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Chaos in brain's response to a single dose of a stimulant drug

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Abstract

A dynamic model of the brain's response to a stimulant drug, recently published by Amigó, Caselles and Micó, lightly modified (a discrete-delay differential equation is substituted by a continuous-delay differential equation), is used to study the conditions that a given individual have to assume (values of the parameters of the model) in order to his or her response to a single dose of a stimulant drug becomes chaotic (sensitive to initial conditions or pseudorandom).
The base dynamic model is constituted by four coupled differential equations with seven parameters. A genetic algorithm is used to generate combinations of values of the parameters. Series of values of the four state-variables are generated with the model; and the corresponding possible chaos is analyzed using fast Lyapunov exponents among other possible tests. The result of such operations is a set of intervals of the possible values of the parameters of the model that produces chaos in the brain's response to a single dose of a stimulant drug. The names of the 7 referred parameters and 4 initial values of the state-variables, which are characteristic of the considered individual and the concrete situation, are the following: *dose* (initial non-assimilated drug), *Inhibitor effect delay*, *Assimilation rate*, *Consumption rate*, *Tonic or basal activation level* (trait), *Initial activation level* (initial state), *Homeostatic control rate*, *Excitation effect power*, *Inhibitor effect power*, *Initial drug in blood, Initial inhibitor effect* (normally zero).

Key words: chaos, human brain activity, dynamic model, stimulant drug.

Introduction

A dynamic mathematical model of the effects that a stimulant drug (such as cocaine) has on the brain is proposed by Amigó et al. [2]. It models the evolution over time of the brain activation (measured with a subjective scale of hedonic tone), which is a consequence of a single stimulant drug intake, as well as the different responses of different human beings to the same dose of a given drug. Not all human beings respond equally and such a differential response is very important because it may be a cause of vulnerability to drug misuse [4][6]. While considering individual differences, we highlight the necessity to introduce some personality variables into the model. Concretely, extraversion will be chosen as the basic personality trait because it has the general brain activation system as its biological base [1]. Moreover, if drugs modify the brain activation level and people consuming drugs differ with regard to their base activation level, then the joint consideration of the drug activation effect and personality in a dynamic

mathematical model will decisively contribute to predicting the effects of specific drugs on different types of people.

Now, the questions we are going to try to help to answer are: which is the drug dose that produces chaotic effects (important changes in low time periods) in a given individual? In which kind of individual (with determined physic and personality characteristics) a determined drug doses produce chaotic effects?

The model

This kind of questions ought to be answered by a model such as the model proposed by Amigó et al. [2], but it includes a discrete delay in the equations that makes difficult to work with. Thus, Micó et al. [5] propose an alternative continuous delay model that reproduces the same dynamics than the discrete delay model and promises to be easier to manage mathematically. Nevertheless, both models are linear and cannot answer the previous questions (chaos is not a property of linear systems). We have found a very similar non-linear model that reproduces the same dynamics than the previously mentioned ones and, consequently, can be used to study its possibilities of chaotic behavior. Such a model is constituted by four coupled differential equations with its initial conditions (see equations (1), (2), (3) and (4)):

$$\left.\begin{aligned} \frac{dc(t)}{dt} &= -\alpha \cdot c(t) \\ c(0) &= c_0 \end{aligned}\right\} \quad (1) \qquad \left.\begin{aligned} \frac{ds(t)}{dt} &= \alpha \cdot c(t) - \beta \cdot s(t) \cdot y(t) \\ s(0) &= s_0 \end{aligned}\right\} \quad (2)$$

$$\left.\begin{aligned} \frac{dy(t)}{dt} &= a\big(b - y(t)\big) + \frac{p}{b} s(t) - b \cdot q \cdot z(t) \\ y(0) &= y_0 \\ \frac{dz(t)}{dt} &= -z(t)/\tau + s(t) \cdot y(t) \\ z(0) &= 0 \end{aligned}\right\} \quad (3)$$

Where:
c = amount of non-assimilated drug in body (for instance, cocaine in nose)
s = amount of assimilated drug in blood
y = brain activity level (hedonic scale)
z = delayed depressive effect (see equation (4))
c_0 = amount of drug intake (initial non-assimilated drug in body)
s_0 = initial drug in blood
y_0 = initial brain activity level
α = drug absorption rate
β = drug consumption rate by cells
τ = delay of the depressive effect of the drug
a = power of the homeostatic mechanism
b = normal (genetic) brain activity level of the individual
p = exciting power of the drug
q = depressing power of the drug

The model has seven parameters and four initial conditions (data input) corresponding to the four state variables (*c, s, y, z*) determining the phase space. The four initial conditions (c_0, s_0, y_0, $z_0=0$) represent the state of the individual in the moment is taking a drug dose of c_0 units. The seven parameters (α, β, τ, *a, b, p, q*) represent individual characteristics, some of them with respect to a given drug. With respect this model, our intention is twofold:

1. Given a concrete individual and a given drug (that is, given the values of α, β, τ, *a, b, p, q*) to determine which are the doses (c_0), the initial states of drug in blood (s_0) and the brain activity levels (y_0) that lead to a chaotic trajectory (set of consecutive points which coordinates are *c, s, y, z,* that can seem pseudorandom). The range of possible values of *c, s,* and *y* can vary from 0 to maybe 1000 or more.
2. Given a concrete dose c_0, a concrete amount of drug in blood s_0, and, a concrete brain activity level y_0, which are the kinds of individuals (values of α, β, τ, *a, b, p, q*) that would suffer a chaotic trajectory?. The range of possible values of α, β, τ, *a, b, p, q* varies from 0 to an unknown value.

Detecting chaos in the model

Detecting the presence of chaos (essentially sensitivity to initial conditions) in a dynamical system, in general, is an important problem that is solved habitually by measuring the largest Lyapunov characteristic exponent (LCE). Lyapunov exponents are quantities that characterize the rate of separation of infinitesimally close state-space trajectories and estimate the amount of chaos in a system. If the initial separation of two trajectories is δZ_0 they would diverge $|\delta Z_t| \approx e^{\lambda t} |\delta Z_0|$ where λ is the Lyapunov exponent. The rate of separation can be different for different orientations of the initial separation vector. Thus, there are a number of Lyapunov exponents equal to the number of dimensions of the *phase space* (number of state variables, four in our case). It is common to just refer to the largest one, (LCE), because a positive LCE is an indication that the system is able to show chaotic behaviour.

Rosenstein et al. [7] offers an interesting method to calculate LCE. Nevertheless, given the amount of situations we intend to test (combination of values of *c, s,* and *y* in the case 1, and combination of values of α, β, τ, *a, b, p, q* in the case 2) we need a method faster enough.

The method presented by Froeschlé et al. [3], based on the variation with time of the length of vectors evolving in tangential space, promise to distinguish very quickly between regular and chaotic trajectories, be closely related to the computation of the LCE and, be easily applied to the study of a large set of trajectories. They define their Fast Lyapunov Indicator (FLI) (and affirm that it is the one between other tested ones which is least dependent on the initial conditions) as follows. Starting with a *p*-dimensional basis

$$Vp(0) = (v_1(0), v_2(0), \ldots, v_p(0)),$$

embedded in an n-dimensional space and with an initial condition

$$P(0) = (x_1(0), x_2(0), \ldots, x_n(0)),$$

take at each iteration the largest among the vectors of the evolving basis.

$$FLI = sup_j \, ||v_j(t)|| \quad j = 1, \ldots, p$$

On the other hand, according to these authors, when looking at a regular trajectory the variation with time of the FLI is quite similar to that of the LCE but in chaotic trajectories is much faster and, this is related to the fact that for very regular trajectories it takes a long time for problems of overflow or underflow to appear. Consequently, the early detection of overflow or underflow announces chaos. With such a kind of

characteristics we decided to choose this method as a part of our algorithm, for the moment.

The genetic algorithm

The genetic algorithm we have designed to build combinations of the parameters of the model and to test whether they lead to a chaotic trajectory or not is the following:

Introduce the names of the parameters or initial conditions going to vary among those of the list: c_0, s_0, y_0, α, β, τ, *a, b, p, q.*
Introduce the values of the parameters to keep constant and the maximum values of the parameters going to vary (the minimum for all is 0).
Introduce the width of the grid, the period to simulate and the time step.
Introduce the chaos threshold: ***thr*** *for (FLI – initialFLI)/time.*
Calculate the respective ranges of variation of the parameters.
Calculate the number of possible combinations of a value for each parameter.
Introduce the specific data for the genetic algorithm:
    The size of the population to be treated: ***P****.*
    The number of immigrants per generation: ***mm****.*
    The proportion of mutant genes: ***tt****.*
    The proportion of reproducers of each generation (the best ones): ***rr*** *%.*
    The number of generations to simulate: ***gg****.*
Create the first population:
    Take a random sample of combinations of values of the varying parameters.
    Put them in a file or a matrix: Population1.
Do:
    Calculate the maximum and minimum values of FLI in Population1.
    Select the top ***rr*** *% of Population1 as reproducers and put them in Population2.*
    Incorporate ***mm*** *randomly chosen individuals into Population2.*
    Reproduce the individuals of Population2 up to ***P****:*
        For each varying parameter:
            Choose two individuals of Population2 as "father" and "mother".
            Randomly choose one of the two values for the "child" vector.
            Substitute a ***tt*** *% of times this value for a random one.*
    Calculate FLI and ch = |FLI – initialFLI|/time for each individual of Population2.
    Kill Population1 and rename Population2 as Population1.
Repeat until the number of generations be equal to ***gg*** *or all ch* ≥ ***thr****.*

To put into practice this algorithm we have designed a Visual-C program using the Runge-Kutta-4 method to solve the model.

Application case

The parameters of the model have been fitted with respect to an individual in fast that has taken two cups of coffee (c_0 = 330 mg. of caffeine) (Micó et al., 2008). The brain activation level has been evaluated with a subjective scale through the list of 12

adjectives of the *sensation seeking scale* obtained from MAACL (Zuckerman & Lubin, 1965). The individual fills the questionnaire 20 times (each 4.5 minutes during 90 minutes after the intake).The adjustment process, for a concrete individual, has produced the following results: τ=*200.0 min*; α=*0.0018 min*$^{-1}$; β=*0.00002 min*$^{-1}$; *a*= 1.1385 *min*$^{-1}$; *b*=11.385 *u*; *p*=85.0 *u*^{2}·*mg*$^{-1}$·*min*$^{-1}$; *q*=0.*0005 u*$^{-1}$·*mg*$^{-1}$; y_0=*11 u*. Obviously, s_0=*0 mg*, and z_0=*0 u·mg·min*$^{-1}$ (where *u* is units, *mg* is milligrams and *min* is minutes). Observe that z_0 is always zero because *z* is defined as:

$$z(t) = \int_0^t exp((x-t)/\tau) \cdot s(x) \cdot y(x) \cdot dx \qquad (4)$$

The first test (test 1) to be performed consists of finding the initial conditions (c_0, s_0, y_0) that produce a chaotic evolution of the brain activation level in this individual. The obtained results show that the only possibility for this individual to have a chaotic behavior in his brain activity is having s_0=*1000 mg* of caffeine in blood (the top extreme of the studied range) and some concrete pairs of values of c_0 and y_0 (see Figure 1).

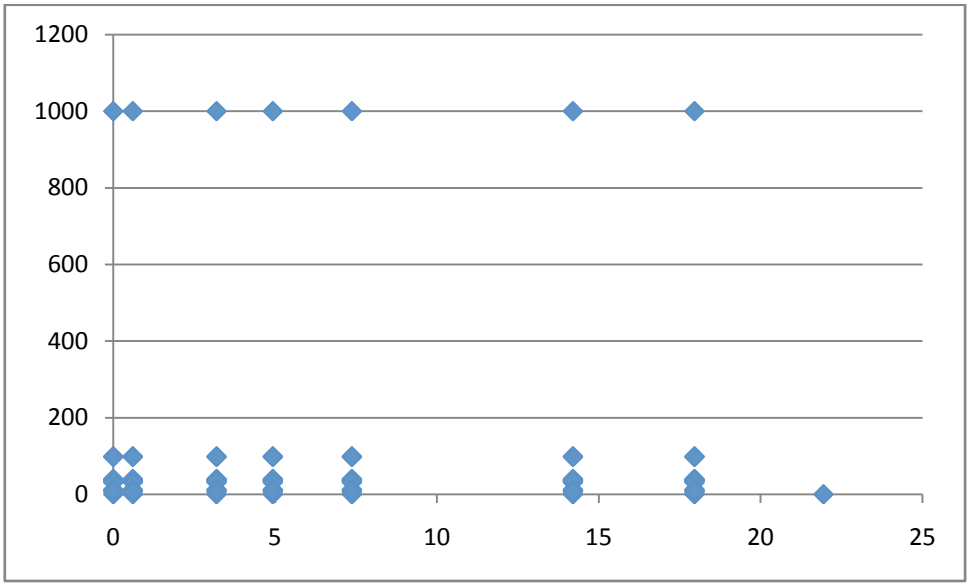

Figure 1: Chaotic zones of y_0 (abscise axis) and c_0 (ordinate axis) for test 1.

The second test (test 2) that we intend to perform consists of finding the kind of individual that with the initial conditions c_0 =*330 mg,* s_0=*0 mg,* y_0=*11 u,* would enter into a chaotic trajectory of brain activity. At present, this test is in processing state.

Discussion

A non-linear system of four coupled differential equations has been suggested for the behaviour of the brain activity level after a stimulant drug intake taking into account the theories related with and cited in this paper. This model tries to incorporate a more realistic explanation of the inhibition effect (a continuous and non linear response) under the biological point of view with respect to the “father” model [2] as well as being easier to manage mathematically and computationally. The model presented in this paper is validated using experimental results obtained with 330 mg of caffeine and the subjective

responses of 21 individuals. The present study also tries to find a method to search for chaos (and other types of trajectories) in this model and, possibly in many other model types, as well as to identify the biological meaning of the found chaotic dynamics, for instance, the appearance of sharp changes in personality and/or the appearance of antisocial behaviour under determined circumstances, which is bad for society and for the individuals themselves.

Our comment about to the test presented earlier is that such an individual cannot enter in a chaotic brain activity taking coffee naturally, because 1000 mg of caffeine in blood, previous to a new normal intake, are not easy to have.

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