x-y-f) subsystem

We saw in a previous section that the higher $f.L$ was, the higher the equilibrium of x and y was. Here we saw that the higher the value of L is, the higher the value if the finale $f.L$ product is. Therefore, the higher L is, the higher the equilibrium of x and y will be, taking into account the variations of f. This validates our first hypothesis for the (x-y-f) subsystem.

Concerning the second hypothesis, one can see in figure 9 there exists a value of Rb such that, for all values of $f.L$ in the considered variation range, only a low symptom equilibrium exists. That means that no matter the evolution of $f.L$ caused by the evolution of f, no high increase in symptoms will occur. Our second hypothesis is thus validated for the (x-y-f) subsystem.

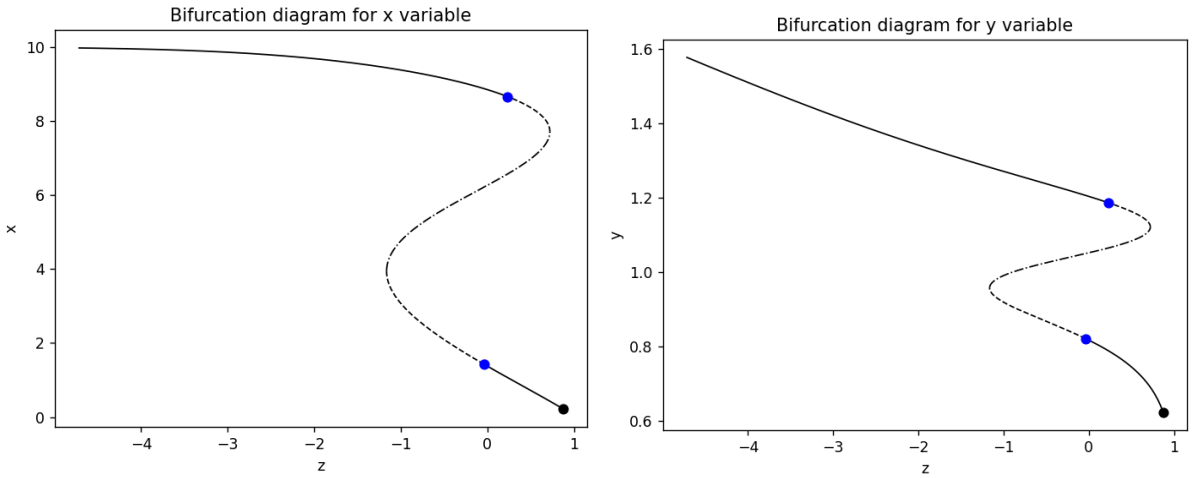
4.3 Analysis of the entire (x-y-f-z) system

4.3.1 Effect of z value on the (x-y) subsystem

The dynamics of x and y are affected by the instantaneous value of z. We computed the bifurcation diagram of z for x and y, considering z as a fixed parameter and f set to 1. You can see the result in figure 13. It can be observed that a modification of the value of z can cause a bifurcation of the (x-y) subsystem.

In practice z allows the system to temporarily exit the attraction domain of a fixed point. At some point, z reaches a value such that the (x-y) subsystem exits the attraction of a fixed point, and then comes back through a trajectory that passes near the other fixed point. In figure 14 you can see two simulations with the same parameters value, one with z fixed at 0 and the other with z variable. We can see that when z is not fixed, x and y show some passages to the low symptom area without stabilization.

As z includes a random process, running multiple simulations is the easiest way to show



(a) x (b) y

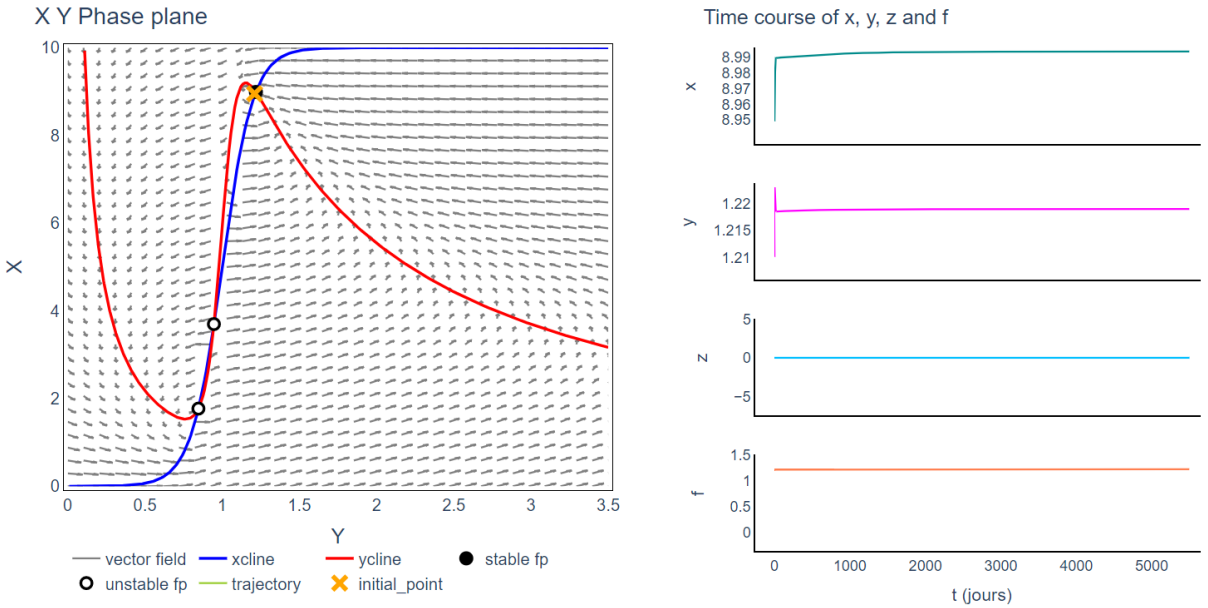
Figure 13: Bifurcation diagram of z considered as a fixed parameter, for x and y, and for $L = 1.01, Rb = 1.04, f = 1$. Continuous lines correspond to stable fixed points, dashed lines to unstable fixed points, blue points to Hopf bifurcations and black points to a limit in the existence of fixed points.

the behaviors it induces.

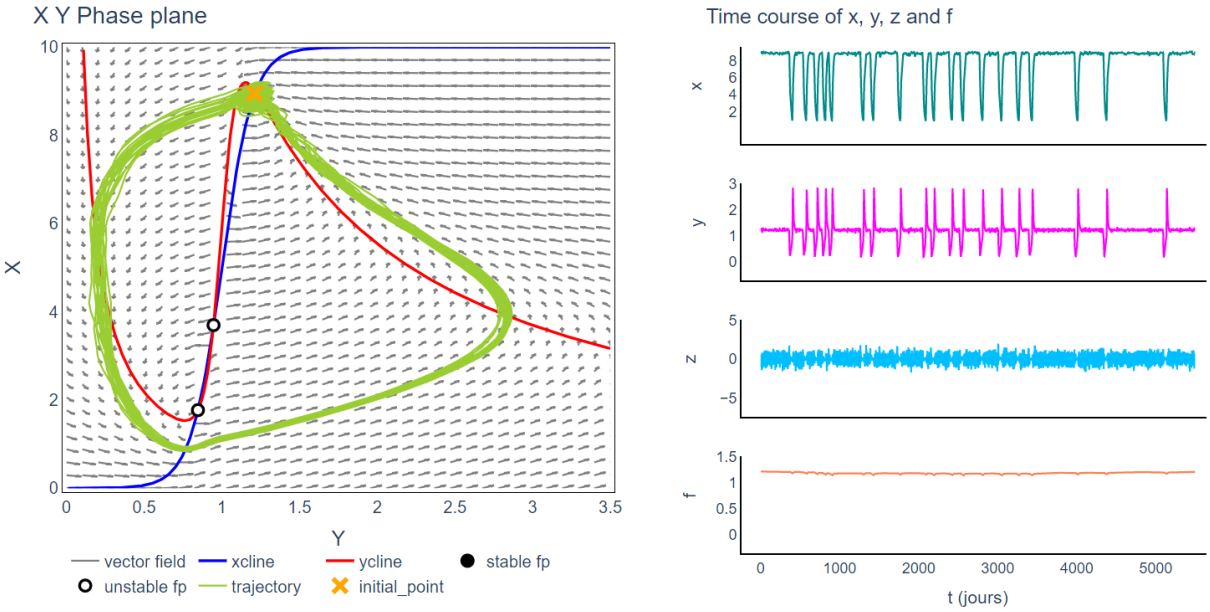
4.3.2 Influence of the value of L

We observed that, above a certain value of L, after reaching the high symptom level area, the system never stabilizes in the low symptoms area (because f has increased as y got to high values) but its trajectory sometimes goes through this low symptoms area without stabilization. However, we could observe that the higher L and the more rarely the system escape the high symptom state: in figure 15 you can see the number of times the system goes down to the low symptoms area between $t = 5000$ days and $t = 6000$ days.

We can observe that the curve is noisy as those oscillations stem from a random process. Below a certain value of L = 0.97, there are no oscillations because the noise is not sufficient for the system to exit the attraction domain of the low stable fixed point. Just above this value of L, the system shows many oscillations and tends to stabilize to the high symptoms fixed point. We can see that the number of oscillations then decreases with L, up to L= 2 after which there are no oscillations anymore. We can therefore conclude that the higher the value of L is, the less likely the noise induced by z was to induce a temporary reduction in symptoms. So the higher the value of L is and the more the system will remain around the high symptom equilibrium.



(a) z fixed to 0



(b) z variable

Figure 14: (x-y) phase plane and x,y,z,f time courses for fixed z and variable z, with $L = 0.9, Rb = 1.04, x_0 = 8.95, y_0 = 1.21, z_0 = 0, f_0 = 1.21$. The trajectory on the (x-y) phase plane is a superposition of the (x-y) trajectory on the (x-y) phase plane computed for z=0 and f=1.21. As the shape of this phase plane evolves during the trajectory, the trajectory does not strictly follow the flow of this phase plane.

4.3.3 Influence of the value of Rb

When Rb is high enough, the noise induced by z is not sufficient for the system to exit the domain of attraction of the low symptom fixed point. Figure 16 is a simulation made with $Rb = 1.15$ and $L = 2.5$ (the most unfavorable L value in our range). It can be observed that despite the perturbations caused by the environment, z, the system never visits the

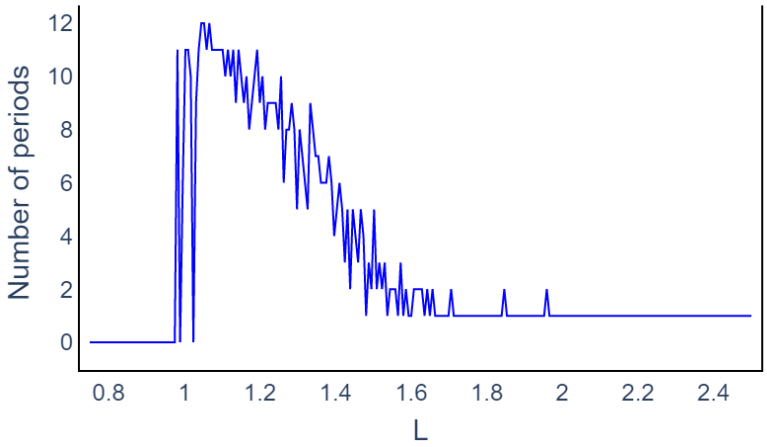


Figure 15: Number of times where the system goes through the low symptom area between $t = 5000$ days and $t = 6000$ days, with respect to the value of L, for $Rb = 1.04$, $x_0 = 0$, $y_0 = 0.1$, $z_0 = 0$, $f_0 = 0$

high symptom area.

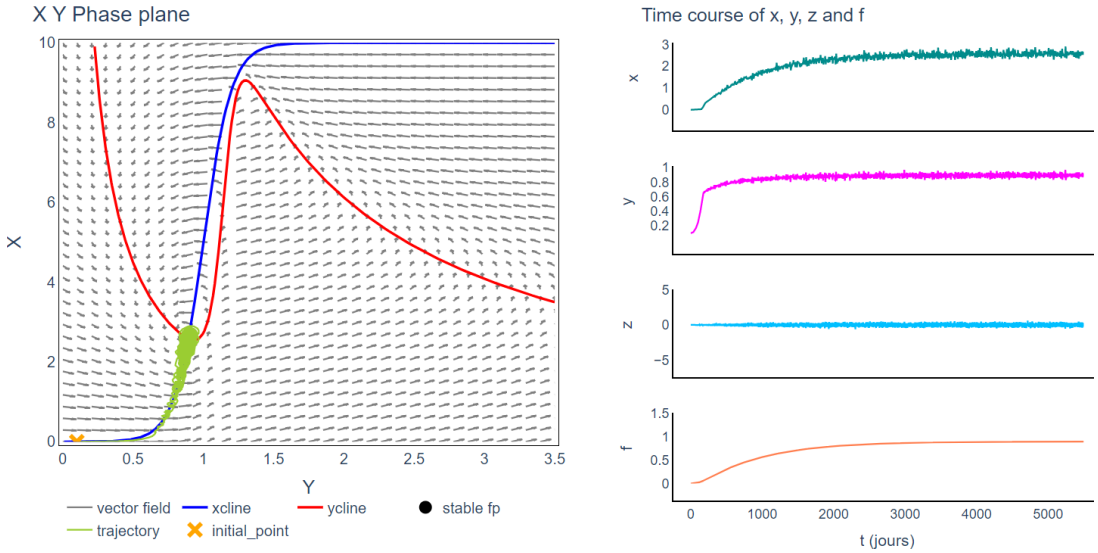


Figure 16: (x-y) phase plane and time course for $Rb = 1.15$, $L = 2.5$, $x_0 = 0$, $y_0 = 0$, $z_0 = 0$, $f_0 = 0$. The trajectory on the (x-y) phase plane is a superposition of the (x-y) trajectory on the (x-y) phase plane computed for z=0 and f=1.2. As the shape of this phase plane evolves during the trajectory, the trajectory does not strictly follow the flow of this phase plane

4.3.4 Conclusion

We saw that the (x-y) equilibrium position of the (x-y-f) subsystem was increasing with L, and when L increases the noise induced by z is less and less likely to induce a temporary reduction in symptoms, and so the higher the symptoms will be in overall. In this sense, we can say that the level of symptom increases with L, which validates our first hypothesis for the entire system.

The second hypothesis is also valid as we saw that, for a certain Rb, for the worst L value, and despite the perturbation induced by z, x and y remain in the low symptom area.

5 Discussion

We have shown, through the analysis of the model's dynamics, that our hypotheses were valid for a chosen set of parameters and variation ranges for L and Rb. This result thus only holds for these parameter values, which were chosen because they allowed the system to reproduce well the dynamical behavior of certain clinical cases. The next step in the analysis of this model would be to compare it with real data, to adjust or justify the value of the parameters.

The analysis of the impact of the variations of z was not made in a systematic way but through simulations. To really characterize the dynamics of the entire system, a deeper analysis would be needed. In particular, we could guess the existence of several limit cycles; one around the upper and the lower fixed point, marking out their domain of attraction, and a big one guiding the oscillations between the high and low symptom areas. A precise description of the evolution of these limit cycles would help a formal description of the influence of z on the (x-y) dynamics, as well as a better understanding of the model.

6 Conclusion

Even though our hypotheses were obvious from a clinical perspective, their validity for the model was not obvious. We could show that this model was indeed reproducing well some general clinical properties that are not directly described by its equations. A general description of its dynamic was also performed, paving the way for other analyses.
This model was created with the objective of better understanding and/or discovering new clinical properties, so even though we did not learn anything new, this work also shows that it is possible to do it.

During this project, I first reproduced the simulations shown in Gauld and Depannemaecker 2023. To do so, I created numerical tools useful for the analysis of the model, including a visualization dashboard and multiple programs. This will be usefull for the future work and analyses on this model. Then I investigated the dynamics of the model in general and observed certain properties. We chose to focus on two of them, which I investigated more and presented in this report.

Machine learning and AI for healthcare and research are very popular nowadays and as a student, I have mainly worked on modeling projects involving statistical parameter inference or machine learning. Here the modeling approach is mechanistic and still in investigation. It is very different from what have done so far and I find it very stimulating to take part in the creation of a model like this one. Furthermore, I could be confronted with an investigation task and learn methods that will be very usefull for my future professional life.

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