Cocaine addiction and personality: A mathematical model

Antonio Caselles¹*, Joan C. Micó² and Salvador Amigo³
¹Departament de Matemàtica Aplicada, Universitat de València, Spain
²Institut Universitari de Matemàtica Pura i Aplicada, Universitat Politécnica de València, Spain
³Departament de Personalitat, Avaluació i Tractaments Psicològics, Universitat de València, Spain

The existence of a close relation between personality and drug consumption is recognized, but the corresponding causal connection is not well known. Neither is it well known whether personality exercises an influence predominantly at the beginning and development of addiction, nor whether drug consumption produces changes in personality. This paper presents a dynamic mathematical model of personality and addiction based on the unique personality trait theory (UPTT) and the general modelling methodology. This model attempts to integrate personality, the acute effect of drugs, and addiction. The UPTT states the existence of a unique trait of personality called extraversion, understood as a dimension that ranges from impulsive behaviour and sensation-seeking (extravert pole) to fearful and anxious behaviour (introvert pole). As a consequence of drug consumption, the model provides the main patterns of extraversion dynamics through a system of five coupled differential equations. It combines genetic extraversion, as a steady state, and dynamic extraversion in a unique variable measured on the hedonic scale. The dynamics of this variable describes the effects of stimulant drugs on a short-term time scale (typical of the acute effect); while its mean time value describes the effects of stimulant drugs on a long-term time scale (typical of the addiction effect). This understanding may help to develop programmes of prevention and intervention in drug misuse.

1. Introduction

Personality is a major explanatory factor in understanding the start and development of drug addiction. Various personality factors have been considered as precedents for addiction, such as impulsiveness and nonconformism (Kandel, 1978) and sensation-seeking (Zuckerman, 1994), or as factors related to addiction itself, such as...
neuroticism and psychoticism (King, Enrico, & Parsons, 1995; Nishith, Mueser, & Gupta, 1994). There are also signs that drug consumption can change personality (Trull & Sher, 1994).

A set of studies show the existence of a broad latent factor with a large genetic component called labelled externalizing, which would explain the co-occurrence of antisocial conduct disorders and drug dependence, and the disinhibitory personality trait (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Jang, Vernon, & Livesley, 2000; Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000). This is a hierarchical model that defines the externalizing spectrum, which links normal personality with psychopathology.

Other studies also established the relationships between normal personality and psychopathology (Trull & Sher, 1994). Since they deal with cross-sectional studies of unrelated persons, however, it is not possible to state causal connections between personality and psychopathology (Nathan, 1988; Tarter, 1988).

The existence of a close relationship between personality and drug consumption is recognized, but the corresponding causal connection is not well known. None of the aforementioned studies clarifies this relationship. Neither is it well known whether personality exercises an influence predominantly at the beginning and development of addiction, nor whether drug consumption produces changes in personality. Thus, studying in depth the connection between personality and addiction is an important challenge in understanding the phenomenon of addiction. This understanding may help to develop programmes of prevention and intervention in drug misuse.

System-inspired models of personality – such as the individuality theory (Royce & Powell, 1983) and Pelechano’s parameter model (Pelechano, 1973, 2000) – can be found in the specialized literature. On the other hand, mathematical models based on the systems dynamics to explain alcohol consumption (Warren, Hawkins, & Sprott, 2003), nicotine addiction (Fan & Elketroussi, 1989; Gutkin, Dehaene, & Changeaux, 2006), biochemical effects of cocaine (Nicolaysen & Justice, 1988), addiction as a neuropharmacological and learning process (Redish, 2004), and the economic models of addiction (Becker & Murphy, 1988; O’Donoghue & Rabin, 1999) can also be found. These models involve psychological variables such as decision-making or self-control, but they do not use personality traits. Thus, a dynamic model that integrates the effects of personality and addiction has yet to be presented in the specialized literature.

In this paper, a dynamic model that studies the relationship between personality and drug addiction is presented, based on the unique personality trait theory (UPTT; Amigó, 2005). The UPTT attempts to integrate personality, the acute effect of drugs, and addiction and, therefore, appears to offer a way forward in the study of the aforementioned relation between personality and drugs. Following empirical studies (Amigó, 2002; Amigó & Seshadri, 1999) on the relation between personality and drug consumption, Amigó (2005) revises the principal theories about temperamental personality traits (of biological nature), and the empirical, theoretical, and neurobiological evidence of Eysenck’s and Gray’s approach (Eysenck & Eysenck, 1985; Gray, 1972, 1981, 1982). As a consequence of this review, Amigó proposes that anxiety and impulsivity are the two poles of a single dimension called extraversion which is the most basic and fundamental trait of the hierarchy of personality traits. This trait of extraversion (with its poles of impulsivity, extraversion and high psychoticism on the one hand and anxiety, introversion and low psychoticism on the
other) is a unique (understood as the most basic and fundamental) personality trait. Thus, the word *extraversion* is used to denote a continuous extraversion–introversion dimension, following a convention proposed by Eysenck which is widely accepted today. Thus, extraversion is a similar factor to the above-mentioned labelled externalizing factor, although it is an integrator factor of complete personality, which in its own definition, considers both the externalizing component and the internalizing one (on the internalizing spectrum, see Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005; Widiger & Clark, 2000).

Amigo´, Caselles, and Micó (2008) study the relationship between personality dynamics and the acute effect of a single stimulant drug (cocaine) intake. Thus, the model presented herein is an extension of that study that considers repeated drug consumption leading to addiction.

Stimulant drug addiction requires repeated consumption. A different effect of sensitization or drug habituation can be observed depending on the consumption pattern. For instance, Dalia et al. (1998) administered intermittent cocaine injections (40 mg kg$^{-1}$ at 3-day intervals) to rats, observing a sensitization response to a challenge dose (7.5 mg kg$^{-1}$). Later, they implanted an osmotic pump into the rats that released cocaine continuously (80 mg kg$^{-1}$ day$^{-1}$) for 7 days. Habituation was observed as a consequence of a challenge dose 1 day after removing the pump.

With respect to the simulations carried out with the suggested model and reported in this paper, a hypothetical (and, obviously, very atypical) strong cocaine addiction with a constant drug consumption per week is simulated in order to confirm that the model reproduces the three classical phases of the addictive process independently of the drug intake pattern. Finally, the following time pattern with three separate phases is simulated in the context of our model: (1) a progressive and intermittent increase of doses which produces sensitizing; (2) a large and continuous increase of doses which produces habituation; and (3) a slow return to genetic extraversion due to the abandonment of the drug consumption or, in the context of a ‘limit’ consumption pattern, due to the null effect caused by the cocaine consumption. The results of such simulations are expected to be in accordance with those described in the cited literature (which is the case and is demonstrated below).

Drug-seeking behaviour has not been modelled at this stage. This is another problem that merits a specific study. Thus, we restrict the objectives of the modelling process to try to reproduce the excitation dynamics described in the literature, that is, to build a model explaining sensitization as a result of discontinuous drug intake in the first stages of the addiction process and, habituation as a result of continuous drug intake in the late stages of the addiction process (for a review, see Gawin, 1991; Goudie & Emmett-Oglesby, 1991; Johanson & Fischman, 1989; Martin-Iverson & Burger, 1995; Morgan & Roberts, 2004).

In the context of the UPTT, the tonic activation level (or basal activation level), which is the genetic activation level and takes place in the organism in a repose state, is distinguished from the phasic activation level, which occurs as the response to a determined stimulus such as a drug unit dose. On the short-term time scale (typical of the acute effect of a stimulant drug), the extravert presents a lower tonic activation level and a stronger (longer in time and higher in activation level) phasic activation level than the introvert, whose tonic activation level is higher and who has a weaker phasic activation level (Amigo, 2005; Amigo et al., 2008). On the long-term time scale (typical of addiction), the pattern of consumption is such that a lower and intermittent
consumption precedes a higher and continuous consumption. The first intakes in the first phases of this consumption pattern (lower and intermittent) produce a high phasic activation level which makes the return to the tonic activation level easy; whereas the last phases of this consumption pattern (higher and continuous) produce a high tonic activation level, before each intake, which makes the return to the initial value before consumption difficult (see Grace, 1995, 2000). Thus, an evolution from extraversion to introversion occurs. In other words, a change of personality happens as the consumption pattern develops in time, in such a way that a change in the consumption habits generates a change of personality; and at the same time a change of personality generates a change in the consumption habits, as Trull and Sher (1994) point out (but without considering dynamics). The main goal of this paper is to present a dynamic mathematical model of personality and addiction that mathematically describes such an interrelation and co-evolution, and to use this model to simulate different seemingly realistic scenarios, which include a possible strategy for intervention in drug misuse.

The dynamic model (referred to henceforth as DBRAIN), has been obtained by following the general modelling methodology (GMM) (Caselles 1992, 1993, 1994, 1995) within the general systems theory context that he also developed. This methodology consists of 10 stages (Caselles, 1994) which do not run sequentially, rather natural feedback processes take place among them. With these 10 steps, Caselles generalized the scientific method, or the hypothetico-deductive method, with a view to adapting it to complex systems modelling. Generally, an interdisciplinary approach is needed to understand such systems, which also applies to our case, and the model validation in these systems may prove difficult, or even impossible, given the design of experiments within the real system that are needed. Furthermore, a model may only come about through differences in experts’ opinions (which often come to light in the scientific literature). In this way, once the model has been validated and computer-programmed, it may be used to perform the simulations required to solve the problems raised (this may be interpreted as the model being used to design experiments).

The basic structure of variables and interrelations of the dynamic model of personality and addiction presented in this paper arises from the UPTT. Following the GMM, DBRAIN has been obtained as a system of five coupled differential equations for five state variables: the non-absorbed drug in the body, the drug level in the body, the power of the excitation effect, the power of the inhibitor effect, and the activation level. In addition, extraversion and activator effect are dynamic variables involved in DBRAIN and are computed, respectively, as the mean values for each time instant of the activation level and of the drug level in the body. The simulations performed using DBRAIN demonstrate that the time patterns reported by the UPTT (previously described) to explain the dynamics of extraversion hold, i.e. these simulations reproduce such dynamics.

Finally, the dynamic model presented by Amigó et al. (2008) is a simplification of the model presented herein, being restricted to the case in which a single drug unit dose is considered (so that addiction is not studied). Moreover, this work can be considered the closest work to that presented herein.

The proposed model (DBRAIN) has the following intuitive structure:

1. Cocaine intake remains in the nose for a period while it is distributed and enters the blood.
2. Then it produces a stimulant effect that depends on the extraversion of the individual and on the stimulant power of the drug.
(3) The stimulant effect increases the excitation of the brain.
(4) The excitation of the brain induces a short-term homeostatic effect, a long-term (delayed) depressive effect, and modifies the instantaneous extraversion of the individual.
(5) The depressive effect also depends on the depressive power of the drug.
(6) The stimulant power, the depressive power, and the delay of the depressive power vary depending on the past history of drug intakes.

Figure 1 shows the proposed structure in a little more detail, and Figure 2 will complete the necessary details when variables, equations, and parameters are introduced.

Such a structure is inspired by the works of Amigó et al. (2008), Grossberg (2000), Solomon and Corbit (1974), and by the literature on the genetic regulation of brain activity (see, for instance, Beretta, Robertson, & Graybiel, 1992; Colby, Whisler, Steffen, Nestler, & Self, 2003; Hiroi et al., 1998; Hyman, 1996; Torres & Rivier, 1993; Werme et al., 2002; Young, Porrino, & Iadarola, 1991), and is obtained after a long trial and error process proceeding from the idea that the model reproduces the three phases of the addiction process (sensitization, habituation, and return) suggested by Amigó (2005), Gutkin et al. (2006), and Redish (2004) after repeated drug intakes and stopping. The parameters of the model have to be able to be adjusted to a given individual, and the model has to be useful to determine the optimal dose and delay between consecutive doses of cocaine (or alternative drug) that make the return phase as short and comfortable as possible for the drug addict.

The rest of this paper is organized as follows. The stimulus is modelled in Section 2 by integrating the two coupled differential equations corresponding to the variables *non-absorbed drug in the body* and *drug level in the body*. The time function of the stimulus corresponds to the second of these variables. Therefore, this function is the so-called input variable of the addiction module formed by three coupled differential equations which correspond to the rest of the variables involved. These equations are determined in Section 3. The results of the simulations carried out with the model, designed to validate the model by contrast

![Figure 1. Structure implicit in the proposed model (dashed arrows denote influence).](image-url)
with the existing literature and to try out a strategy of intervention, are shown in Section 4, as are the conclusions reached from the simulations. A general discussion is provided in Section 5.

2. Stimulus equation

Before presenting a complete description of DBRAIN in Section 3, we focus on the dynamics of the stimulus produced by a stimulant drug. Two state variables are involved in the dynamics of the stimulus (Amigó et al., 2008): non-absorbed drug in the body, \( c(t) \), or the amount of drug present that is not distributed at instant \( t \) in the organism (for instance, cocaine powder in the nose); and drug level in the body, \( s(t) \), or the amount of drug in plasma being consumed by cells at the same instant \( t \) (see Figure 2 for the structure of relations between these variables). We suppose that the variable \( s(t) \) produces the organism’s acute response to the drug, and is therefore representative of the stimulus. Previous studies on the effect of different stimulant drugs in animals and humans (see, for instance, Fowler et al., 2008; Kufahl, Rowe, & Li, 2007; Tsibulsky & Norman, 2005) suggest that the time needed for cocaine to reach the brain is very short (about 4 min to the highest concentration). Thus, given that our study is concerned with addiction, and addiction is a matter of months, such an elapsed time may be considered negligible. Furthermore, Javaid, Musa, Fischman, Schuster, and Davis (1983) confirm that ‘After intranasal administration, cocaine kinetics conform to a one-compartment model with first-order absorption and first-order elimination’. Consequently, and in order to simplify the model, we assume that the difference in drug concentration between plasma and brain is not significant at the time scale considered, and adopt a one-compartment pharmacokinetic model.

Let us assume that a number \( N \) of repeated drug unit doses occur with doses \( M_1, M_2, \ldots, M_N \), respectively, at instants \( t_1, t_2, \ldots, t_N \), after an initial instant \( t_0 \geq 0 \), so that \( t_{i-1} < t_i, i = 1, 2, \ldots, N \). The variation of \( c(t) \) with time is caused by a flow that makes \( c \) increase \( A(t) \), produced by the repeated drug unit dose, and also by a flow that makes \( c \) decrease produced by the drug being distributed in plasma, \( C(t) \), that is:

\[
\frac{dc(t)}{dt} = A(t) - C(t),
\]

where \( c_0 \) is the amount of non-absorbed drug at the initial instant \( t_0 \).

On the one hand, \( A(t) \) has the following structure:

\[
A(t) = \begin{cases} 
M_i, & t = t_i, \\
0, & t \neq t_i, i = 1, 2, \ldots, N.
\end{cases}
\]

On the other hand, if we assume that the drug distribution occurs at a constant rate (the absorption rate constant), \( \alpha > 0 \), for each instant we obtain:

\[
C(t) = \alpha c(t).
\]

The absorption rate constant is a parameter that depends on each individual. The variation of \( s(t) \) over time is given by the same distribution flow in plasma \( C(t) \), which is
now a growth flow, and by another reducing flow which would represent the drug elimination, \( R(t) \), that is:

\[
\frac{ds(t)}{dt} = C(t) - R(t),
\]

\( s(t_0) = s_0. \) \( \tag{4} \)

Let us assume that there is a level \( s_0 \) of drug in the body at the initial instant, just as the initial condition of \( (4) \) indicates. Let us furthermore assume that the elimination from plasma is proportional to the level of the drug in the body with an elimination rate constant \( \beta > 0 \). Then

\[
R(t) = \beta s(t). \] \( \tag{5} \)

The elimination rate constant is also a parameter that depends on each individual. By substituting \( (2) \) in \( (1) \) and \( (5) \) in \( (4) \), we obtain a system of two coupled differential equations:

\[
\frac{dc(t)}{dt} = A(t) - \alpha c(t),
\]

\[
\frac{ds(t)}{dt} = \alpha c(t) - \beta s(t),
\]

\( s(t_0) = s_0, \)

\( c(t_0) = c_0. \) \( \tag{6} \)

In \( (6) \), function \( A(t) \) is structured as in \( (2) \). In order to obtain the solution \( s(t) \) (which represents the desired time function of the drug level in the body), we can break down system \( (6) \) into \( N + 1 \) subsystems which correspond to each of the intervals \([t_i, t_{i+1}]\), \( 0 \leq i \leq N \). At each initial instant of every interval, the initial condition for \( c(t) \) will be the amount of non-absorbed drug present in the organism at this instant, \( c(t_i) \), plus the new drug dose intake at instant \( t_i \), \( M_i \). Specifically, for the initial interval \([t_0, t_1] \), which has no new intake \( (M_0 = 0) \), the corresponding subsystem is:

\[
\frac{dc(t)}{dt} = -\alpha c(t),
\]

\( c(t_0) = c_0, \)

\[
\frac{ds(t)}{dt} = \alpha c(t) - \beta s(t),
\]

\( s(t_0) = s_0. \) \( \tag{7} \)

The solution of \( (7) \) for \( c(t) \) and \( s(t) \) with \( t \in [t_0, t_1] \) is:

\[
c(t) = c_0 \exp(-\alpha(t - t_0)), \]

\( \tag{8} \)

\[
s(t) = s_0 \exp(-\beta(t - t_0)) + c_0 \beta(t - t_0), \]

\( \tag{9} \)
where
\[
v(t) = \begin{cases} 
\frac{\alpha}{\beta - \alpha} (\exp(-\alpha t) - \exp(-\beta t)) & \beta \neq \alpha, \\
\alpha t \exp(-\alpha t) & \beta = \alpha.
\end{cases}
\] (10)

The intake, \(M_1\), of a new dose (the first intake after the initial situation) is produced at instant \(t = t_1\). The amount of still non-absorbed drug present in the organism at this instant is \(c(t_1) = c_0 \exp(-\alpha(t_1 - t_0))\) plus the first intake dose \(M_1\), while the amount of drug level in the body and that being consumed by the cells is \(s(t_1) = s_0 \exp(-\beta(t_1 - t_0)) + c_0 t(t_1 - t_0)\). Both values represent the initial conditions of \(c(t)\) and \(s(t)\), respectively, in the following subsystem, valid for interval \([t_1, t_2]\), as shown by the following equations:
\[
\begin{align*}
\frac{dc(t)}{dt} &= -\alpha c(t), \\
c(t_1) &= c_0 \exp(-\alpha(t_1 - t_0)) + M_1, \\
\frac{ds(t)}{dt} &= \alpha c(t) - \beta s(t), \\
s(t_1) &= s_0 \exp(-\beta(t_1 - t_0)) + c_0 t(t_1 - t_0),
\end{align*}
\] (11)

whose solution for \(t \in [t_1, t_2]\) is
\[
\begin{align*}
c(t) &= c_0 \exp(-\alpha(t - t_0)) + M_1 \exp(-\alpha(t - t_1)), \\
s(t) &= s_0 \exp(-\beta(t - t_0)) + c_0 t(t - t_0) + M_1 t(t - t_1).
\end{align*}
\] (12, 13)

If we reason by induction for the drug intake \(1 \leq j \leq N\) with \(t \in [t_0, t_{j+1}]\), we obtain the time functions \(c(t)\) and \(s(t)\) we were looking for:
\[
\begin{align*}
c(t) &= c_0 \exp(-\alpha(t - t_0)) + \sum_{i=1}^{j} M_i \exp(-\alpha(t - t_i)), \\
s(t) &= s_0 \exp(-\beta(t - t_0)) + c_0 t(t - t_0) + \sum_{i=1}^{j} M_i t(t - t_i).
\end{align*}
\] (14, 15)

Solutions (14) and (15) are valid for any \(t \geq t_N\), that is, for the last consumption intake if \(j = N\), and they represent the corresponding time functions after the drug addict stops consuming permanently.

Let us go on to specify a consumption intake pattern that is more closely linked to a real consumer. For this purpose, we first have to consider a simple case in which the consumer takes a constant drug dose \(M\) with a certain frequency \(T > 0\) as from the initial instant \(t_0\). If he/she takes the drug \(N\) times, he/she will do so at the instants \(t_j = t_0 + jT, 1 \leq j \leq N\), and for time lasting \(NT\) starting from the instant of the first intake. In this case, the time functions (14) and (15) corresponding to intake \(1 \leq j \leq N\),
Cocaine addiction and personality

are rewritten with $t \in [t_0, t_0 + (j + 1)T]$, as

$$c(t) = c_0 \exp(-\alpha(t - t_0)) + \sum_{i=1}^{j} \exp(-\alpha(t - t_i)), \quad (16)$$

$$s(t) = s_0 \exp(-\beta(t - t_0)) + c_0 t(t - t_0) + \sum_{i=1}^{j} t(t - t_i). \quad (17)$$

For the final intake, that is if $j = N$, solutions (16) and (17) are valid for any $t \geq t_0 + TN$. They also represent the corresponding time functions after the drug addict stops consuming permanently.

An even more realistic case is obtained by generalizing the final intake. Under normal circumstances, the drug taker takes a constant $M_0$ dose $N_0$ times, with a frequency of $T_0 > 0$, for a period of duration $N_0T_0$. In a second subsequent period of $N_1T_1$ duration, the drug taker consumes a constant $M_1$ dose which is equal to or greater than the former with a lower consumption frequency ($T_1 < T_0$). Then he/she continues with a similar consumption pattern for $n$ different periods of $N_jT_j$ duration, with $M_j \geq M_{j+1}$ and $T_j < T_{j+1}$, $j = 0, 1, 2, \ldots, n - 1, n > 0$. This way, the drug taker will improve the agreeable effects of the first intakes during a first phase (the sensitization phase), although he/she will unsuccessfully attempt to reproduce these first phase agreeable effects at a second phase. At the habituation phase, the drug taker will even notice a progressive worsening of such effects in relation to the first phase. Finally, this individual will become an addict after a period of $N_nT_n$ duration, during which he or she will hardly reproduce any agreeable effect no matter how much the dose or frequency is increased.

Let us thus assume that we are in period $j = 0, 1, \ldots, n - 1$, characterized by a number $N_j$ of intakes, with a $T_j$ frequency and constant $M_j$ doses. Let us consider any arbitrary $i_j$ consumption in this period ($i_j = 1, 2, \ldots, N_j$). Suppose we have defined $H_{j-1}$, the time which has elapsed from $t_0$ to the beginning of period $j$:

$$H_{j-1} = \begin{cases} 
0 & j = 0, \\
\sum_{r=0}^{j-1} N_rT_r & j > 0.
\end{cases} \quad (18)$$

Then the time functions $c(t)$ and $s(t)$ for $t \in [t_0 + H_{j-1} + i_jT_j, t_0 + H_{j-1} + (i_j + 1)T_j]$ will be expressed as

$$c(t) = c_0 \exp(-\alpha(t - t_0)) + \sum_{k=0}^{j} M_k \sum_{i_k=0}^{i_j} \exp(-\alpha(t - i_kT_k - H_{k-1} - t_0)), \quad (19)$$

$$s(t) = s_0 \exp(-\beta(t - t_0)) + c_0 t(t - t_0) + \sum_{k=0}^{j} M_k \sum_{i_k=0}^{i_j} t(t - i_kT_k - H_{k-1} - t_0). \quad (20)$$

For the final intake (if $j = n - 1$ and $i_{n-1} = N_{n-1}$), solutions (19) and (20) are valid for any $t \geq t_0 + \sum_{j=0}^{n-1} T_jN_j$, and represent the corresponding time functions after the drug taker, now considered an addict, stops consuming permanently (the return phase).
3. The dynamic addiction module

The UPTT asserts that the stress system is the biological basis for the unique trait extraversion. Let the *activation level* variable and the *extraversion* variable be the dynamic variables representative of extraversion as a trait. Both variables are measured on the hedonic scale. (The ranges assumed for these and other variables of the model are shown in Table 1.) Why two variables and not one? Because each plays its own role at

<table>
<thead>
<tr>
<th>Parameters, input variables, and output variables</th>
<th>Value attributed to characteristics of</th>
<th>Symbol</th>
<th>Dimensions</th>
<th>Range (assumed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug unit dose</td>
<td>Individual</td>
<td>$M$</td>
<td>$M$</td>
<td>[0,120]</td>
</tr>
<tr>
<td>Resistance time</td>
<td>Drug and individual</td>
<td>$t_0$</td>
<td>$T$</td>
<td>[0,10^5]</td>
</tr>
<tr>
<td>Delay reducing rate</td>
<td>Drug and individual</td>
<td>$\varphi$</td>
<td>$T^{-1}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Absorption rate constant</td>
<td>Drug and individual</td>
<td>$\alpha$</td>
<td>$T^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Elimination rate constant</td>
<td>Drug and individual</td>
<td>$\beta$</td>
<td>$T^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Tonic or basal activation level</td>
<td>Individual</td>
<td>$b$</td>
<td>AU</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Homeostatic control rate</td>
<td>Drug and individual</td>
<td>$a$</td>
<td>$T^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Rate of increase of the excitation effect power</td>
<td>Drug and individual</td>
<td>$\delta$</td>
<td>$T^{-1}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Rate of decrease of the excitation effect power</td>
<td>Drug and individual</td>
<td>$\epsilon$</td>
<td>AU^{-1}T^{-2}M^{-2}</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Rate of increase of the inhibitor effect power</td>
<td>Drug and individual</td>
<td>$\eta$</td>
<td>$T^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Rate of decrease of the inhibitor effect power</td>
<td>Drug and individual</td>
<td>$\iota$</td>
<td>$T^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Consumption rate</td>
<td>Individual decision</td>
<td>$A(t)$</td>
<td>$MT^{-1}$</td>
<td>[0,1500]</td>
</tr>
<tr>
<td>Absorption rate</td>
<td>Equations</td>
<td>$C(t)$</td>
<td>$MT^{-1}$</td>
<td>[0,1500]</td>
</tr>
<tr>
<td>Ingested and non-absorbed drug</td>
<td>Equations, individual decision</td>
<td>$c(t), c_0$</td>
<td>$M$</td>
<td>[0,1500]</td>
</tr>
<tr>
<td>Elimination rate</td>
<td>Equations</td>
<td>$R(t)$</td>
<td>$MT^{-1}$</td>
<td>[0,1500]</td>
</tr>
<tr>
<td>Drug level in the body</td>
<td>Equations, initial value</td>
<td>$s(t), s_0$</td>
<td>$M$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Activator effect</td>
<td>Equations</td>
<td>$S(t)$</td>
<td>$M$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Homeostatic control</td>
<td>Equations</td>
<td>$B(t)$</td>
<td>AU^{-1}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Excitation effect</td>
<td>Equations</td>
<td>$X(t)$</td>
<td>AU^{-1}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Inhibitor effect</td>
<td>Equations</td>
<td>$D(t)$</td>
<td>AU^{-1}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Excitation–inhibitor balance</td>
<td>Equations</td>
<td>$X(t) - D(t)$</td>
<td>AU^{-1}</td>
<td>[−10, 10]</td>
</tr>
<tr>
<td>Activation level</td>
<td>Equations, initial value</td>
<td>$y(t), y_0$</td>
<td>AU</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Extraversion</td>
<td>Equations</td>
<td>$E(t)$</td>
<td>AU</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Increase of the excitation effect power</td>
<td>Equations</td>
<td>$IP(t)$</td>
<td>AU M^{-1}T^{-2}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Reduction of the excitation effect power</td>
<td>Equations</td>
<td>$RP(t)$</td>
<td>AU^{-1}M^{-1}T^{-2}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Excitation effect power</td>
<td>Equations, initial value</td>
<td>$p(t), p_0$</td>
<td>AU^{-1}T^{-1}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Delay</td>
<td>Equations, initial value</td>
<td>$\tau(t), \tau_0$</td>
<td>$T$</td>
<td>[0,50]</td>
</tr>
<tr>
<td>Increase of the inhibitor effect power</td>
<td>Equations</td>
<td>$IQ(t)$</td>
<td>AU^{-1}M^{-1}T^{-2}</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Reduction of the inhibitor effect power</td>
<td>Equations</td>
<td>$RQ(t)$</td>
<td>AU^{-1}M^{-1}T^{-2}</td>
<td>[0,20]</td>
</tr>
</tbody>
</table>

*Note.* AU, activation units on the hedonic scale; M, drug unit dose; T, time.
each time scale: the activation level on the short-term time scale (typical of the acute effect of a drug unit dose), and extraversion on the long-term time scale (typical of addiction), although both are involved in the dynamics of the two time scales. Biologically, the activation level variable represents the instantaneous state of the brain (on the hedonic scale). The extraversion variable is defined as the mean value, at each time instant, of the activation level variable, and thus has a cumulative sense. In other words, the extraversion variable is interpreted here as the ‘mean perception’ of the activation level over time. In addition, the extraversion variable, thus defined, behaves by the UPTT for the extraversion dynamics as expected.

The UPTT states the existence of a genetic extraversion particular to each individual that characterizes his or her natural personality, in the absence of any stimuli that can change it. To put it quantitatively, the activation level variable must have a value that is a steady state. This steady state is the so-called tonic (or basal) activation level. Due to the definition of the extraversion variable as the mean value that takes into account all the past history at each time instant of the activation level variable, the tonic level is also a steady state of the extraversion variable.

Given that two variables are defined as mean instantaneous values that take into account all the corresponding past history (the extraversion variable and the activator effect presented below), let \( \langle z(t) \rangle \) be an arbitrary mean value of a generic \( z(t) \) variable. This is given by

\[
\langle z(t) \rangle = \lim_{t_m \to +\infty} \frac{1}{t + t_m} \int_{-t_m}^{t} z(x) \, dx. \tag{21}
\]

In equation (21), \( t_m \) is called the memory time and, although theoretically it recovers all the history of the \( z(t) \) variable, in practice it is represented by a finite value (the value \( t_m = 1 \) year has been obtained as a result of the calibration of the model). In addition, if \( t_0 \) is the initial time, the values that \( z(t) \) takes before this time depend on its own nature. If \( z(t) \) is the mean value of the amount of drug in the blood (the activator effect), \( z(t < t_0) \) will be zero, because we assume that the individual has never consumed cocaine before, and he/she does not have any history of cocaine in blood. If \( z(t) \) is the mean value of the activation level (the extraversion variable), \( z(t < t_0) \) will be its tonic value, because we assume that the individual has never consumed cocaine or other drugs before, and its activation level remains around its tonic level. From a physiological point of view, our hypothesis is that the finite value given to \( t_m \) represents the time that brain recalls when faced with the effects of new drug unit doses. This is why we have named \( t_m \) the memory time.

Let \( y(t) \) be the activation level, such that \( t \in [t_0, +\infty[ \), and let \( y(t_0) = y_0 \) be its initial condition, i.e. the activation level prior to the stimulus produced by the first stimulant drug unit dose. Therefore, the extraversion, \( E(t) \), is defined according to (21) as \( E(t) = \langle y(t) \rangle \), with \( y(t) = b \) when \( t < t_0 \) and \( b > 0 \) the tonic level of \( y(t) \).

The UPTT states that extraversion can vary with time due to the effect of drug consumption. The variation of extraversion with time as a consequence of drug stimulus is examined here by studying the flows that influence the derivative of the activation level variable with respect to time. Three flows have been considered (Amigó et al., 2008) in the variation process of the activation level once a stimulus is produced: the excitation effect, \( X(t) \), considered as a growth flow; the inhibitor
effect, $D(t)$, considered as a reducing flow; and the homeostatic control, $B(t)$, considered as a neutral flow. We have

$$\frac{dy(t)}{dt} = B(t) + X(t) - D(t),$$

$y(t_0) = y_0.$

Following the UPTT, the dynamics of extraversion depends on its genetic value, that is, on the tonic level. Let $b > 0$ be the parameter that represents it. Its value on the hedonic scale depends on each individual's biology, and it determines the individual's personality in the absence of drug use. Furthermore, the initial value of the activation level $y_0$ must coincide with the tonic level $b$ in repose conditions, or in the absence of stimuli that are specific to a substantial change of the brain's state. The dependence on the tonic level is present in our approach in the mathematical structure of the homeostatic control:

$$B(t) = a(b - y(t)).$$

Equation (23) has been taken directly from Grossberg (2000). Its mathematical structure shows that, in the absence of the other two flows, a small variation of $y(t)$ in (22) with respect to the tonic level $y = b$ produces a response that tends asymptotically to the steady state. Thus, in absence of the other two flows, the tonic level behaves as a real steady state. However, we observe in the simulations that, also in the presence of the other flows, the tonic level behaves as a steady state. In (23), the positive parameter $a$, known as the homeostatic control rate, depends on each individual's biological characteristics, exactly as the $b$ value does.

In relation to the excitation effect, we assume the following functional dependence:

$$X(t) = \frac{p(t)s(t)}{E(t)}.$$

In (24), $s(t)$ is the stimulus, the drug level in the body obtained in (20). The $p(t)$ variable is called the excitation effect power. Therefore, on the one hand, we are assuming that the excitation effect is directly proportional to the stimulus, with $p(t)$ as proportionality variable, since the greater the stimulus, the greater the excitation. On the other hand, the inverse dependence of $X(t)$ on $E(t)$ in (24) must be explained. On the short-term time scale, the most representative variable of extraversion is the activation level. The dynamics of this time scale has to be reproduced, i.e. if the effects on the activation level have to be higher for smaller values of the tonic level and vice versa then an inverse dependence on the tonic level should occur. That could be explained from the tonic/phasic model of the dopamine regulation system (Grace, 1995, 2000). Thus, the functional dependence should be $X(t) = p(t)s(t)/b$. Nevertheless, the real activation after some drug unit doses is not given by the genetic activation, but by the mean activation $E(t)$, and then (24) holds.

The time-dependence of the proportionality variable, the excitation effect power $p(t)$, must also be explained. We suppose that the variation with time of $p(t)$ depends on two flows: IP$(t)$, or increase of the excitation effect power; and RP$(t)$, or reduction
of the excitation effect power, expressed as

\[ \frac{dp(t)}{dt} = IP(t) - RP(t), \]
\[ p(t_0) = p_0. \] (25)

The initial value \( p_0 \) should depend on each individual’s biology. On the other hand, and in order to model sensitization, \( IP(t) \) has been considered to be proportional to the so-called activator effect \( S(t) \), defined as the mean instantaneous value of the drug level in the body. So, \( IP(t) \) and \( S(t) \) would be

\[ IP(t) = \gamma S(t), \]
\[ S(t) = s(t), \]
\[ S(t) = s(t) = 0, \quad t < t_0, \] (26)

where \( \gamma \) is the elevating rate of the excitation effect power. Otherwise, \( RP(t) \) is assumed proportional to \( p(t) \), which means it loses part of the excitation effect power at each instant, contributing to model the habituation phase:

\[ RP(t) = \delta p(t), \] (27)

where \( \delta \) is the reducing rate of the excitation effect power. If we substitute (26) and (27) in (25), we obtain

\[ \frac{dp(t)}{dt} = \gamma S(t) - \delta p(t), \]
\[ p(t_0) = p_0. \] (28)

Both \( \gamma \) and \( \delta \) are parameters whose values also depend on the biology of each individual. The previous assumptions are based on well-known genetic regulation mechanisms. Thus, \( p(t) \) would represent the number of D1, AMPA, and NMDA synaptic receptors, the increase of such receptors \( IP \) is proportional to the activator effect \( S \) (comparable with dopamine and glutamate, which increase is a consequence of the average drug level in the body), the decrease of such receptors \( RP \) comes from feedback loops implying the regulator genes Fos and GluR2 among others. The delays implied in the starting of such mechanisms are represented in the model by \( t(t) \) and \( t_m \). (See, for instance, Beretta et al., 1992; Hyman, 1996; Torres & Rivier, 1993; Young et al., 1991).

For the inhibitor effect, \( D(t) \), we assume the following functional dependence:

\[ D(t) = \begin{cases} 
q(t)E(t - \tau(t))s(t - \tau(t))y(t - \tau(t)) & t > t_0 + \tau(t), \\
0 & t \leq t_0 + \tau(t). 
\end{cases} \] (29)

Equation (29) is a generalization of the equation proposed by Grossberg (2000), which supposes that the inhibitor effect \( D(t) \) is equal to the product of the drug level in the body \( s(t) \) and the activation level \( y(t) \). Note that our proposal is more complex. We have considered the inhibitor effect \( D(t) \) to be directly proportional to the product of the mean activation \( E(t) \), the activation level \( y(t) \), and the drug level in the body \( s(t) \). The proportionality variable, \( q(t) \), is called the inhibitor effect power. In addition,
the functional dependence of the inhibitor effect appears with a delay variable, $\tau(t)$, such as the opposing process theory by Solomon and Corbit (1974) proposes.

The reason for introducing the direct mean activation dependence is similar to the reason used in the excitation effect case: following the UPTT, if the effects on the activation level have to be higher for smaller values of the tonic level and vice versa, a direct dependence on the tonic level should occur. Thus, in the present case, the functional dependence should be $D(t) = q(t)b(t)s(t)(t)$. Nevertheless, the real activation after some drug unit doses is not given by the genetic activation $b$, but by the mean activation $E(t)$, so that $D(t) = q(t)E(t)s(t)(t)$. This assumption lends stronger support to the mathematical role of the memory time, $t_m$: again, $t_m$ allows $E(t)$ to behave as the tonic activation $b$ does in the first intake. Furthermore, in the context of the opposing process theory of Solomon and Corbit (1974), the inhibitor effect appears with a delay after a drug unit dose. Biologically, this delay represents the time that long-term regulator genes need to produce regulation effects and it may differ from person to person (Nestler, 2001). This delay, $t(t)$, is a variable that depends on time because we assume that it depends on the mean amount of drug present in plasma in each instant, i.e. on the activator effect $S(t)$. If we consider this delay in the time-dependence on $E(t)$, $s(t)$, and $y(t)$ then equation (29) holds.

The variation of the delay variable with time must be such that, on the one hand, it remains equal to its initial value, $t_0$, while the activator effect is close to zero, and, on the other hand, for very high values of the activator effect (i.e. after many repeated intakes) it tends to zero. This last idea is taken from Solomon and Corbit (1974), and states that one way in which the organism becomes accustomed to drug consumption is by responding earlier with the inhibitor effect after each drug unit dose. An equation which provides this dynamics for $t(t)$ is

$$t(t) = t_0 \exp(-O(t)), \quad (30)$$

where $O$ is the delay reducing rate. Both parameters, $t_0$ and $O$, depend on the biology of each individual.

The time-dependence of the proportionality variable, the inhibitor effect power $q(t)$, must be also explained. Variation with time of $q(t)$ has been considered to depend on two flows: IQ($t$), or increasing inhibitor effect power, and RQ($t$), or reducing inhibitor effect power. In addition, because it is involved in the computation of the inhibitor effect, its effects have been considered to take place with a delay, that is, from the time value $t_0 + \tau(t)$, which leads to

$$\frac{dq(t)}{dt} = IQ(t) - RQ(t),$$

$$q(t) = q_0, \quad t \leq t_0 + \tau_0. \quad (31)$$

The initial value $q_0$ will depend on each individual’s biology. IQ($t$) has been considered to be proportional to the delayed activator effect, that is

$$IQ(t) = \varepsilon S(t - \tau(t)), \quad (32)$$

where $\varepsilon$ has been called the elevating rate of the inhibitor effect power, and in coherence with equation (21), $\langle S(t - \tau(t)) \rangle = \langle S(t - \tau(t)) \rangle$. 

462 Antonio Caselles et al.
On the other hand, RQ(t), which contributes to the model for the return phase, is considered to be proportional to \( q(t) \), that is, it loses a part of the inhibitor effect power at each instant

\[
RQ(t) = \eta q(t),
\]

where \( \eta \) is the reducing rate of the inhibitor effect power. Both \( \varepsilon \) and \( \eta \) are parameters whose values depend also on the biology of each individual. The previous assumptions are also based on the well-known gene regulation mechanisms, some of them already considered in equation (28). Biologically, \( q(t) \) would be represented by the gene products FosB, ΔfosB, 33 kDa, ΔfosB, 35–37 kDa; these are the technical names of some proteins and genes implied in the referred regulation processes. To describe the function of each one is beyond the scope of the paper; (for instance, see Colby et al., 2003; Hiroi et al., 1998; Werme et al., 2002). If we substitute (32) and (33) in (31), we obtain

\[
\frac{dq(t)}{dt} = \frac{1}{2h}q(t)^2,
\]

\[
q(t) = q_0, \quad t \not\in [t_0 + \tau_0],
\]

Equation (35) is a non-linear delayed integro-differential equation which reproduces the activation level dynamics measured on the hedonic scale as a representative variable of the global brain state of an individual submitted to repeated stimulant drug unit doses. This equation, along with the differential equations (28) and (34), and with the extraversion variable and the activator effect variable, provides the desired dynamic addiction model, which we have called DBRAIN. The hydrodynamic diagram of this model may be seen in Figure 2, and represents the structure of the relations among all its variables. The names, dimensions and symbols of these variables are shown in Table 1.

Now, let us see how the model of Amigó et al. (2008) can be derived as a particular case of the model presented in this paper. This is done by introducing the following restrictions in the model:

1. Only one drug unit dose is considered; thus, (19) and (20) become

\[
c(t) = c_0 \exp(-\alpha(t - t_0)),
\]

\[
s(t) = s_0 \exp(-\beta(t - t_0)) + c_0 \tau(t - t_0).
\]

2. Extraversion, excitation effect power, inhibitor effect power, and delay variables are assumed constant:

\[
E(t) = b, \quad p(t) = p_0, \quad q(t) = q_0, \quad \tau(t) = \tau_0.
\]
If the results (36), (37), and (38) are inserted in (35), the outcome is:

$$\frac{dy(t)}{dt} = \begin{cases} 
  a(b - y(t)) + \frac{p_0 s(t)}{b} & t_0 < t \leq t_0 + \tau_0, \\
  a(b - y(t)) + \frac{p_0 s(t)}{b} - q_0 b s(t - \tau_0)y(t - \tau_0)y(t_0) = y_0 & t > t_0 + \tau_0. 
\end{cases} \quad (39)$$

The delay differential equation (39) along with (37) has an analytical solution and describes the dynamics of the activation level, such as Grossberg (2000) and Solomon and Corbit (1974) previewed; see Amigó et al. (2008) for these results. In addition,
the simulations on the short-term time scale, typical of the acute effect of each intake, reproduce similar results for the activation level dynamics to those obtained by Amigó et al. (2008). The comparison of both models provides a theoretical confirmation of the outcomes provided herein.

4. Simulations performed with the DBRAIN model

The system of coupled differential equations (28), (34), and (35) completed with (15), or by (20) (depending on the considered intake pattern) to calculate the concentration of the drug in the blood after the last drug intake, does not have a complete analytical solution (that is, for all the variables). For this purpose, results are obtained by an approximation to finite differences programmed in the Visual Basic language in the environment provided by the expert SIGEM system designed by Caselles (1992, 1993, 1994).

The characteristics of the simulations to be performed are the same as those considered by Amigó et al. (2008), namely:

(1) Cocaine is assumed to be consumed intranasally (sniffed).
(2) The time unit for computation is the minute. A week has 10,080 min. In the context of these simulations, a ‘month’ has 4 weeks (40,320 min) and a ‘year’ has 13 months. Within a given month, cocaine intake is assumed to have constant frequency and elapsed time. A week before consuming is computed in all simulations in order to present the graphics in a clearer manner.
(3) The measurement units for the activation level and the extraversion variables are the ‘activation units’ (AU) on a psychological hedonic scale \([a, b]\). In future research, with this scale, the model can be verified experimentally using data obtained from questionnaires filled by experimental subjects.
(4) The model has been calibrated using the hedonic scale \([0, 20]\). The formula to convert the model outcomes into outcomes belonging to another arbitrary hedonic scale \([b, k]\) is \(x = (k - b)y/20 + b\), where \(y \in [0, 20]\) and \(x \in [b, k]\).
(5) On the \([0, 20]\) scale, the tonic activation level \(b = 10.0\) AU corresponds to an ambiverted individual. The values of \(b\) situated close to the minimum of this scale correspond to the most extraverted individuals. A zero or negative value of the activation level \(y\) would represent the collapse of the individual. The values of \(b\) situated close to the maximum on this scale correspond to the most introverted individuals. Nevertheless, this maximum can be exceeded by the model results in some simulations. Such results would correspond to extreme cases such as cocaine binges. For these extreme cases, the values exceeding the maximum have to be considered as being equal to the maximum value when the model is verified using a hedonic scale.
(6) The values of the parameters in the calibrated model, as well as estimated ranges of possible values, are shown in Table 2. The value of \(\beta = 0.013\) min\(^{-1}\) (elimination rate) is estimated from data in Winhusen et al. (2006; 0.014 ± 0.001 min\(^{-1}\) for 20 mg injected and 0.012 ± 0.002 min\(^{-1}\) for 40 mg injected). The value of \(\alpha = 0.059\) min\(^{-1}\) (distribution rate) is estimated from data in Jeffcoat, Perez-Reyes, Hill, Sadler, and Cook (1989; 11.7 min half-life for intranasal cocaine).
Cocaine intake ($M$) is measured in milligrams. A common cocaine unit for abusers may be between 10 and 120 mg and a cocaine line may contain between 10 and 30 mg (Kleankids page). Thus, we will consider it to vary in the range [0, 120].

Three typical personalities have been considered, distinguished by the corresponding value of $b_{\frac{1}{2}} = 0.13$; 20, the tonic activation level value (while the other parameter values remain constant and equal to the calibrated values, provided by Table 2): the extraverted personality (with $b = 7.0$ AU or $b = 5.0$ AU for binge simulations), the ambiverted personality (with $b = 10.0$ AU), and the introverted personality (with $b = 13.0$ AU or $b = 15.0$ AU to simulate the individual collapse). The value provided for the initial activation level – for all the simulations carried out – is the same as that given to the tonic level. This means that the individual starts his/her addiction process in rest conditions and not influenced by other stimulants.

The goals of the simulations are as follows:

1. To demonstrate that the model predicts the three phases of sensitization, habituation, and return (Simulations 1-1, 1-2, 1-3, 1-4, 1-5).
2. To show the co-influence between personality and addiction, that is, to show how personality influences the addiction process and how the addiction process influences personality (Simulations 2-1, 2-2, 2-3).

### Table 2. Parameters and values taken for the calibrated model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Units</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug unit dose</td>
<td>$M$</td>
<td>30 mg</td>
<td>mg</td>
<td>[0,120]</td>
</tr>
<tr>
<td>Memory time</td>
<td>$t_m$</td>
<td>$10.080 \times 4 \times 13$ min (a year)</td>
<td>min</td>
<td>[0,105]</td>
</tr>
<tr>
<td>Initial delay</td>
<td>$\tau_0$</td>
<td>30 min</td>
<td>min</td>
<td>[0,50]</td>
</tr>
<tr>
<td>Reducing delay rate</td>
<td>$\varphi$</td>
<td>15 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Initial drug level in the body</td>
<td>$s_0$</td>
<td>0 units</td>
<td>mg</td>
<td>[0,1500]</td>
</tr>
<tr>
<td>Absorption rate constant</td>
<td>$\alpha$</td>
<td>0.059 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Elimination rate constant</td>
<td>$\beta$</td>
<td>0.013 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Tonic or basal activation level</td>
<td>$b$</td>
<td>5, 7, 10, 13, 15 AU</td>
<td>AU</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Initial activation level</td>
<td>$y_0$</td>
<td>5, 7, 10, 13, 15 AU</td>
<td>AU</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Homeostatic control rate</td>
<td>$a$</td>
<td>0.001 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Initial excitation effect power</td>
<td>$p_0$</td>
<td>10 AU$^2$ min$^{-1}$ mg$^{-1}$</td>
<td>AU$^2$ min$^{-1}$ mg$^{-1}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Increasing rate of the excitation effect power</td>
<td>$\gamma$</td>
<td>9.0 AU$^2$ min$^{-2}$ mg$^{-2}$</td>
<td>AU$^2$ min$^{-2}$ mg$^{-2}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Reducing rate of the excitation effect power</td>
<td>$\delta$</td>
<td>1.5 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,20]</td>
</tr>
<tr>
<td>Initial inhibitor effect power</td>
<td>$q_0$</td>
<td>0.000001 AU$^{-1}$</td>
<td>AU$^{-1}$ min$^{-1}$ M$^{-1}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Increasing rate of the inhibitor effect power</td>
<td>$\epsilon$</td>
<td>0.0000001 AU$^{-1}$</td>
<td>AU$^{-1}$ min$^{-2}$ mg$^{-2}$</td>
<td>[0,1]</td>
</tr>
<tr>
<td>Reducing rate of the inhibitor effect power</td>
<td>$\eta$</td>
<td>0.00001 min$^{-1}$</td>
<td>min$^{-1}$</td>
<td>[0,1]</td>
</tr>
</tbody>
</table>

Note. AU: activation units on the hedonic scale.

(7) Cocaine intake ($M$) is measured in milligrams. A common cocaine unit for abusers may be between 10 and 120 mg and a cocaine line may contain between 10 and 30 mg (Kleankids page). Thus, we will consider it to vary in the range [0, 120].

(8) Three typical personalities have been considered, distinguished by the corresponding value of $b \in [0, 20]$, the tonic activation level value (while the other parameter values remain constant and equal to the calibrated values, provided by Table 2): the extraverted personality (with $b = 7.0$ AU or $b = 5.0$ AU for binge simulations), the ambiverted personality (with $b = 10.0$ AU), and the introverted personality (with $b = 13.0$ AU or $b = 15.0$ AU to simulate the individual collapse). The value provided for the initial activation level – for all the simulations carried out – is the same as that given to the tonic level. This means that the individual starts his/her addiction process in rest conditions and not influenced by other stimulants.
(3) To show that the short-term dynamics of the addiction process in its different phases (Simulations 3-1, 3-2, 3-3) are the same as forecast by Amigo et al. (2008), Grossberg (2000), and Solomon and Corbit (1974).

(4) To suggest a possible use of the model to determine the way to conduct the return phase (controlling dose and elapsed time between doses) in order that the addict reaches a comfortable state (Simulations 4-1, 4-2). Observe that we do not attempt to return the addict to his/her tonic level. The tonic level can represent either an impulsive state that would return the extraverted individual to consumption, or an anxious state that would close the introverted individual to new experiences representative of happiness.

We now describe the simulations and the conclusions that can be obtained from them.

### 4.1. Simulation 1-1: Constant intake and frequency

The three phases of sensitization, habituation, and return take place. This non-realistic simulation is performed in order to check that the model reproduces the three phases independently of possible variations of dose and frequency. An ambiverted individual with a constant drug unit dose ($M = 30.0 \text{ mg}$) and a constant elapsed time between intakes (every 10,080 min, i.e. once a week), for 1 year, is simulated. Observe in Figure 3 that after a short period where the sensitization and habituation phases - for both activation level and extraversion variables - are quickly reached, a long period with an approximately oscillating effect around the tonic level follows, ending with the return phase.

Simulation 1-1 was carried out to demonstrate that the model presented here can reproduce the same phases as, on one hand, the model of Gutkin et al. (2006) reproduces for the nicotine addiction process, and on the other hand, the model of Amigo et al. (2008) reproduces for the phasic response of a unique intake of cocaine. Simulation 1-2 considers a more suitable consumption pattern for a person who may become an addict, likewise reproducing the three phases.

### 4.2. Simulation 1-2: A realistic addiction process

Simulations 1-2, 1-3, and 1-4 represent the three common consumption patterns (the diary pattern, the episodic pattern, and the combined pattern) described by American Psychiatric Association (2000). Doses and frequencies are obtained from the

![Figure 3](image-url). Activation level (left) and extraversion (right) versus time for Simulation 1-1, for an ambivert ($b = y_0 = 10.0 \text{ AU}$).
clinical experience of the authors in the Drug Detoxification Centre (Centro de Desintoxicación de Drogas) of Bétera (Valencia, Spain) and from the literature (for a review, see Goudie & Emmett-Oglesby, 1991). The probable addiction process for an ambiverted individual over a period of 13 months may be the following: constant drug unit doses of 30 mg, with equally time elapsed frequencies of 4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10 times each month. This consumption pattern is more realistic than the consumption pattern of Simulation 1-1 because an increase in frequencies is observed in addicts and, on the other hand, the final frequency can be related to the financial limitations of the consumer. Observe in Figure 4 that this consumption pattern reproduces the sensitization, habituation, and return phases more clearly than that obtained in Simulation 1-1. Such phases are observed both in the activation level variable and in the average perception represented by the extraversion variable.

4.3. Simulation 1-3: Weekend binges
An extraverted individual binges on cocaine on Saturday nights between midnight and noon. An extreme extraverted personality \( b = 5.0 \text{ AU} \) is considered in this simulation because he/she has more inclination to binges (Amigó et al., 2008). He/she consumes 30 mg of cocaine every two hours (amount related to what he/she can afford), that is, six times in 12 h, and non-consumption for the rest of the week, for a year, plus a week of non-consumption after the last binge. Figure 5 shows that this consumption pattern reproduces the sensitization, habituation, and return phases. Observe that, with binge consumption, the maximum of the scale can be exceeded, and the short time responses are higher than the ones provided by Simulations 1-1 and 1-2. In addition, the individual’s personality, characterized by the extraversion variable, undergoes a great change.

Figure 4. Activation level (left) and extraversion (right) versus time for Simulation 1-2, for an ambivert \( b = y_0 = 10.0 \text{AU} \).

Figure 5. Activation level with all outcomes (left), activation level on the [0,20] scale (middle), and extraversion (right) versus time for Simulation 1-3, for an extreme extrovert \( b = y_0 = 5.0 \text{AU} \).
4.4. Simulation 1-4: Weekend binges plus regular consumption pattern

The consumption pattern of weekend binges is the same as in Simulation 1-3, but the individual regularly once a week takes an additional 30 mg. Figure 6 shows that this consumption pattern reproduces the sensitization, habituation, and return phases. As in Simulation 1-3, the maximum of the scale can be exceeded and, the short time responses are higher than those provided by Simulation 1-3 due to the additional consumption during the week. Besides, the individual’s personality, characterized by the extraversion variable, undergoes a great change.

4.5. Simulation 1-5: A consumption pattern leading to collapse

The consumption pattern of an introverted individual considered in Simulation 1-2 is used to study the possibility of individual collapse (i.e. he/she either suffers a coma or dies). The collapse can be observed in an extreme introvert ($b = 15$ AU) approximately 3 months, 3 weeks, and 1 day after starting the consumption pattern (without stopping the supply of drug). The conclusion of this simulation is the equivalence between an extreme individual’s introversion and an extreme consumption pattern. The collapse (see Figure 7) is represented by the fall to zero of the activation level variable (observe that the model continues to run, in spite of collapse, until the simulation time ends; that is an option in the modelling process).

The general conclusions from Simulations 1-1 to 1-5 are that the model reproduces the three phases of sensitization, habituation, and return, firstly, when the consumption pattern is characterized by a constant drug unit dose and a constant elapsed time between intakes (Simulation 1-1); secondly, with a more realistic

---

Figure 6. Activation level with all outcomes (left), activation level in the [0, 20] scale (middle) and extraversion (right) versus time for Simulation 1-4, for an extreme extrovert ($b = y_0 = 5.0$ AU).

Figure 7. Activation level (left) and extraversion (right) versus time for Simulation 1-5, for an introvert ($b = y_0 = 15.0$ AU).
consumption pattern characterized by a progressive increase in drug doses and frequencies until reaching a physiologically limit constant dose (Simulation 1-2); and, finally, with two patterns of binging (Simulations 1-3 and 1-4). The model also predicts that a common consumption pattern in an extreme introvert drives the individual to collapse (Simulation 1-5).

4.6. Simulation 2-1: Personality and addiction, the extravert case
Let us suppose that an extraverted individual \(b = y_0 = 7.0\) AU becomes addicted by following the consumption pattern of Simulation 1-2 for 13 months, with a constant intake of 30 mg. Let us also suppose that the consumer stops consumption for a year. The development of the activation level and the extraversion is shown in Figure 8. Observe the three phases of sensitization, habituation, and return (especially the part of the last phase after the abandonment of consumption) for the activation level variable. The dynamics of this variable shows that no values below the tonic level are observed. Nevertheless, the dynamics of the extraversion variable shows a slow tendency to its tonic level (which should come as no surprise because it is an average).

4.7. Simulation 2-2: Personality and addiction, the ambivert case
Let us consider an ambiverted individual \(b = y_0 = 10.0\) AU consuming cocaine for a year with the same consumption pattern considered in Simulation 2-1, also with a second
year without consumption. Figure 9 reproduces the three phases of sensitization, habituation, and return (especially after the abandonment of consumption) for the activation level variable. The dynamics of this variable shows that the maximum increase of the sensitization phase with respect to its tonic value is not as high as for an extraverted individual (Simulation 2-1) and the values below the tonic level are strengthened in this phase. The habituation phase is larger than that for an extraverted individual (Simulation 2-1). Again the dynamics of the extraversion variable shows a very slow tendency to its tonic level.

4.8. Simulation 2-3: Personality and addiction, the introvert case

Let us consider an introverted individual ($b = 13.0$ AU) consuming cocaine for a year with the same consumption pattern as considered for Simulations 2-1 and 2-2, and also a year more without consumption. Figure 10 reproduces the three phases of sensitization, habituation, and return (especially after the abandonment of consumption) for the activation level variable. The dynamics of this variable shows that, for the first dose, the negative effect is greater than the positive effect; the sensitization phase is shorter and smaller than in Simulation 2-2; the habituation phase continues being very large and high under its tonic level but more than in Simulation 2-2. In this case, the dynamics of the extraversion variable shows a large decrease under its tonic level, followed by a slow tendency to the tonic level. The relatively high first dose decrease of activation is due to the negative effects that a stimulant drug produces on an introverted individual. This decrease is not observed in the extraverted and in the ambiverted individuals (Simulations 2-1 and 2-2).

The general conclusion from simulations 2-1, 2-2, and 2-3 is that they show the co-dependence between personality and addiction. On the one hand, the tonic (genetic) activation level – which describes the personality before the addiction process – influences the dynamics of addiction: the lower the tonic (genetic) activation level is, the higher the sensitization phase is (the maximum reached over its tonic level is higher) and the lower the habituation phase is (the minimum reached under its tonic level keeps near its tonic value or is negligible). And vice versa: the higher the tonic (genetic) activation level is, the lower the sensitizing phase is (the maximum reached over its tonic level is lower) and the higher the habituation phase is (the minimum reached under its tonic level reaches points far from its tonic level). These conclusions are similar to those of Amigo et al. (2008) for the dynamic patterns of different individual personalities as a consequence of a single stimulant drug unit dose. Moreover, the addiction process changes the personality of individuals: the addiction process converts extraverts

---

**Figure 10.** Activation level (left) and extraversion (right) versus time for Simulation 2-3, for an introvert ($b = y_0 = 13.0$ AU).
(low tonic or genetic level) into introverts (high mean activation perception given by the extraversion variable) and introverts (high tonic or genetic level) into extraverts (low mean activation perception given by the extraversion variable). Furthermore, this change of personality is characterized by a great inertia: the dynamics of the extraversion variable shows that, when drug consumption stops, this variable tends to recover its tonic (genetic) value very slowly (no surprise, because \( E(t) \) is an average over time). Thus, the new personality of an individual, obtained as a consequence of his/her addiction process, remains different from his/her tonic (genetic) level during an appreciable and long time.

The next three simulations try to detail what happens in the next 100 min following three chosen points of the addiction process that would correspond, respectively, to the sensitization, habituation, and return phases. So, let us consider the case studied in Simulation 1-2 of an ambivert individual \((b = 10.0 \text{ AU})\) and the dynamics of the activation level, \(y(t)\).

4.9. Simulation 3-1: The short-term dynamics following an intake in the sensitization phase

Let us consider a moment of the sensitization phase, for instance the beginning of the third month after starting to consume, when the individual starts to consume every 8,064 min (five times per month). From this moment, the evolution of \(y(t)\) is shown for 100 min in Figure 11 (left).

4.10. Simulation 3-2: The short-term dynamics following an intake in the habituation phase

Let us consider a moment of the habituation phase, for instance the beginning of the seventh month after starting to consume, when the individual starts to consume every 5,760 min (seven times per month). From this moment, the evolution of \(y(t)\) is shown for 100 min in Figure 11 (middle).

4.11. Simulation 3-3: The short-term dynamics following an intake in the return phase

Let us consider a moment of the return phase, for instance the beginning of the 13th month when the individual starts to consume every 4,032 min (10 times per month). From this moment, the evolution of \(y(t)\) is shown for 100 min in Figure 11 (right).

Figure 11. Activation level versus time for Simulations 3-1 (left), 3-2 (middle), and 3-3 (right). These correspond, respectively, to an intake of the sensitization, habituation, and return phases of Simulation 1-2, in an ambivert \((b = y_0 = 10.0 \text{ AU})\).
Observe that the evolution of $y(t)$ is in correspondence with what has been predicted by Amigo et al. (2008), Grossberg (2000), and Solomon and Corbit (1974). A rise in the curve represents the pleasant sensation felt by the consumer, and the part of the curve under the tonic activation level represents the craving sensation. The curve tends finally to recover asymptotically the tonic activation level until the next intake. Observe also that, the more advanced in phase the intake is the lesser the part of the curve over its tonic level is and the greater the part of the curve under its tonic level is. Thus, the more advanced in phase the intake is the lesser the pleasant sensation for the individual is and the greater the unpleasant sensation (craving) is. In other words, in general, the pleasant sensation evolves from more to less and the unpleasant sensation evolves from less to more in the addiction process.

The final two simulations attempt to determine how to manage the return phase, controlling dose, and elapsed time between doses, in order to reach and maintain a comfortable state. Comfortableness means avoiding excessive extroversion or introversion. Excessive extroversion implies impulsiveness towards drug consumption. Excessive introversion implies anxiety and tendency to avoid new experiences. Thus, with the next two simulations, we aim to keep extroverts and introverts as close as possible to ambiversion.

4.12. Simulation 4-1: Trying to conduct extraverts towards ambiversion

This simulation is the result of testing several doses and elapsed times between doses, over a second year, on the extraverted individual of Simulation 2-1, trying to minimize the number of intakes, to maximize the elapsed time between them and to keep the activation level as high as possible. Figure 12 shows the evolution of the activation level and the extraversion in the second year with a dose of 30 mg every 10,080 min, i.e. once per week. Observe that, in spite of the larger elapsed time between doses, the activation level tends to keep a constant dynamic pattern and the extraversion variable tends to keep closer to its maximum value, 7.8 AU (of Simulation 2-1), and thus, closer to the value 10.0 AU corresponding to an ambivert.

4.13. Simulation 4-2: Trying to conduct introverts towards ambiversion

This simulation is the result of testing several doses and elapsed times between doses, for a second year, on the introverted individual of Simulation 2-3, trying to minimize the number of intakes, to maximize the elapsed time between them and to keep the

Figure 12. Activation level (left) and extraversion (right) versus time for Simulation 4-1, for an extravert ($b = y_0 = 7.0 \text{AU}$).
Figure 13 shows the evolution of the activation level and the extraversion in the second year with a dose of 30 mg every 10,080 min, i.e. once per week. Observe that, in spite of the larger elapsed time between doses, the activation level tends to keep a constant dynamic pattern and the extraversion variable tends to decrease under its minimum value 12.25 AU (in Simulation 2-3), and thus, under the value 10.0 AU corresponding to an ambivert.

A conclusion of Simulations 4-1 and 4-2 is that a possible programme of intervention in cocaine misuse is to consider the administration with a lesser dose or a larger elapsed time between doses of the same drug or an alternative drug that, having similar effects to cocaine, minimizes the shock to the organism of the consumer.

5. Discussion

The UPTT presented in this work attempts to integrate personality, the acute effect of drugs and addiction. The main innovating assertions of the UPTT are the consideration of a unique trait of personality, called extraversion, and the existence of a genetic extraversion that influences the dynamic nature of this trait.

A dynamic mathematical model of a stimulant drug addiction (cocaine), based on the UPTT, is presented in this paper. The model has been named DBRAIN. By using DBRAIN it is possible to reproduce, via the simulations performed, the dynamics of extraversion on a short-term time scale, typical of the acute effect of a drug unit dose, and on a long-term time scale, typical of addiction.

DBRAIN has been obtained by following the GMM. The two representative variables of extraversion are: the activation level, which plays a role on the short-term time scale, and the extraversion variable, which plays a role on the long-term time scale. The conclusions of the simulations with DBRAIN involve these two variables. Let us summarize them.

On the one hand, the extraversion variable, typical of addiction, on the long-term time scale changes in time as a consequence of the drug stimulus, leading to the typical phases of sensitization and habituation, and return to the tonic level (the steady state representative of the genetic extraversion) when the individual stops consuming or enters a limited consumption pattern where the dynamic evolution of the activation level tends to be uniform. The dynamics of the extraversion variable allows for the evaluation of an individual's predisposition to drug misuse: extraverts are more predisposed to this misuse than introverts. On the other hand, the dynamics of the activation level variable, typical of the acute effect of a drug unit dose, on the short-term
time scale leads to the first agreeable phase as opposed to the disagreeable or craving phase, which finally tends to vanish as time passes, unless another drug unit dose is taken. The results of the simulations on this time scale show a time pattern for the activation level similar to that obtained by Amigo et al. (2008), Grossberg (2000), and Solomon and Corbit (1974). In short, the time-dependence manner of both activation level and extraversion shows that the sensitization, habituation, and return phases are reproduced on two time scales, although the tendency towards genetic extraversion on the short-term time scale is slower for the extraversion variable than for the activation level.

These simulation results indicate that, on the one hand, the model is an excellent fit to the process of addiction, and, on the other hand, the model can help explain the interaction between personality and addiction. Thus, this model may act as a springboard for latter developments. These developments could include proposals for intervention in addiction processes by considering personality as a significant factor. Let us summarize the outcomes obtained from the simulations performed.

Simulations 1-1 to 1-5 demonstrate that the model predicts the three phases of sensitization, habituation, and return, which the model of Gutkin et al. (2006) reproduces for the nicotine addiction process, and the model of Amigo et al. (2008) reproduces for the phasic response to a unique intake of cocaine.

Simulations 2-1 to 2-3 show the co-influence between personality and addiction. Extraverted individuals, characterized by a low tonic (genetic) activation level, reproduce longer and higher sensitization and habituation phases than introverted individuals, characterized by a high tonic (genetic) activation level. Therefore, an important conclusion obtained from this work by observing the results of these simulations is that high extraversion means a predisposition to stimulant drug intake and abuse, particularly to stimulants such as cocaine.

Simulations 3-1 to 3-3 reproduce, respectively, the short-term time scale dynamics of the three phases of the addiction process, and they prove that their predictions are the same as those forecast by Amigo et al. (2008), Grossberg (2000), and Solomon and Corbit (1974).

Finally, Simulations 4-1 and 4-2 suggest a possible programme of intervention in the addiction process. Assuming robustness of the model with respect to parameters (not yet checked), a drug consumption pattern that tries to minimize the frequency of intakes (or tries to maximize the elapsed time between intakes) has been tested in order to keep the addict away from the extreme values of extraversion. Bear in mind that cocaine can be substituted by an alternative drug that, having the same effects of cocaine, minimizes the shock on the organism of the consumer.

DBRAIN receives indirect experimental confirmation through the corroborations of the theories by Eysenck and Gray, which have been integrated into the UPTT. For example, Gray (1972, 1981, 1982) presents evidence that neuroticism amplifies both extraversion and introversion. In DBRAIN, neurotic extraversion would correspond to the upward curve section at which the extravert’s versus the introvert’s greatest hedonic response to cocaine would be responsible for the sensitization process. This is so because the repeated stimulant drug intake progressively produces an increased internal excitability, the equivalent to an increase of neuroticism. In this way, the neurotic extravert would show a gradually increased response to the drug, and the opposite would occur with the introvert. The downward curve section would represent the neurotic introvert’s response, and therefore the habituation phase, with a decreasing hedonic response to cocaine. Unlike Gray’s theory, these two factors
(neurotic extraversion and neurotic introversion) are clearly related in DBRAIN. Furthermore, the scores corresponding to neurotic extraversion obtained by an individual progressively evolve towards scores in neurotic introversion from a specific stimulation level (frequency and quantity of intake). This is also deduced from a large amount of empirical evidence which, in relation to both theories by Eysenck and Gray, is also presented in the work by De Juan and García (2004). On the other hand, DBRAIN predicts the acquisition process of pathology: addiction, from a personality variable (extraversion) and from a repeated stimulant drug intake. A relation between personality and psychopathology has been confirmed in various studies. Thus, a profile of disorders has been observed from the DSM I-axis (such as anxiety, depression, and substance abuse) and the five-factor model (NEO-FFI, Costa & McCrae, 1992). Therefore, Trull and Sher (1994) obtained the following triad of traits as characteristics of different pathologies, including drug abuse: high neuroticism, introversion, and low concordance. If, as some research work has shown, such as Goldsberg and Rosolack (1994), low concordance and conformity to the five-factor model corresponds to the psychoticism of Eysenck’s model, then we may conclude that it is common practice to find the pattern of both neurotic introversion and high psychoticism in the I-axis clinical disorders. Indeed, psychoticism allows for an explanation of the differences in seriousness among people diagnosed with the same disorder (Rachman & Eysenck, 1978). These same results were found in a Spanish sample from EPQ-R and CAQ (Forns et al., 1998; Sandin et al., 2002), except for externalizing disorders such as psychopathic deviation. This is consistent with Millon’s (1985) opinion that this type of people (diagnosed with an antisocial personality disorder) resists chronic stress, which would be the equivalent to high neuroticism, in accordance with our proposal.

As previously stated, given that the scientific literature insists that those subjects who gain high scores in sensation-seeking and psychoticism (see for example, Kandel, 1978; Rydelius, 1983), who are therefore extraverts according to our criteria, have a greater predisposition to drug abuse, and that an extended pattern of drug abuse is that of neurotic introversion (as seen in Trull & Sher, 1994), it is then thought that addicts have modified their personality (from the extraversion to the introversion pole), which is further indirect empiric evidence in favour of DBRAIN.

DBRAIN suggests and permits important application and development possibilities for future research. For instance, new simulations could explore the stationary values of extraversion obtained with different consumption schedules and different values of the tonic extraversion \( b \), or could explore the stability of the model. Moreover, DBRAIN may prove useful in designing experimental studies which may not only directly confirm the aforementioned predictions (receiving direct experimental confirmation, that is, directly verifying experimentally the model), but also (now using the model) helping in the diagnosis and prognosis of cocaine addicts from knowledge of their activation level (by means of an EEG or a brain image assessment) and their stage of addiction. On the other hand, it may also prove useful, after sensitivity analysis over the parameters, to assay different ways of drug intake (varying parameters) and different stimulant drugs, as well as to design therapies which permit the recovery of optimum activation levels with no drug intake, and also to predict their therapeutic success rates. In short, DBRAIN may be of great use in solving into the profound knowledge of the biological mechanisms involved in addiction, human personality, psychopathology, and integrating all these aspects in a unique comprehension model, which has been our intention in this study.
References


Received 3 April 2008; revised version received 21 July 2009