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Biology and personality: a mathematical approach to the body-mind problem

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Abstract

Purpose – The purpose of this paper is to investigate the body-mind problem from a mathematical *invariance principle* in relation to personality dynamics in the psychological and the biological levels of description.

Design/methodology/approach – The relationship between the two mentioned levels of description is provided by two mathematical models: the *response model* and the *bridge model*. The response model (an integro-differential equation) is capable to reproduce the personality dynamics as a consequence of a determined stimulus. The invariance principle asserts that the response model can reproduce personality dynamics at the two levels of description. The bridge model (a second order partial differential equation) can be deduced as a consequence of this principle: it provides the co-evolution of the General Factor of Personality (GFP) (mind), the c-fos and DRD3 gens, and the glutamate neurotransmitter (body).

Findings – An application case is presented by setting up two experimental designs: a previous pilot AB pseudo-experimental design with one subject and a subsequent ABC experimental design with another subject. The stimulus used is the stimulant drug Methylphenidate (MPD). The response and bridge models are validated with the outcomes of these experiments.

Originality/value – The mathematical approach here presented is based on a holistic personality model developed in the last few years: the Unique Trait Personality Theory, which claims for a single personality trait to understand the overall human personality: the GFP.

***Keywords*:** body-mind problem; general factor of personality; response model; integro-differential equation; bridge model; second order partial differential equation; c-fos; DRD3; glutamate; methylphenidate.

1. Introduction

The objective of this paper is to provide a mathematical approach to the body-mind problem based on a holistic personality model developed in the last few years: the *Unique Trait Personality Theory* (UTPT) [1, 2]. The UTPT claims for a unique trait, as synonymous of single

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trait, to understand the overall human personality. The concept "unique trait" is substituted latter by the equivalent concept of *General Factor of Personality* (GFP) in the reference [2], in order to follow the generally accepted term by the scientific community.

The studies about the central concept of GFP proposed by the UTPT define a new, emergent and novel field inside personality research. It treats about "the single general factor hypothesis" and proposes a general factor of personality within the Big Five Factors (B5F) model (the five factors are: Extraversion, Responsibility, Neuroticism, Openness to Experience and Agreeableness), occupying the GFP the apex of the hierarchy of personality factors [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. The *Five-Adjective Scale of the General Factor of Personality* (GFP-FAS) [14, 15] offers the possibility to measure the dynamical change of the GFP in a single individual, due to its strong correlation with the GFP questionnaire [2]. The GFP-FAS is a dynamically observable instrument to measure the GFP. Such an instrument is essential for validating the here presented dynamical mathematical approach to the body-mind problem.

In addition, the GFP has a physiological base, given by the *general activation* of the stress system (general activation, GA, for short). The GA is also particularly asserted as representing the brain activation level when it is particularized to the GA in brain [2, 16]. Moreover, two kinds of GA can be distinguished depending on the conditions acting on the stress system: the *tonic GA* (the state of the GA in absence of stimuli), and the *phasic GA* (the dynamic response of the GA as a consequence of one or more stimuli). Both the psychological level of description, given by the GFP, and its corresponding physiological level of description, given by the GA, can change along time as a consequence of a stimulus.

The biological level of description has to be taken into account for an overall personality description. This biological level is constituted by the biochemical indicators related to personality and their dynamical interrelationships. The three biochemical indicators considered in this paper are the regulator gens c-fos and DRD3, and the neurotransmitter glutamate. They have been chosen due to their close relationship with personality, such as the following paragraphs try to demonstrate.

The scientific literature shows a close relationship between personality and c-fos expression. Take into account that c-fos expression is considerably increased in the brain's regions involved in the regulation of arousal states; regions such as the locus coeruleus (noradrenergic neurons) and the medial preoptic area (non-GABAergic neurons) [24]. In [22] it is demonstrated that the response model is capable to reproduce the joint dynamics of the immediate-early gen c-fos (body) and the GFP (mind) as a consequence of a Methylphenidate (MPD) dose and suggests the need to deepen into this relationship from a mathematical approach.

There is also a close relationship between personality and DRD3 expression. For instance, DRD3 is considered to play a major role in cognition and emotion [25], in neuropsychiatric diseases [26], and in personality [27]. Furthermore, there is evidence that DRD3 plays a role in addiction mechanisms, such as drug-seeking and drug-taking behavior [28, 29]. In fact, reference [30] demonstrates that the MPD and the self-regulation therapy produces changes in the GFP (mind) and in the DRD3 expression (body), such as it happens in the experimental designs of [2], which brings us again the need to deepen into this relationship from a mathematical approach.

Besides, glutamate is not only a neurotransmitter. Glutamate has regulatory functions in immune-component cells and in nervous system. Glutamate is an indicator of the organism's general state of activation, and thus of the GFP. In fact, the joint dynamics of glutamate and the

GFP has been successfully described with the response model as a consequence of a methylphenidate dose in [31]. Reference [31] demonstrates again the need to deepen into this relationship from a mathematical approach.

The use of MPD as the stimulus considered in the application case presented here is suitable. Actually, such as the works [32, 33] demonstrate, a previous dopamine deficit in brain favors a greater increase of dopamine in brain in response to a dose of MPD [1]. Note that the increase of dopamine in brain is equivalent to an increase of the general activation, and thus of the GFP.

The here presented response model is an integro-differential equation that is a generalization of the model presented in [16]. It has been validated in [21] when the stimulus is caffeine and in [22] when the stimulus is MPD. The model reproduces accurately the dynamic patterns of the brain activation as a consequence of a stimulant drug intake, such as it is predicted by the works [17, 18, 19, 20]. These works predict a general dynamic pattern given by an inverted U-shape, but other exceptional patterns can also be observed, such as: an inverted-U followed by a recovering U; a decaying U from the beginning up to the end of the experimental period; or a growth that tends to maintain a constant value along the experimental period. In addition, the generalized response model is the here used one to reproduce the respective dynamics of the GFP, the c-fos, the DRD3 and the glutamate, as a consequence of a MPD dose intake.

An important assumption when relating mathematically the psychological level of description (mind) with the biological level of description (body) is the *invariance principle*. It asserts that the response model has to use the same mathematical structure to describe both dynamics: that of the GFP (mind) and that of the biochemical indicators related to personality (body) (c-fos, DRD3 and glutamate). As a consequence of the invariance principle, the so-called bridge model (a second order partial differential equation) can be deduced. The bridge model provides the co-evolution or dynamical relationship between every biochemical indicator and the GFP along time (through its time dependence on the stimulus).

Two previous versions of the bridge model have also been used in personality theory [34, 35]. However, the here deduced bridge model version presents a theoretical advance respect to the ones presented in [34, 35]. On a hand, the bridge model proposed in [35] relates the Big Five Factors (B5F) with the GFP and time. It has the restriction that no inhibitor delay (see Section 2, for the meaning of this term) is present in the simplified version of the response model that the authors applied to both the GFP and the B5F dynamics. Its validation takes place in the context of an experimental design where the participants consumed caffeine. In that case, the deduced bridge model is a first order partial differential equation that relates every component of the B5F with the GFP and time. On the other hand, the referred inhibitor delay is considered in [12] to develop a first mathematical approach about the body-mind problem by using another bridge model: a set of two coupled first order partial differential equations relating c-fos and glutamate with the GFP response and time. Its validation takes place in the context of an experimental design where the participants consumed methylphenidate. However, despite its generality, obtained by including the inhibitor delay term, that model produces in some cases artificial singularities due to the difficulty to state precise boundary conditions, which makes difficult to handle it numerically. The bridge model proposed in the present paper reformulates the two coupled partial differential equations as a second order partial differential equation, on which two boundary conditions are precisely formulated and no singularities are observed, which makes easier to handle it numerically.

In the following paragraphs the body-mind problem is described from a historical and a philosophical point of view, trying to put the presented mathematical approach in the context of some theoretical frames proposed in that view.

Reference [36] presents a good summary of this problem in the history of knowledge: the first rational approach to the body-mind problem is attributed to Plato as a dualism between sensitive (body) and intelligible (mind) worlds. Aristotle substitutes Plato's dualism by a matter-shape dualism, considering in his approach psychology (in the early ages of philosophy) as a part of physiology. In the Middle Ages the Christian dualism between body and soul (mind) is the dominant thought. Descartes defends a substantial dualism of body and mind but connected through the pineal glandule, although Spinoza and Leibnitz reduce the dualism to two aspects of an all, rather than two totally separated aspects. In the twentieth century positivism proposes association as a way to study the relationship between body and mind through the scientific method.

At the beginning of the 20th century, Wittgenstein, as opposed to the dualism body-mind, defends that people do not know phenomena by their physical manifestations, but by their behavior [37]. In fact, Wittgenstein defends that behavior is the actual expression of mind. This idea is supported as well by the dominant behaviorist psychology [36] of the 20th and 21st centuries, which maintains that only behavior can be object of scientific study.

Neuroscience has made possible the search for more global explanations for the mind-body problem, reframing it as a mind-brain problem with the neuroplasticity concept [38]. Also with the help of Psychoimmunology [39, 40] the scientific study of the relationship between body and mind is better understood. Both works emphasize that the negative consequence of the mentioned interaction can be found in the general activation of the stress system at long term. Due to the close relationship between the GFP and the general activation, the use of a stimulus-response model (the response model) is supported by the two last cited works.

Basically, ending the twentieth century and starting the twenty-first century, two philosophers of science have studied deeply the body-mind problem: Karl R. Popper [41] and Mario Bunge [42]. Popper's work tackles the problem with the theory of the three worlds. Following Motterlini's review [43] of Popper's work: "world 1 is the realm of physical bodies and their physical and physiological states; world 2, of mental states; and world 3, of the products of the human mind, such as theories, languages, arguments, works of art, and generally all the objective contents of thought". In system language, world 1, world 2 and world 3 are three interrelated subsystems that have arisen hierarchically as a consequence of the biological evolution. However, the early Luecken's review work [44] criticizes the absence of concretion in the definition of Popper's worlds. Despite the absence of concretion, also shared by Ben & Chaim [45], this work emphasizes the fact that learning takes place in world 3, being its dynamics of a stimulus-response kind. As a hypothesis, the here presented response model would describe a general feature (GFP) of the world 2 in Popper's context, and its biological indicators (c-fos, DRD3 and glutamate) in world 1, being the bridge model, in world 3, the relationship between world 1 and world 2.

Bunge's work [42] points out that there are three general trends to understand the body-mind problem: neural, holistic and systemic. The neural and holistic trends, following Bunge, are not the most suitable ones to solve the body-mind problem. He presents a dynamic network model of the central nervous system that relates subsystems represented by different sets of neurons

(neuron assemblies). The obtained theoretical results must be contrasted with the experimental ones with the observation of representative biological data, such as the blood flow in the different subsystems. Observe that the here presented approach is, using Bunge's terminology, rather holistic; it would measure the GFP with the response model, as related with the general activation of the stress system, but not presenting comparable results between the different subsystems by the moment. However, neither experimental designs describing the dynamics of the biological indicators nor relationships between personality and biological indicators are presented in Bunge's approach, such as it is done in this paper.

An interesting work about the so denominated the neuron approach by Bunge is the one of Gold & Stoljar [46]: they offer a defense and description of the interdisciplinary neuron approaches to solve the body-mind problem; and present some open peer commentaries and the corresponding Gold & Stoljar's answers. The open peer commentary done by Zanker [47] stresses that: "a more clearly defined experimental paradigm seems necessary to solve this exciting and substantial problem". The work by Agassi [48] revises as well the different approaches but insisting again in the need to perform testable explanations. Haken's theory of Synergetics [49] and its application to brain functioning and cognition responds to Bunge's neuron trend by searching the wave dynamic patterns from the lighthouse model of neuron.

Other works such as those of Brearley [50] and Scalzone [51] postulate the dialogue between psychoanalysis and neuroscience based on the assumption that both deal with virtual structures, without stating any mathematical approximation but proposing a common qualitative language between neurons and behavior. The work of Basar & Guntekin [52] attempts to approach the problem from the quantum physics and chaos theory, but it is just a set of intentions rather than a stated model to solve the body-mind problem. The same comments can be done about the work of Dvoryanchikova, Delamer & Martinez [53] that attempts to provide some tries to focus the problem from the structure of intelligent systems.

This paper is organized as follows. In Section 2 the response model is presented and explained. In Section 3 the bridge model is deduced from the response model through the invariance principle. Section 4 is devoted to present the experimental designs. The results obtained from them are used to validate the response model for the GFP and the biological indicators (c-fos, DRD3, and glutamate) in Section 5, and to validate the bridge model in Section 6. The conclusions of the work are presented in Section 7, together with the paper discussion.

2. The response model

The response model is the mathematical tool used to compute the short term dynamics of the GFP as a result of a stimulus produced by a single dose intake of a drug, such as it has been used in [16, 21, 22, 31, 34, 35]. Let us recall the response model in the following paragraphs.

Assuming that no drug is present in the organism before consuming it, the stimulus time dependence *s(t)*, i.e., the amount of drug in the organism not yet consumed (or metabolized) by cells at time *t*, is provided by the function:

$$s(t) = \begin{cases} \frac{\alpha \cdot M}{\beta - \alpha}(\exp(-\alpha \cdot t) - \exp(-\beta \cdot t)) : \alpha \neq \beta \\ \alpha \cdot M \cdot t \cdot \exp(-\alpha \cdot t) : \alpha = \beta \end{cases} \quad (1)$$

In Eq. 1, M is the initial amount of a drug single dose, α is the drug assimilation rate, and β is the stimulus elimination rate.

The dynamics of the *GFP* is given by the following equation:

$$\left.\begin{array}{c}\frac{dy(t)}{dt} = a(b - y(t)) + \frac{p}{b}s(t) - b{\cdot}q{\cdot}\int_0^t e^{\frac{x-t}{\tau}}{\cdot}s(x){\cdot}y(x)\,dx \\ y(0) = y_0\end{array}\right\} \quad (2)$$

Eqs. 1 and 2 represent the response model. In Eq. 2, $s(t)$ represents the stimulus given by Eq. 1; $y(t)$ represents the GFP dynamics; and b and y_0 are respectively its tonic level and its initial value. The dynamics of Eq. 2 is a balance of three terms, which provide the time derivative of the *GFP*: the *homeostatic control* ($a(b - y(t))$), i.e., the cause of the fast recovering of the tonic level b, the *excitation effect* ($p{\cdot}s(t)/b$), which tends to increase the GFP, and the *inhibitor effect* ($\int_0^t e^{\frac{x-t}{\tau}}{\cdot}s(x){\cdot}y(x)\,dx$), which tends to decrease the GFP and is the cause of a continuously delayed recovering, with the weight $e^{\frac{x-t}{\tau}}$. Parameters a, p, q and τ are named respectively the *homeostatic control power*, the *excitation effect power*, the *inhibitor effect power* and *the inhibitor effect delay*. All the parameters of the model depend on the individual personality or individual biology and on the type of stimulus. The correct interpretation of the tonic level b is important to be stressed: its value is situational and depends on the individual and the kind of stimulus. The response model provided such as Eq. 2 is fundamental to deduce the bridge model.

Besides, Eq. 2 can be transformed into a system of two coupled differential equations. To do this, let us define the $z(t)$ variable as:

$$z(t) = \int_0^t e^{\frac{x-t}{\tau}}{\cdot}s(x){\cdot}y(x)\,dx = e^{-\frac{t}{\tau}}\int_0^t e^{\frac{x}{\tau}}{\cdot}s(x){\cdot}y(x)\,dx \quad (3)$$

Then, by taking the time derivative of $z(t)$ we obtain:

$$\left.\begin{array}{c}\frac{dy(t)}{dt} = a(b - y(t)) + \frac{p}{b}s(t) - b{\cdot}q{\cdot}z(t) \\ y(0) = y_0\end{array}\right\} \quad (4)$$

$$\left.\begin{array}{c}\frac{dz(t)}{dt} = -\frac{z(t)}{\tau} + s(t){\cdot}y(t) \\ z(0) = 0\end{array}\right\} \quad (5)$$

Eqs. 1, 4 and 5 define a mathematical structure of the response model equivalent to that given by Eqs. 1 and 2, and they are used to obtain its numerical solutions in an easy way.

3. The bridge model

In order to deduce the bridge model, the starting point is assuming the invariance principle, i.e., the dynamical response of every biological indicator can be also described by the response model, but with different parameter values. Thus, let us call E_i to each one of the three biological indicators, with $1 \leq i \leq 3$: $E_1 \equiv C$ (c-fos), $E_2 \equiv D$ (DRD3) and $E_3 \equiv G$ (glutamate). In addition,

if $E_i^{(0)}$is the corresponding initial value in $t=0$, and A_i, B_i, P_i, Q_i and T_i are the corresponding parameters, the response model corresponding to the biological indicators can be written as:

$$\left.\begin{array}{c} \frac{dE_i(t)}{dt} = A_i(B_i - E_i(t)) + \frac{P_i}{B_i}s(t) - B_i \cdot Q_i \cdot \int_0^t e^{\frac{x-t}{T_i}} \cdot s(x) \cdot E_i(x)\, dx \\ E_i(0) = E_i^{(0)} \end{array}\right\} \quad (6)$$

Note that $1 \le i \le 3$ in Eq. 6. From now onwards the subscripts will hold this meaning. In addition, note also that $s(t)$ is the stimulus function, i.e., it is the same as in Eq. 1, which means that it is the same for the three biological indicators and for the GFP. The invariance principle assumes that the influence of the stimulus on the three biological indicators and on the GFP is the same. Therefore, from this hypothesis, $s(t)$ only depends on the individual biology and on the kind of stimulus. As a consequence, α (assimilation rate) and β (elimination rate) have the same value for the three biological indicators and for the GFP.

Note again that with the change specified in the following equation:

$$F_i(t) = \int_0^t e^{\frac{x-t}{T_i}} \cdot s(x) \cdot E_i(x)\, dx = e^{-\frac{t}{T_i}} \int_0^t e^{\frac{x}{T_i}} \cdot s(x) \cdot E_i(x) dx \quad (7)$$

Eq. 6 becomes a system of two coupled differential equations:

$$\left.\begin{array}{c} \frac{dE_i(t)}{dt} = A_i(B_i - E_i(t)) + \frac{P_i}{B_i}s(t) - B_i \cdot Q_i \cdot F_i(t) \\ E_i(0) = E_i^{(0)} \end{array}\right\} \quad (8)$$

$$\left.\begin{array}{c} \frac{dF_i(t)}{dt} = -\frac{F_i(t)}{T_i} + s(t) \cdot E_i(t) \\ F_i(0) = 0 \end{array}\right\} \quad (9)$$

Eqs. 8 and 9 constitute a mathematical structure of the response model equivalent to that given by Eq. 6, and they are used to obtain its numerical solutions in an easy way.

To find the mathematical relationship among the biological indicators (E_i), the GFP (y) and time (t), the starting point is to consider that it can be written as:

$$E_i = E_i(t,y) \quad (10)$$

Taking the time derivative in Eq. 10:

$$\frac{dE_i(t,y)}{dt} = \frac{\partial E_i(t,y)}{\partial t} + \frac{\partial E_i(t,y)}{\partial y}\frac{dy}{dt} \quad (11)$$

Substituting Eqs. 2 and 6 in Eq. 11, taking into account Eqs, 5 and 9, and considering now that the time function $E_i(t)$ is, from Eq. 10, a two-variables function $E_i(t,y)$:

$$A_i(B_i - E_i(t,y)) + \frac{P_i}{B_i}s(t) - B_i \cdot Q_i \cdot F_i(t,y) =$$

$$\frac{\partial E_i(t,y)}{\partial t} + \frac{\partial E_i(t,y)}{\partial y}\left(a(b-y) + \frac{p}{b}s(t) - b \cdot q \cdot z(t)\right) \quad (12)$$

In Eq. 12, $z(t)$ is given by Eq. 3, and $F_i(t,y)$, considering Eq. 7, is given by:

$$F_i(t,y) = \int_0^t e^{\frac{x-t}{T_i}} \cdot s(x) \cdot E_i(x,y) dx = e^{-\frac{t}{T_i}} \int_0^t e^{\frac{x}{T_i}} \cdot s(x) \cdot E_i(x,y) dx \quad (13)$$

Differing from the equation presented in [35] as the bridge model, Eq. 12 is a partial integro-differential equation, where the integral term is due to Eq. 13, which makes difficult to handle the model mathematically. An alternative way to solve this difficulty is to consider the substitution of Eq. 10 by $E_i = E_i(t,y,z)$. This approach is held in [41], and the alternative model to Eq. 12 is provided by a set of two coupled first order partial differential equations. However, although an analytical solution seems to be impossible for both approaches, obtaining a numerical solution presents some difficulties due to the artificial dependence on z in $E_i(t,y,z)$. The way to avoid this dependence and to avoid the direct work with a partial integro-differential equation such as Eq. 12, is to convert it into a second order partial differential equation. To do this, let us derivate Eq. 12 with respect to time:

$$-A_i \frac{\partial E_i(t,y)}{\partial t} + \frac{P_i}{B_i} s'(t) - B_i \cdot Q_i \frac{\partial F_i(t,y)}{\partial t} = \frac{\partial^2 E_i(t,y)}{\partial t^2} + \frac{\partial^2 E_i(t,y)}{\partial t \, \partial y} \left(a(b-y) + \frac{p}{b} s(t) - b \cdot q \cdot z(t) \right) + \frac{\partial E_i(t,y)}{\partial y} \left(\frac{p}{b} s'(t) - b \cdot q \cdot z'(t) \right) \quad (14)$$

Note from Eq. 5 that $z'(t) = -\frac{1}{\tau} z(t) + s(t) \cdot y$, and from Eq. 13:

$$\frac{\partial F_i(t,y)}{\partial t} = -\frac{1}{T_i} e^{-\frac{t}{T_i}} \int_0^t e^{\frac{x}{T_i}} \cdot s(x) \cdot E_i(x,y) dx + e^{-\frac{t}{T_i}} \cdot e^{\frac{t}{T_i}} \cdot s(t) \cdot E_i(t,y) = -\frac{1}{T_i} F_i(t,y) + s(t) \cdot E_i(t,y) \quad (15)$$

The substitution of Eqs. 5 and 15 in Eq. 14 provides:

$$-A_i \frac{\partial E_i(t,y)}{\partial t} + \frac{P_i}{B_i} s'(t) + \frac{B_i \cdot Q_i}{T_i} F_i(t,y) - B_i \cdot Q_i \cdot s(t) \cdot E_i(t,y) = \frac{\partial^2 E_i(t,y)}{\partial t^2} + \frac{\partial^2 E_i(t,y)}{\partial t \, \partial y} \left(a(b-y) + \frac{p}{b} s(t) - b \cdot q \cdot z(t) \right) + \frac{\partial E_i(t,y)}{\partial y} \left(\frac{p}{b} s'(t) + \frac{b \cdot q}{\tau} \cdot z(t) - b \cdot q \cdot s(t) \cdot y \right) \quad (16)$$

The next step is the elimination of the integral term $B_i \cdot Q_i \cdot F_i(t,y)$ in Eq. 16. First, the term is isolated from Eq. 12:

$$B_i \cdot Q_i \cdot F_i(t,y) = A_i (B_i - E_i(t,y)) + \frac{P_i}{B_i} s(t) - \frac{\partial E_i(t,y)}{\partial t} - \frac{\partial E_i(t,y)}{\partial y} \left(a(b-y) + + \frac{p}{b} s(t) - b \cdot q \cdot z(t) \right) \quad (17)$$

Subsequently Eq. 17 is substituted in Eq. 16, and after reorganization:

$$\frac{\partial^2 E_i(t,y)}{\partial t^2} + \left(a(b-y) + \frac{p}{b}s(t) - b{\cdot}q{\cdot}z(t)\right)\frac{\partial^2 E_i(t,y)}{\partial t\,\partial y} + \left(\frac{p}{b}s'(t) + \frac{b{\cdot}q}{\tau}{\cdot}z(t) - b{\cdot}q{\cdot}s(t){\cdot}y + \frac{1}{T_i}\left(a(b-y) + \frac{p}{b}s(t) - b{\cdot}q{\cdot}z(t)\right)\right)\frac{\partial E_i(t,y)}{\partial y} + \left(A + \frac{1}{T_i}\right)\frac{\partial E_i(t,y)}{\partial t} = \frac{A_i}{T_i}$$
$$(B_i - E_i(t,y)) - B_i{\cdot}Q_i{\cdot}s(t){\cdot}E_i(t,y) + \frac{P_i}{T_i{\cdot}B_i}s(t) + \frac{P_i}{B_i}s'(t) \quad (18)$$

Eq. (18) must be completed with the boundary conditions:

$$E_i(0,y) = E_i^{(0)} \quad (19)$$

$$\frac{\partial E_i}{\partial t}(0,y) = A_i\left(B_i - E_i^{(0)}\right) \quad (20)$$

Eqs. 18, 19 and 20 provide the new version of the bridge model. Note that Eq. 19 provides the initial condition for each one of the biological indicators, while Eq. 20 is obtained from Eq. 6 due to $s(t) = 0$ before the drug consumption. For computation purposes in Eq. 18, $s(t)$ is the time function given by Eq. 1 and $s'(t)$ is its time derivative, while $z(t)$ is considered a time function obtained from the numerical solution of the system given by Eqs 4 and 5. Note that from Eq. 3, the $z(t)$ term in Eq. 18 considers that its solutions assume all the past history of the GFP since the stimulus is provided.

4. The experimental designs

The application case here considered in order to validate the response and bridge models is performed with two experimental designs on two participants that we name Case 1 and Case 2. The first design is a previous AB pseudo-experimental design set up for Case 1 and the second one is a subsequent ABC experimental design set up for Case 2. In fact, the AB design is not a real experimental design but an exploratory case study. Once positive results have been obtained informing about a change in the scores over the considered scales of personality when taking 20 mg of methylphenidate with respect to those of the base-line for Case 1, the authors decided to repeat the experiment with another subject, Case 2, but this time with a single case experimental design with three phases: A, B and C. Phase A is again the base-line, Phase B corresponds to a 20 mg MPD intake, and Phase C to 40 mg MPD intake.

The participants (Case 1 and Case 2) are two males 50 and 52 years old respectively. They are two voluntaries of the university teaching staff. The instruments are the Five-Adjective Scale of the General Factor of Personality (GFP-FAS) [14, 15]. The 5 adjectives are: adventurous, daring, enthusiastic, merry and bored. Each adjective is evaluated by the participants from 0 to 5. Thus the scale for the GFP is $y \in [0,25]$.

The biological analyses to obtain the referred biological indicators are of two kinds. To obtain the c-fos and DRD3 samples, the lymphocytes of the blood samples were isolated by density centrifugation on Lymphoprep. Finally, an automated mass spectrometry platform (Sequenom, MassARRAY Quantitative Gene Expression) was used for quantification of the c-fos and the DRD3 concentrations in lymphocytes. β-actin was used as internal standard RNA. In addition, a mass spectrometer was used to obtain the glutamate level in blood. C-fos and DRD3 are measured by their molar concentration (mc) in lymphocytes in blood. The c-fos measures are

taken on a scale multiplied by 10^{18} mc and the DRD3 measures are taken on a scale multiplied by 10^{21} mc. With these scales, the c-fos ($E_1 \equiv C$) and DRD3 ($E_2 \equiv D$) concentrations vary in the interval $C,D \in [0, 100]$. Glutamate $E_3 \equiv G$ is measured by the direct molar concentration (mc) in blood and it is used within a scale multiplied by 10^{18} mc. With this scale, the glutamate concentration varies in the interval $G \in [0,60]$.

In all phases participants fill out the GFP-FAS form each fifteen minutes (17 registers each phase) and peripheral blood samples are obtained each one hour (5 samples each phase). In addition the experimental conditions take place in a hospital room a morning with an empty stomach, with no drug consumption and inside a resting and isolated atmosphere, trying to minimize the external stimuli in Phases A and also to maximize the effect of MPD in Phases B and C.

The AB pseudo-experimental design is set up for Case 1. Phase A is the base-line, without treatment. A week later, in Phase B, Case 1 receives a dose of 20 mg of MPD immediately after filling out the first list of the GFP-FAS form and the initial blood sample is obtained. In the following, Case 1 fills out 16 lists of the GFP-FAS, one each fifteen minutes, and a blood sample is obtained each hour along 4 hours.

One week later, the ABC experimental design is set up for Case 2. Phases A and B of Case 2 are set up in the same way than for Case 1, with Phases A and B separated for one week. One week later than Phase B, in Phase C, Case 2 receives a dose of 40 mg of MPD immediately after filling out the first list of the GFP-FAS form and the initial blood sample is obtained. In the following, Case 2 fills out 16 lists of the GFP-FAS form, one each fifteen minutes, and a blood sample is obtained each hour along 4 hours.

Observe that for Case 1 in Phase B and for Case 2 in Phases B and C, each one of the measures before consuming represent the initial conditions for the response model, which is evaluated with the initial condition plus the 16 lists of the GFP-FAS. Also the response model is evaluated with the initial condition plus the 4 blood samples for the biological indicators. In addition, the bridge model can only be evaluated with those outcomes that coincide in time, i.e., with the outcomes obtained each one hour. The results of both experiments are presented in the following sections in tables and graphics, in the context of the response and bridge models validation.

5. Validation of the response model

The aim of this section is to validate the response model by calibration for both the GFP and the three biological indicators for both experimental designs.

The calibration method consists in comparing the experimental data obtained from the different lists of scores with the theoretical values provided by the response model. On a hand, the experimental GFP-FAS scores are compared with the theoretical outcomes provided by the $y(t)$ model variable given by Eqs. 1 and 2. On the other hand, the experimental biological scores are compared with the theoretical outcomes provided by the $E_i(t)$ model variables given by Eqs. 1 and 6.

To obtain the theoretical outcomes, Eqs. 2 and 6 have been programmed in C++ language, solving the equivalent differential equations (Eqs. 4 and 5 for Eq. 2, and Eqs. 8 and 9 for Eq. 6), by the 4th Runge-Kutta method. The C++ program includes the algorithm to compare the

experimental scores and the theoretical outcomes. It consists in minimizing the sum of squares of the differences between both sets of data, being the theoretical ones obtained by the corresponding equations from generating random numbers for the parameters' values. Observe that in the method development the initial value of Eq. 4, y_0, and that of Eq. 8, $E_i^{(0)}$, are known because they are the corresponding values obtained before the MPD stimulus is taken.

Validation only has sense when the MPD stimulus is provided, that is, for Phase B in the AB pseudo-experimental design and for Phases B and C in the ABC experimental design. In addition, the goodness of validation is here provided by: (a) the visual inspection of Figure 1 that represents jointly the experimental and the theoretical outcomes (GFP, c-fos, DRD3 and glutamate); (b) the determination coefficient (R^2), which varies in the interval [0,1]: the closer to the unit the determination coefficient is the better the fitting degree of both data sets is.

Phases A of both experimental designs play the role of a control base-line: the observable differences between Phases A and Phases B and C (where the MPD stimulus is provided) indicate that the stimulus produces an appreciable change.

Let us start with Case 1, corresponding to the AB pseudo-experimental design. Phase A of Case 1 is represented in Fig. 1 (a)-(d). Note that for this case, the responses to the quietness and isolation conditions of Phase A work as a control base-line. On a hand, the experimental values change around a constant value such as it happens in Fig. 1(a) for the GFP or in Fig. 1(b) for c-fos. On the other hand, Fig. 1(c) shows a slight inverted U-shape for DRD3, and Fig. 1(d) a more stressed U-shape for glutamate. However, the observed trends are different to those present in Phase B. In fact, besides, Phase B of Case 1 is represented in Figs. 1(f) – (i) as a consequence of a dose of 20 mg. Note that both the GFP (Fig. 1(f)) and c-fos (Fig. 1(g)) present a stressed inverted U-shape dynamics, while the DRD3 dynamics (Fig. 1(h)) is oscillatory and the glutamate dynamics presents a slight inverted U-shape (Fig. 1(i)). All determination coefficients range between 0.85 and 0.97. Thus, the response model can be considered validated for Phase B of Case 1.

In order to validate the model with Case 2, with data corresponding to the ABC experimental design, Phase A of Case 2 is represented in Fig. 1 (j)-(m), Phase B of Case 2 is shown in Figs. 1 (o)-(r), which illustrates the GFP, c-fos, DRD3 and glutamate dynamics as a consequence of a dose of 20 mg of MPD. We proceed analogously to case 1 (using the same arguments). Let us remark that all determination coefficients range between 0.85 and 0.99. Thus the response model can be considered as validated for Phase B of Case 2. Similar arguments are used for validation in Phase C of Case 2. Fig. 1(s)-(v) shows the determination coefficients ranges that are situated between 0.82 and 0.99.

The corresponding optimal values of the model parameters for Phase B of Case 1 and for Phases B and C of Case 2 are presented in Table 1. Note that the parameters corresponding to the stimulus equation have the same value for the GFP and for the three biological indicators.

6. Validation of the bridge model

The theoretical values provided by the bridge model, $E_i(t,y)$, are given by the numerical solutions of Eqs.18, 19 and 20, with the optimal parameter values obtained in the calibration process of the response model (Table 1). These numerical solutions have been obtained using the NDSolve function of MATHEMATICA 10.4. On a hand, the validation of the bridge model is provided by visual inspection: the joined representation of the experimental scores and the theoretical values $E_i(t,y)$ of the biological indicators versus the experimental values of the GFP. On the other hand, the validation is supported by the corresponding determination coefficients of both sets of data. Note that this validation has only sense for Phase B of Case 1 and for Phases B and C of Case 2.

Let us consider Phase B of Case 1 and the corresponding optimal values of Table 1 to obtain the theoretical values by using the bridge model. Fig. 2 (a)-(d) presents the joined results of the experimental biological indicators and the corresponding theoretical values versus the GFP experimental values. Note that, both the visual inspection of the figures and the determination coefficients (ranging between R^2=0.85 and R^2=0.97), provide a good validation of the bridge model for Phase B of Case 1. Similar arguments can be used to validate the bridge model for the Phase B of Case 2 with determination coefficients that range between R^2=0.85 and R^2=0.99 (see Fig. 2(e)-(g)) and, for Phase C of Case 2 with determination coefficients that range between R^2=0.82 and R^2=0.99 (see Fig. 2(h)-(k)).

The general conclusion of this section is that the bridge model can be considered as validated from the outcomes of both experimental designs.

7. Conclusions and discussion

The response model has been validated by calibration in the context of a previous (pilot) AB experiment and a subsequent ABC experimental design. As a consequence of getting the optimal parameter values for the response model, the presented bridge model has also been validated. Thus, it is confirmed that the GFP and the three biological indicators, c-fos, DRD3 and glutamate, vary jointly in response to a dose of a stimulating drug (MPD). In addition, the validation of the bridge model in the context of both experimental designs provides the co-evolution of the GFP (mind) and the three biological indicators, c-fos, DRD3 and glutamate, (body). However, it seems obvious that future experimental designs might consider more subjects and more phases, due to the present study is centered on individuals, not in groups. The experimental designs for groups would provide statistical significations, which would increase the consistency of the response and bridge models. Besides, other kinds of stimuli should be considered in alternative experimental designs, such as caffeine, alcohol, self-regulation therapy, etc., which would also consolidate the value of the response and bridge models to study the body-mind problem.

Significant associations between the 5HTT, DRD4, DRD2, DRD3 A1/A2 polymorphisms and personality traits have been studied from different models and instruments of personality evaluation (EPQ-R, TPC, NEO, etc.) [54, 55]. In this article, we have proposed a biochemical basis (the three previously mentioned indicators) for the whole personality (General Factor of Personality) from a dynamic perspective, based on the effect of a single dose of MPD. However, in future experiments with MPD, it would be interesting to include other biochemical markers

(such as adenosine, for instance) and further explaining the homeostatic process that occurs after taking a single dose of MPD. Now, we are going to suggest for future research a two-phase model of the effect of a single dose of MPD including some of these new markers.

MPD works in a biphasic action, including phasic and tonic release of dopamine (DA). Phasic releases of DA are large but brief and activate postsynaptic DA receptors [56, 57]. On the other hand, tonic DA release from the VTA is regulated by presynaptic NMDA receptors by glutamatergic afferents from the PFC [58].

MPD treatment produces an increase in DA signaling through multiple actions, including blockade of the DA reuptake transporter (DAT), amplification of DA response duration and activation of D1 receptors on the postsynaptic neuron [59]. Besides, MPD blockades the norepinephrine transporter (NET) resulting in elevated concentration of norepinephrine (NE) at synapses. The afferent input of glutamatergic neurons from the PFC to DA neurons in the VTA can be stimulated by MPD [60]. Low-dose MPD potentiates NMDAR functions mainly through norepinephrine system [61]. All these mechanisms correspond to the phasic action. From there the homeostatic mechanism starts.

The VTA neurons contain both D1 and D2 DA receptors. Low doses of MPD activate mainly D2-like DA auto-receptors which lead to the attenuation of DA release in response to a stimulus [56, 57]. On the other hand, MPD increases glutamate uptake mainly expressed in glial cells. It removes the amino acid from the synaptic cleft preventing an excessive glutamatergic stimulation and thus neuronal damage [62]. This may result in a plausible regulation mechanism of the glutamatergic tone.

An important candidate to modulate dopaminergic and glutamatergic signaling and, in this way, to integrate their interactions, is adenosine. Adenosine is a *neuromodulator*. In the hippocampus, adenosine exerts a tonic inhibitory effect on NMDAR function via stimulation of A1Rs, thus attenuating NMDAR-mediated currents [63]. On the other hand, the adenosine-dopamine receptor–receptor interacts as an integrative and homeostatic mechanism in the basal ganglia. The stimulation of adenosine receptors counteracts the behavioral effects of dopamine receptor stimulation [64].

It is known the existence of A2A–D2 and A1–D1 receptor heteromers in the brain [64,65]. The A1–D1 heteromeric receptor complex may be the molecular basis for the well-documented antagonistic A1–D1 receptor/receptor interactions found in the neuronal networks of the brain [64,66,67]. So, adenosine A1 receptor activation enhances of dopamine D1 receptor desensitization [68]. It has been proved the up-regulation of adenosine A1 receptor in the frontal cortex by acute administration of MPD. Since activation of adenosine A1 receptors trigger anxiolytic effects in rodents [69], this transient up-regulation of adenosine A1 receptors could be involved in the anxiolytic effects of MPD [70], as an effect of the tonic action.

In addition, mGlu5R/A2AR/D2R interactions play an important modulatory role in the function of the ventral striopallidal GABA pathway, which might have implications for the treatment of schizophrenia and drug addiction [71].

On the other hand, even though MPD does not increase the extracellular serotonin concentration in the brain [72] and its affinity to the serotonin transporter is very low [73], the serotonin can be involved in the MPD effect. So, MPD modulate the Dorsal Raphe neuronal activity as a result of an acute or repetitive dose [74], and produces selective agonist-like activity at the 5-HT1A receptor [75]. In addition, the inhibitory effect of serotonin on dopaminergic

system has been proposed as a mechanism to produce the calming effects of MPD [76]. We can speculate that this calming effect is a result of a modulating mechanism of serotonin in the tonic action of the MPD.

Finally, Acetylcholine (Ach) appears also to be involved in the phasic-tonic response balance of dopaminergic neurons. The cholinergic input from the laterodorsal tegmental nucleus (LDT) to ventral tegmental area (VTA) is required for burst firing of dopamine cells. Activity of LDT cholinergic neurons is modulated by mAChRs (metabotropic muscarinic ACh receptors) and nAChRs (ionotropic nicotinic ACh receptors) in the LDT. The mAChRs mediating LDT-evoked striatal dopamine release may involve M3 and M5 subtypes that have been localized in the VTA. However, M3 mAChR activation appears to be involved in reducing, rather than enhancing, excitatory transmission in dopamine midbrain cells by presynaptic mechanisms [77].

These mechanisms may be playing an important role in the homeostasis produced by the MPD, since it has been verified that the MPD increases ACh efflux in cortical region, nucleus accumbens and hippocampus [78], and actives muscarinic receptors [79].

This homeostatic mechanism can be altered by the administration of high doses or by the repeated taking of MPD. The neuroadaptative mechanisms of the biological markers considered in the previous paragraphs would have to be considered in future experiments and in the corresponding mathematical models. The present research is based only on the short term dynamics described by the response model. But the response model presented in [23] provides predictions at long term. A long term stimulus-response model such as the one presented in [23] is necessary when an individual consumes many doses of a stimulant drug for a more or less long period, even of several years, with different amounts and frequencies. In fact, the model simulations of [23] predict for a period of three years, with different patterns of dose amounts and frequencies. However, the continuous consumption of different doses can elicit behavioral withdrawal, sensitization and habituation (or tolerance). These effects have been observed particularly with methylphenidate in different works [80-82]. The model presented in [23] is applied to cocaine. However, methylphenidate and cocaine share similar chemical properties and physiological effects [83-85], thus all results obtained in [23] can be translated partially to the long term effects of methylphenidate. In addition, the aforementioned biological markers would be included in these long-term models. For example, the role of adenosine receptors in psychostimulant addiction has been also proposed [86]. Therefore, a corresponding bridge model deduced under the invariance principle from the response model of [23] would be suitable to simulate changes in biology and personality at long term. This further bridge model would provide a tool to solve, for instance, problems of addiction from the double behavioral and biological perspective.

Let us stress that the bridge model is a consequence of the assumption of the mathematical invariance principle, which determines the suitability of the same mathematical structure to describe the dynamics of the GFP and that of the three biological indicators. Thus, it is here observed in action the assumption about the general applicability in behavioral sciences of the differential models used by physics and other disciplines related with applied mathematics. This assumption has been demonstrated in the last centuries in science as a method to study successfully dynamics, complexity and nonlinearity. In fact, both the response and the bridge models have been demonstrated that are two successful mathematical tools to study the co-evolution of the GFP and the three biological indicators, as a consequence of a stimulus, such as

a single dose of MPD. Then, both models provide a new perspective to study the body-mind problem.

This new perspective has to be framed in practical applications in future. In fact, a concrete application of the bridge model would consist in being used to simulate changes in biology from the self-regulation therapy: those changes that would steer biology towards suitable dynamical states for the individual personality.

Summarizing, a unified theory must consider the emergency of the physiological level from the biochemical or molecular level and, in addition, the emergency of the psychological level from the physiological level, following the three worlds of Popper's theory [41].

However, the mathematical approach here presented does not attempt to link the molecular level with the psychological level inside a reductionist "top-down" research approach. It rather attempts to state a bridge between both levels of description in the following way:

1. Both the individual dynamics of the biological molecules (molecular level) and the GFP dynamics (psychological level) can be described by the same mathematical model (the response model). Thus, in the molecular level, the response model describes the dynamics of the individual molecules involved in the mind processes, but not the complex interrelations among them.
2. The invariance principle permits to obtain the bridge model, through which the dynamics of the individual molecules can be related with the GFP dynamics in the psychological level of description.

In fact, the overall understanding of the body-mind problem must be developed in a slow step by step way that science must run in the future. For instance, one of such steps would be the study of the relationship between the physiological level of description and the psychological one, following Bunge's approach [42]. However, first of all, the own dynamics of the physiological level must be understood. Bunge presents in [42] a mathematical model of the nervous system. From the author's point of view this study can also be circumscribed to the spatio-temporal brain dynamics [87], with which the brain patterns can be studied by electrophysiological, neurobiological or fMRI data. Subsequently, the link between the GFP (psychological level) and the brain dynamics should be stated.

Finally, it is over understood by the authors that a complete solution of the body-mind problem should consider the understandings of the three levels of description: (a) at the molecular level the overall biology, which involves much more biological indicators than those here presented and their dynamical interrelationships; (b) at the physiological level, the dynamics of the nervous system activity (the general activation), and particularly the brain activity dynamics; (c) at the psychological level, the personality dynamics, both at short and at long term, including the disordered personality dynamics. And, of course, the understanding of the emergencies among the three levels must be investigated to deepen into the complexity of the body-mind problem.

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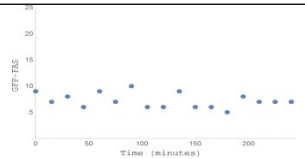
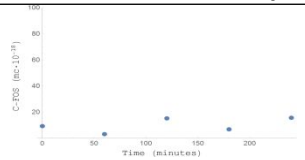
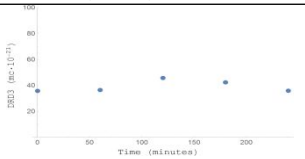
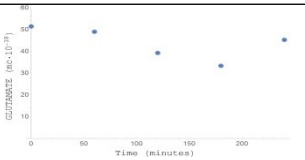
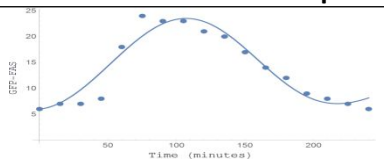
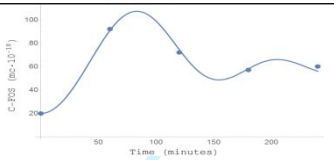
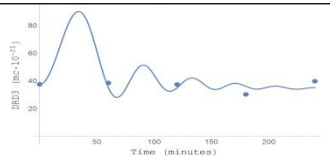
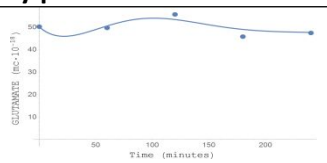
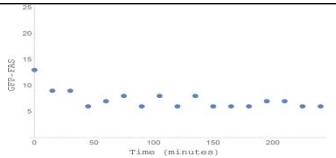
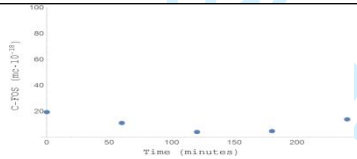
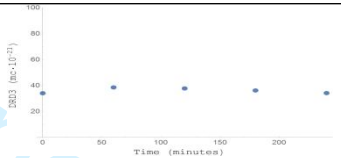
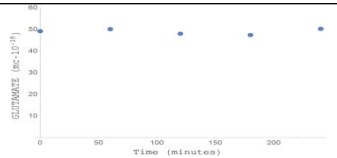
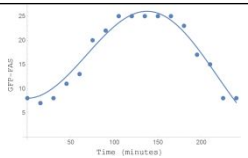
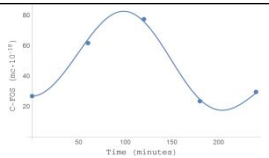
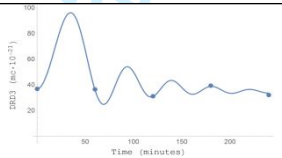
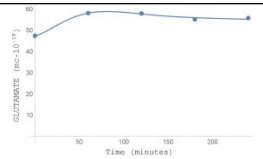
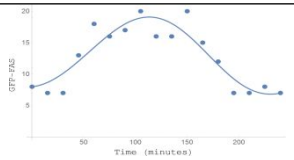
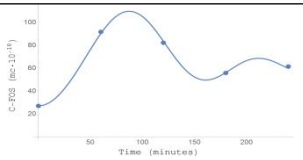
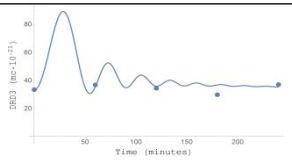
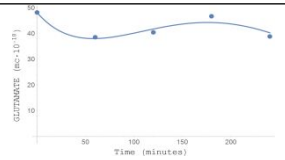
Design	GFP-FAS	C-FOS	DRD3	GLUTAMATE
PHASE A. CASE 1. **Experimental values (dots).**				
AB.	 (a)	 (b)	 (c)	 (d)
PHASE B. CASE 1. **Experimental values (dots) and theoretical values (curve). Dose of 20 mg of methylphenidate.**				
AB.	 (f) R^2=0.91.	 (g) R^2=0.97.	 (h) R^2=0.93	 (i) R^2=0.85
PHASE A. CASE 2. **Experimental values (dots) corresponding to the pseudo-experimental design AB.**				
ABC.	 (j)	 (k)	 (l)	 (m)
PHASE B. CASE 2. **Experimental values (dots) and theoretical values (curve). Dose of 20 mg of methylphenidate.**				
ABC.	 (o) R^2=0.97.	 (p) R^2=0.99.	 (q) R^2=0.95.	 (r) R^2=0.85.
PHASE C. CASE 2. **Experimental values (dots) and theoretical values (curve). Dose of 40 mg of methylphenidate.**				
ABC.	 (s) R^2=0.83.	 (t) R^2=0.99.	 (u) R^2=0.99.	 (v) R^2=0.82.

Figure 1 Validation of the response and bridge models.

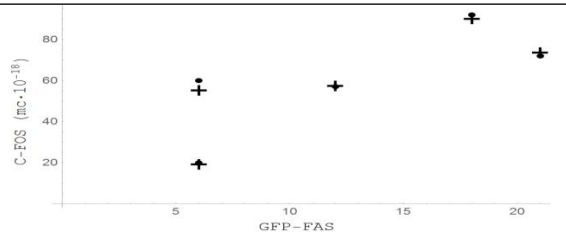
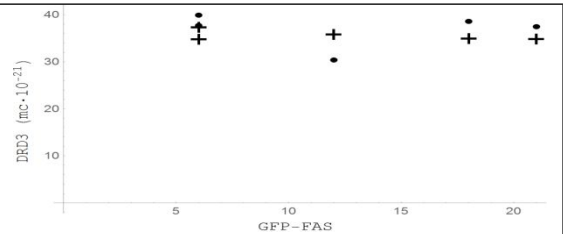
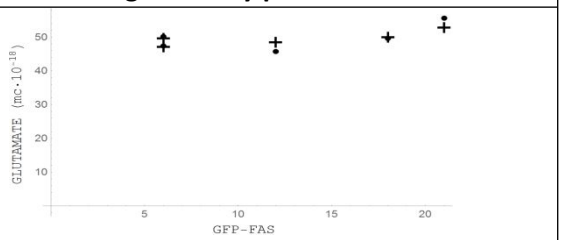
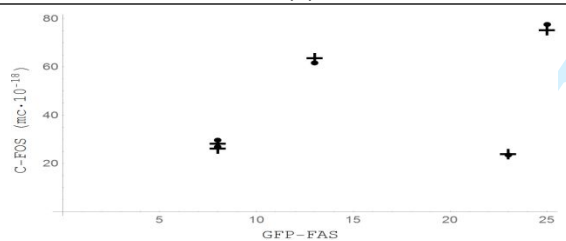
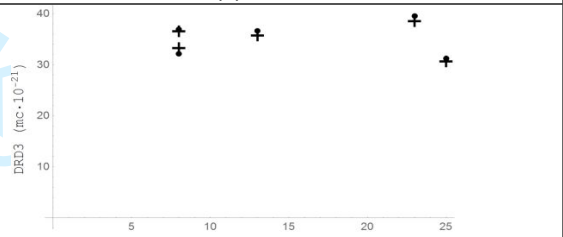
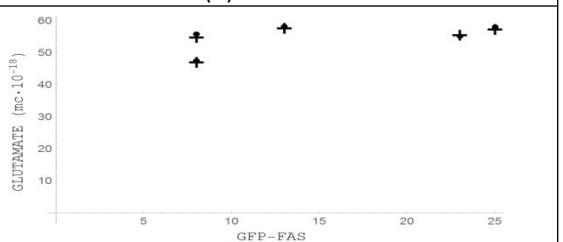
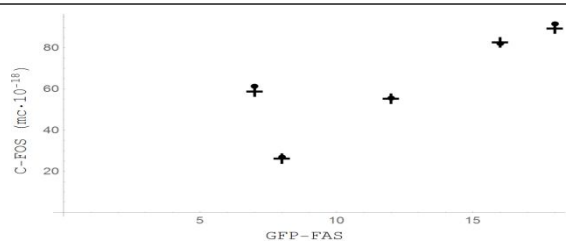
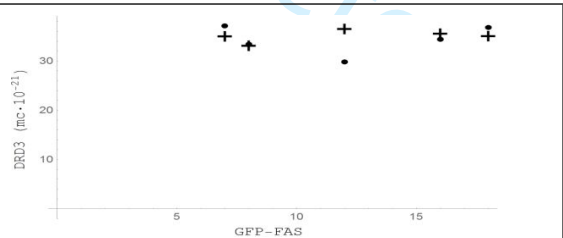
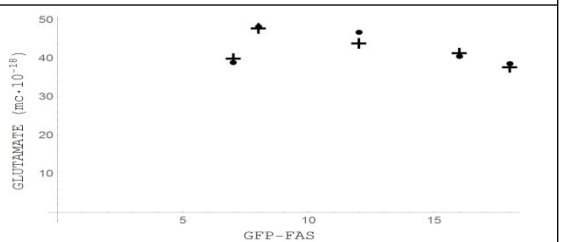
Design	***PHASE B. CASE 1*. Experimental values (dots) and theoretical values (crosses). Dose of 20 mg of methylphenidate**		
AB.	 (a) R^2=0.97.	 (c) R^2=0.94.	 (d) R^2=0.85.
ABC.	 (e) R^2=0.99.	 (f) R^2=0.95.	 (g) R^2=0.85.
***PHASE C. CASE 2.* Experimental values (dots) and theoretical values (crosses). Dose of 40 mg of methylphenidate.**			
ABC.	 (h) R^2=0.99.	 (j) R^2=0.99.	 (k) R^2=0.82.

Figure 2. Comparison between theoretical and experimental values of GFP-FAS in the different cases and doses

AB Design . PHASE B. CASE 1. Dose of 20 mg of methylphenidate.				
Parameters	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	2.0000e+001	2.0000e+001	2.0000e+001	2.0000e+001
Inhibitor effect delay (T_i)	1.0213e+002	4.3812e+001	3.0735e+001	3.6923e+001
Assimilation rate (α)	3.2861e-003	3.2861e-003	3.2861e-003	3.2861e-003
Distribution rate (β)	8.8380e-004	8.8380e-004	8.8380e-004	8.8380e-004
Homeostatic control power (A_i)	4.9064e-003	6.3018e-004	4.0129e-003	1.7164e-002
Tonic level (B_i)	1.0924e+001	1.4871e+001	1.6519e+001	2.3570e+001
Excitation effect power (P_i)	1.3322e+000	1.4456e+001	6.3232e+001	8.5710e+000
Inhibitor effect power (Q_i)	1.2676e-005	2.8545e-005	2.3233e-004	8.4998e-006
ABC Design. PHASE B. CASE 2. Dose of 20 mg of methylphenidate.				
	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	2.0000e+001	2.0000e+001	2.0000e+001	2.0000e+001
Inhibitor effect delay (Ti)	1.7473e+002	8.2863e+001	3.1139e+001	1.1166e+001
Assimilation rate (α)	5.3711e-003	5.3711e-003	5.3711e-003	5.3711e-003
Distribution rate (β)	1.5732e-003	1.5732e-003	1.5732e-003	1.5732e-003
Homeostatic control power (Ai)	2.6764e-004	0	2.8734e-004	1.2631e-002
Tonic level (Bi)	4.6680e+000	2.0365e+001	1.8213e+001	5.3462e+001
Excitation effect power (P_i)	2.4243e-001	6.1950e+000	4.4131e+001	1.1024e+001
Inhibitor effect power (Qi)	8.4485e-006	5.7396e-006	1.2699e-004	6.2781e-006
ABC Design . PHASE C. CASE 2. Dose of 40 mg of methylphenidate.				
	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	4.0000e+001	4.0000e+001	4.0000e+001	4.0000e+001
Inhibitor effect delay (Ti)	9.1556e+001	4.7736e+001	2.4158e+001	9.8056e+002
Assimilation rate (α)	1.0778e-003	1.0778e-003	1.0778e-003	1.0778e-003
Distribution rate (β)	7.4257e-004	7.4257e-004	7.4257e-004	7.4257e-004
Homeostatic control power (Ai)	1.7457e-003	0	5.3887e-003	1.4485e-002
Tonic level (Bi)	1.6158e+001	2.5438e+001	8.4389e+000	1.8165e+001
Excitation effect power (P_i)	1.6580e+000	3.1705e+001	7.2391e+001	2.7192e+000
Inhibitor effect power (Qi)	9.4120e-006	2.0085e-005	1.2778e-003	1.3752e-006

Table 1 . Optimal values of the response model for different cases.

Biology and personality: a mathematical approach to the body-mind problem

Abstract

Purpose – The purpose of this paper is to investigate the body-mind problem from a mathematical *invariance principle* that relates personality dynamics in two levels of description: the psychological and the biological levels.

Design/methodology/approach – The relationship between the two levels of description is provided by two mathematical models: the *response model* and the *bridge model*. The response model, an integro-differential equation, is capable to reproduce the personality dynamics as a consequence of a determined stimulus. The invariance principle asserts that the response model can reproduce the personality dynamics at the two levels of description. As a consequence, the bridge model, a second order partial differential equation, can be deduced: it provides the co-evolution of the GFP (mind) and the c-fos, DRD3 and glutamate (body).

Findings – An application case is presented by setting up two experimental designs: a previous pilot AB pseudo-experimental design with a subject and a subsequent ABC experimental design with another subject, where the stimulus used is the stimulant drug methylphenidate. With the outcomes of the application case the response and the bridge models are validated.

Originality/value – The mathematical approach presented is based on a holistic personality model developed in the last years: the Unique Trait Personality Theory, which claims for a single trait, the General Factor of Personality, to understand the overall human personality.

***Keywords*:** body-mind problem; general factor of personality; response model; integro-differential equation; bridge model; second order partial differential equation; c-fos; DRD3; glutamate; methylphenidate.

1. Introduction

The objective of this paper is to provide a mathematical approach to the body-mind problem based on a holistic personality model developed in the last years: the *Unique Trait Personality Theory* (UTPT) [1, 2]. The UTPT claims for a unique trait, as synonymous of single trait, to understand the overall human personality. The concept "unique trait" is substituted latter by the equivalent concept of *General Factor of Personality* (GFP) in the work [2], in order to follow the generally accepted scientific term.

The studies about the central concept of GFP proposed by the UTPT define a new, emergent and novel field inside personality research. It treats about "the single general factor hypothesis" and proposes a general factor of personality within the Big Five Factors (B5F) model (the five factors are: Extraversion, Responsibility, Neuroticism, Openness to Experience and Agreeableness), occupying the GFP the apex of the hierarchy of personality factors [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. The *Five-Adjective Scale of the General Factor of Personality* (GFP-FAS) [14, 15] offers the possibility to measure the dynamical change of the GFP in a single individual, due to its strong correlation with the GFP questionnaire [2]. Thus, having a dynamically observable instrument to measure the GFP (the GFP-FAS) is fundamental for the here presented dynamical mathematical approach to the body-mind problem.

In addition, the GFP has a physiological base, given by the *general activation* of the stress system (general activation, for short). The general activation is also particularly asserted as the brain activation level if it is particularized to the general activation in brain [2, 16]. Moreover, two kinds of general activation can be distinguished depending on the conditions acting on the stress system: the *tonic general activation* (the state of the general activation in absence of stimuli), and the *phasic general activation* (the dynamic response of the general activation as a consequence of one or more stimuli). Both the psychological level of description, given by the GFP, and its corresponding physiological level of description, given by the general activation, can change along time as a consequence of a stimulus.

The biological level of description has to be taken into account for an overall personality description. The biological level is constituted by the biochemical indicators related to personality and their dynamical interrelationships. The three biochemical indicators considered in this paper are the regulator gens c-fos and DRD3, and the neurotransmitter glutamate. They have been chosen due to their close relationship with personality, such as it is tried to be demonstrated in the following paragraphs.

The scientific literature shows a close relationship between personality and c-fos expression. Take into account that c-fos expression is considerably increased in brain's regions involved in the regulation of arousal states, such as the locus coeruleus (noradrenergic neurons) and the medial preoptic area (non-GABAergic neurons) [24]. In [22] it is demonstrated that the response model is capable to reproduce the joint dynamics of the immediate-early gen c-fos (body) and the GFP (mind) as a consequence of a methylphenidate dose and suggests the need to deepen into this relationship from a mathematical approach.

There is also a close relationship between personality and DRD3 expression. For instance, DRD3 is considered to play a major role in cognition and emotion [25], in neuropsychiatric diseases [26], and in personality [27]. Further, there is evidence that DRD3 plays a role in addiction mechanisms, such as drug-seeking and drug-taking behavior [28, 29]. In fact, the work [30] demonstrates that, such as it happens in the experimental designs of [2], a self-regulation therapy produces changes in the GFP (mind) and the DRD3 expression (body), which brings us again the need to deepen into this relationship from a mathematical approach.

Besides, glutamate is not only a neurotransmitter. Glutamate has regulatory functions in immune-component cells and in nervous system. Glutamate is an indicator of the organism's general state of activation, and thus of the GFP. In fact, the joint dynamics of glutamate and the GFP has been successfully described with the response model as a consequence of a methylphenidate dose in [31]. This work [31] demonstrates again the need to deepen into this relationship from a mathematical approach.

The use of methylphenidate as the stimulus in the application case presented here is suitable. Actually, such as the works [32, 33] demonstrate, a previous dopamine deficit in brain favors a greater increase of dopamine in brain in response to a dose of methylphenidate [1]. Note that the

increase of dopamine in the brain is equivalent to an increase of the general activation, and thus of the GFP.

The here presented response model is an integro-differential equation that is a generalization of the model presented in [16]. It has been validated in [21] when the stimulus is caffeine and in [22] when the stimulus is methylphenidate. The model reproduces accurately the dynamic patterns of the brain activation as a consequence of a stimulant drug intake, such as it is predicted by the works [17, 18, 19, 20]. These works predict a general dynamic pattern given by an inverted U-shape, but other exceptional patterns can also be observed, such as an inverted-U followed by a recovering U, a decaying U from the beginning until the end of the experimental period or a growth that tends to maintain a constant value in the experimental period. In addition, the generalized response model is the here used one to reproduce the dynamics of the GFP, the c-fos, the DRD3 and the glutamate, as a consequence of a methylphenidate dose intake.

An important assumption to relate mathematically the psychological level of description (mind) with the biological level of description (body) is the *invariance principle*. It asserts that the response model has the same mathematical structure to describe both the dynamics of the GFP (mind) and the biochemical indicators related to personality (body): c-fos, DRD3 and glutamate. As a consequence of the invariance principle, the so-called bridge model, a second order partial differential equation, can be deduced. The bridge model provides the co-evolution or dynamical relationship between every biochemical indicator, the GFP and time (through the time dependence of the stimulus).

Two previous versions of the bridge model have also been used in personality theory [34, 35]. However, the here deduced bridge model version presents a theoretical advance, respect to the models presented in [34, 35]. On a hand, the bridge model proposed in [35] relates the Big Five Factors (B5F) with the GFP and time. It has the restriction that no inhibitor delay (see Section 2, for the meaning of this term) is present in the simplified version of the response model that the authors applied to both the GFP and the B5F dynamics. Its validation takes place in the context of an experimental design where the participants consumed caffeine. In that case, the deduced bridge model is a first order partial differential equation that relates every component of the B5F with the GFP and time. On the other hand, the referred inhibitor delay is considered in [12] to develop a first mathematical approach about the body-mind problem by using another bridge model: a set of two coupled first order partial differential equations that relates c-fos and glutamate with the GFP response and time. Its validation takes place in the context of an experimental design where the participants consumed methylphenidate. However, despite its generality, obtained by including the inhibitor delay term, that model produces in some cases artificial singularities due to the imprecision to state boundary conditions, which makes difficult to handle it numerically. The bridge model proposed in the present paper reformulates the two coupled partial differential equations as a second order partial differential equation, on which two boundary conditions are precisely formulated and no singularities are observed, which makes easier to handle it numerically.

This paper is organised as follows. Section 2 the response model is presented and explained. Section 3 the bridge model is deduced from the response model by the invariance principle. Section 4 is devoted to present the experimental designs. The results obtained from them are used to

validate the response model for the GFP and the biological indicators (c-fos, DRD3, and glutamate) in Section 5, and to validate the bridge model in Section 6. The conclusions of the work are presented in Section 7, together with the paper discussion.

2. The response model

The response model is the mathematical tool used to compute the short term dynamics of the GFP as a result of a stimulus produced by a single dose intake of a drug, such as it has been used in [16, 21, 22, 31, 34, 35]. Let us recall the response model in the following paragraphs.

Assuming that no drug is present in the organism before consuming it, the stimulus time dependence *s(t)*, i.e., the amount of drug in the organism not yet consumed (or metabolized) by cells at time *t*, is provided by the function:

$$s(t) = \begin{cases} \frac{\alpha \cdot M}{\beta - \alpha}(\exp(-\alpha \cdot t) - \exp(-\beta \cdot t)) : \alpha \neq \beta \\ \alpha \cdot M \cdot t \cdot \exp(-\alpha \cdot t) : \alpha = \beta \end{cases} \quad (1)$$

In Eq. 1, M is the initial amount of a drug single dose, α is the drug assimilation rate, and β is the stimulus elimination rate.

The dynamics of the *GFP* is given by the following equation:

$$\left.\begin{array}{c} \frac{dy(t)}{dt} = a(b - y(t)) + \frac{p}{b}s(t) - b \cdot q \cdot \int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x)\, dx \\ y(0) = y_0 \end{array}\right\} \quad (2)$$

Eqs. 1 and 2 represent the response model. In Eq. 2, $s(t)$ represents the stimulus given by Eq. 1; $y(t)$ represents the GFP dynamics; and b and y_0 are respectively its tonic level and its initial value. The dynamics of Eq. 2 is a balance of three terms, which provide the time derivative of the *GFP*: the *homeostatic control* ($a(b - y(t))$), i.e., the cause of the fast recovering of the tonic level b, the *excitation effect* ($p \cdot s(t)/b$), which tends to increase the GFP, and the *inhibitor effect* ($\int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x)\, dx$), which tends to decrease the GFP and is the cause of a continuously delayed recovering, with the weight $e^{\frac{x-t}{\tau}}$. Parameters a, p, q and τ are named respectively the *homeostatic control power*, the *excitation effect power*, the *inhibitor effect power* and *the inhibitor effect delay*. All the parameters of the model depend on the individual personality or individual biology and on the type of stimulus. The correct interpretation of the tonic level b is important to be stressed: its value is situational and depends on the individual and the kind of stimulus. The response model provided such as Eq. 2 is fundamental to deduce the bridge model.

Besides, Eq. 2 can be transformed into a system of two coupled differential equations. To do this, let us define the $z(t)$ variable as:

$$z(t) = \int_0^t e^{\frac{x-t}{\tau}} \cdot s(x) \cdot y(x)\, dx = e^{-\frac{t}{\tau}} \int_0^t e^{\frac{x}{\tau}} \cdot s(x) \cdot y(x)\, dx \quad (3)$$

Then, by taking the time derivative of $z(t)$:

$$\left.\begin{array}{c}\frac{dy(t)}{dt} = a(b - y(t)) + \frac{p}{b}s(t) - b{\cdot}q{\cdot}z(t) \\ y(0) = y_0\end{array}\right\} \quad (4)$$

$$\left.\begin{array}{c}\frac{dz(t)}{dt} = -\frac{z(t)}{\tau} + s(t){\cdot}y(t) \\ z(0) = 0\end{array}\right\} \quad (5)$$

Eqs. 1, 4 and 5 define an equivalent mathematical structure of the response model given by Eqs. 1 and 2, and they are used to obtain in an easy way its numerical solutions.

3. The bridge model

In order to deduce the bridge model, the starting point is assuming the invariance principle, i.e., the dynamical response of every biological indicator can be also described by the response model, but with different parameter values. Thus, let us call E_i to each one of the three biological indicators, with $1 \leq i \leq 3$: $E_1 \equiv C$ (c-fos), $E_2 \equiv D$ (DRD3) and $E_3 \equiv G$ (glutamate). In addition, if $E_i^{(0)}$is the corresponding initial value in t=0, and A_i, B_i, P_i, Q_i and T_i are the corresponding parameters, the response model corresponding to the biological indicators can be written as:

$$\left.\begin{array}{c}\frac{dE_i(t)}{dt} = A_i(B_i - E_i(t)) + \frac{P_i}{B_i}s(t) - B_i{\cdot}Q_i{\cdot}\int_0^t e^{\frac{x-t}{T_i}}{\cdot}s(x){\cdot}E_i(x)\,dx \\ E_i(0) = E_i^{(0)}\end{array}\right\} \quad (6)$$

Note in Eq. 6 that $1 \leq i \leq 3$. From now on wards the subscripts will hold this meaning. In addition, note also that $s(t)$ is the stimulus function, i.e., it is the same than in Eq. 1, which means that it is the same for the three biological indicators and for the GFP. The invariance principle assumes that the influence of the stimulus on the three biological indicators and on the GFP is the same. Therefore, from this hypothesis, $s(t)$ only depends on the individual biology and on the kind of stimulus. As a consequence, α (assimilation rate) and β (elimination rate) parameters have the same value for the three biological indicators and for the GFP.

Note again that with the change specified in the following equation:

$$F_i(t) = \int_0^t e^{\frac{x-t}{T_i}}{\cdot}s(x){\cdot}E_i(x)\,dx = e^{-\frac{t}{T_i}}\int_0^t e^{\frac{x}{T_i}}{\cdot}s(x){\cdot}E_i(x)dx \quad (7)$$

Eq. 6 becomes a system of two coupled differential equations:

$$\left.\begin{array}{c}\frac{dE_i(t)}{dt} = A_i(B_i - E_i(t)) + \frac{P_i}{B_i}s(t) - B_i{\cdot}Q_i{\cdot}F_i(t) \\ E_i(0) = E_i^{(0)}\end{array}\right\} \quad (8)$$

$$\left.\begin{array}{c}\frac{dF_i(t)}{dt} = -\frac{F_i(t)}{T_i} + s(t){\cdot}E_i(t) \\ F_i(0) = 0\end{array}\right\} \quad (9)$$

Eqs. 10 and 11 constitute an equivalent mathematical structure of the response model given by Eq. 6, and they are used to obtain in an easy way its numerical solutions.

To find the mathematical relationship among the biological indicators (E_i), and the GFP (y) and time (t), the starting point is to consider that it can be written as:

$$E_i = E_i(t,y) \tag{10}$$

Taking the time derivative in Eq. 10:

$$\frac{dE_i(t,y)}{dt} = \frac{\partial E_i(t,y)}{\partial t} + \frac{\partial E_i(t,y)}{\partial y}\frac{dy}{dt} \tag{11}$$

Substituting Eqs. 2 and 6 in Eq. 11, taking into account Eqs, 5 and 9, and considering now that the time function $E_i(t)$ is, from Eq. 10, a two-variables function $E_i(t,y)$:

$$A_i(B_i - E_i(t,y)) + \frac{P_i}{B_i}s(t) - B_i \cdot Q_i \cdot F_i(t,y) = \frac{\partial E_i(t,y)}{\partial t} + \frac{\partial E_i(t,y)}{\partial y}\left(a(b-y) + + \frac{p}{b}s(t) - b \cdot q \cdot z(t)\right) \tag{12}$$

In Eq. 12, $z(t)$ is given by Eq. 3, and $F_i(t,y)$, considering Eq. 7, is given by:

$$F_i(t,y) = \int_0^t e^{\frac{x-t}{T_i}} \cdot s(x) \cdot E_i(x,y)dx = e^{-\frac{t}{T_i}} \int_0^t e^{\frac{x}{T_i}} \cdot s(x) \cdot E_i(x,y)dx \tag{13}$$

Differing from the equation presented in [35] as the bridge model, Eq. 12 is a partial integro-differential equation, where the integral term is due to Eq. 13, which makes difficult to handle the model mathematically. An alternative way to solve this difficulty is to consider the substitution of Eq. 10 by $E_i = E_i(t,y,z)$. This approach is held in [41], and the alternative model to Eq. 12 is provided by a set of two coupled first order partial differential equations. However, although an analytical solution seems to be impossible for both approaches, getting a numerical solution presents difficulties due to the artificial dependence on z in $E_i(t,y,z)$. The way to avoid the z dependence and to avoid the direct work with a partial integro-differential equation such as Eq. 12 is to convert it into a second order partial differential equation. To do this, the partial time derivative is took in both sides of Eq. 12:

$$-A_i\frac{\partial E_i(t,y)}{\partial t} + \frac{P_i}{B_i}s'(t) - B_i \cdot Q_i\frac{\partial F_i(t,y)}{\partial t} = \frac{\partial^2 E_i(t,y)}{\partial t^2} + \frac{\partial^2 E_i(t,y)}{\partial t\,\partial y}\left(a(b-y) + \frac{p}{b}s(t) - b \cdot q \cdot z(t)\right) + \frac{\partial E_i(t,y)}{\partial y}\left(\frac{p}{b}s'(t) - b \cdot q \cdot z'(t)\right) \tag{14}$$

Note from Eq. 5 that $z'(t) = -\frac{1}{\tau}z(t) + s(t) \cdot y$, and from Eq. 13:

$$\frac{\partial F_i(t,y)}{\partial t} = -\frac{1}{T_i}e^{-\frac{t}{T_i}}\int_0^t e^{\frac{x}{T_i}} \cdot s(x) \cdot E_i(x,y)dx + e^{-\frac{t}{T_i}} \cdot e^{\frac{t}{T_i}} \cdot s(t) \cdot E_i(t,y) = -\frac{1}{T_i}F_i(t,y) + s(t) \cdot E_i(t,y) \tag{15}$$

The substitution of Eqs. 5 and 15 in Eq. 14 provides:

$$-A_i\frac{\partial E_i(t,y)}{\partial t}+\frac{P_i}{B_i}s'(t)+\frac{B_i\cdot Q_i}{T_i}F_i(t,y)-B_i\cdot Q_i\cdot s(t)\cdot E_i(t,y)$$
$$=\frac{\partial^2 E_i(t,y)}{\partial t^2}+\frac{\partial^2 E_i(t,y)}{\partial t\,\partial y}\left(a(b-y)+\frac{p}{b}s(t)-b\cdot q\cdot z(t)\right)+$$
$$+\frac{\partial E_i(t,y)}{\partial y}\left(\frac{p}{b}s'(t)+\frac{b\cdot q}{\tau}\cdot z(t)-b\cdot q\cdot s(t)\cdot y\right) \quad (16)$$

The next step is the elimination of the integral term $B_i\cdot Q_i\cdot F_i(t,y)$ in Eq. 16. First, the term is isolated from Eq. 12:

$$B_i\cdot Q_i\cdot F_i(t,y)=A_i\left(B_i-E_i(t,y)\right)+\frac{P_i}{B_i}s(t)-\frac{\partial E_i(t,y)}{\partial t}-\frac{\partial E_i(t,y)}{\partial y}$$
$$\left(a(b-y)++\frac{p}{b}s(t)-b\cdot q\cdot z(t)\right) \quad (17)$$

Subsequently Eq. 17 is substituted in Eq. 16, and after reorganization:

$$\frac{\partial^2 E_i(t,y)}{\partial t^2}+\left(a(b-y)+\frac{p}{b}s(t)-b\cdot q\cdot z(t)\right)\frac{\partial^2 E_i(t,y)}{\partial t\,\partial y}+$$
$$\left(\frac{p}{b}s'(t)+\frac{b\cdot q}{\tau}\cdot z(t)-b\cdot q\cdot s(t)\cdot y+\frac{1}{T_i}\left(a(b-y)+\frac{p}{b}s(t)-b\cdot q\cdot z(t)\right)\right)\frac{\partial E_i(t,y)}{\partial y}+\left(A+\frac{1}{T_i}\right)\frac{\partial E_i(t,y)}{\partial t}=\frac{A_i}{T_i}$$
$$\left(B_i-E_i(t,y)\right)-B_i\cdot Q_i\cdot s(t)\cdot E_i(t,y)+\frac{P_i}{T_i\cdot B_i}s(t)+\frac{P_i}{B_i}s'(t) \quad (18)$$

Eq. (18) must be completed with the boundary conditions:

$$E_i(0,y)=E_i^{(0)} \quad (19)$$

$$\frac{\partial E_i}{\partial t}(0,y)=A_i\left(B_i-E_i^{(0)}\right) \quad (20)$$

Eqs. 18, 19 and 20 provide the new version of the bridge model. Note that Eq. 19 provides the initial condition for each one of the biological indicators, while Eq. 20 is obtained from Eq. 6 due to $s(t)=0$ before the drug consumption. For computation purposes in Eq. 18, $s(t)$ is the time function given by Eq. 1 and $s'(t)$ its time derivative, while $z(t)$ is considered a time function obtained from the numerical solution of the system given by Eqs 4 and 5. Note that from Eq. 3, the $z(t)$ term in Eq. 18 considers that its solutions assume all the past history of the GFP since the stimulus is provided.

4. The experimental designs

The application case considered in order to validate the response and bridge models is put in practice for two subjects. A previous AB pseudo-experimental design is set up for Case 1 and a subsequent ABC experimental design is set up for Case 2. In fact, the design AB is not an experimental design, but an exploratory case study. Once positive results have been obtained that inform about a change in the scores of the scales of personality when taking 20 mg of methylphenidate compared with the base-line for Case 1, the authors decided to repeat the experiment with another subject, Case 2, but this time with an experimental design of unique case

with three phases: A, B and C, where Phase A is again the base-line, Phase B with taking 20 mg of methylphenidate, and Phase C with taking 40 mg of methylphenidate.

The participants (Case 1 and Case 2) are two males with 50 and 52 years old. They are two voluntaries of the university teaching staff. The instruments are the Five-Adjective Scale of the General Factor of Personality (GFP-FAS) [14, 15]. The 5 adjectives are: adventurous, daring, enthusiastic, merry and bored. Each adjective is evaluated by the subjects from 0 to 5, thus the scale of the GFP is $y \in [0,25]$.

The biological analyses to obtain the referred biological indicators are of two kinds. To obtain the c-fos and DRD3 samples, the lymphocytes of the blood samples were isolated by density centrifugation on Lymphoprep. Finally, an automated mass spectrometry platform (Sequenom, MassARRAY Quantitative Gene Expression) was used for quantification of the c-fos and the DRD3 concentrations in lymphocytes. β-actin was used as internal standard RNA. In addition, a mass spectrometer was used to obtain the glutamate level in blood. C-fos and DRD3 are measured by their molar concentration (mc) in lymphocytes in blood. The c-fos measures are used with a scale multiplied by 10^{18} mc and the DRD3 measures are used with a scale multiplied by 10^{21} mc. With these scales, the c-fos ($E_1 \equiv C$) and DRD3 ($E_2 \equiv D$) concentrations vary in the interval $C,D \in [0, 100]$. The glutamate $E_3 \equiv G$ is measured by the direct molar concentration (mc) in blood and it is used with a scale multiplied by 10^{18} mc. With this scale, the glutamate concentration varies in the interval $G \in [0, 60]$.

In all phases participants fill out the GFP-FAS each fifteen minutes (17 registers each phase) and peripheral blood samples are obtained each one hour (5 samples each phase). In addition the experimental conditions take place in a hospital room a morning with an empty stomach, with no drug consumption and in resting and isolated atmosphere, trying to minimize the external stimuli in Phases A and also to maximize the effect of methylphenidate in Phases B and C.

The AB pseudo-experimental design is set up for Case 1. Phase A is the base-line, without treatment. A week later, in Phase B, Case 1 receives a dose of 20 mg of methylphenidate immediately after filling out the first list of the GFP-FAS and the initial blood sample is obtained. In the following, Case 1 fills out 16 lists of the GFP-FAS, one each fifteen minutes, and a blood sample is obtained each hour along 4 hours.

One week later, the ABC experimental design is set up for Case 2. Phases A and B of Case 2 are set up in the same way than for Case 1, with Phases A and B separated for one week. One week later than Phase B, in Phase C Case 2 receives a dose of 40 mg of methylphenidate immediately after filling out the first list of the GFP-FAS and the initial blood sample is obtained. In the following, Case 2 fills out 16 lists of the GFP-FAS, one each fifteen minutes, and a blood sample is obtained each hour along 4 hours.

Observe that for Case 1 in Phase B and for Case 2 in Phases B and C, each one of the measures before consuming represent the initial conditions for the response model, which is evaluated with the initial condition plus the 16 lists of the GFP-FAS. Also the response model is evaluated with the initial condition plus the 4 blood samples for the biological indicators. In addition, the bridge model can only be evaluated with those outcomes that coincide in time, i.e., with the outcomes obtained each one hour. The results of both experiments are presented in the following sections in tables and graphics, in the context of the response and bridge models validation.

5. Validation of the response model

The aim of this section is to validate the response model by calibration for both the GFP and the three biological indicators for both experimental designs.

The calibration method consists in comparing the experimental data obtained from the different lists of scores with the theoretical values provided by the response model. On a hand, the experimental GFP-FAS scores are compared with the theoretical outcomes provided by the *y(t)* model variable given by Eqs. 1 and 2. On the other hand, the experimental biological scores are compared with the theoretical outcomes provided by the $E_i(t)$ model variables given by Eqs. 1 and 6.

To obtain the theoretical outcomes, Eqs. 2 and 6 have been programmed in C++ language, solving the equivalent differential equations, respectively, Eqs. 4 and 5 for Eq. 2, and Eqs. 8 and 9 for Eq. 6, by the 4th Runge-Kutta method. The C++ program includes the way to compare the experimental scores and the theoretical outcomes. It consists in minimizing the quadratic sum of both sets of data by generating random numbers. Observe in addition that in the method development the initial value of Eq. 4, y_0, and of Eq. 8, $E_i^{(0)}$, are known because they are the corresponding values before the methylphenidate stimulus is implemented.

Observe that the validation has sense when the methylphenidate stimulus is provided, i.e., for Phase B in the pseudo-experimental design AB, and for Phases B and C in the experimental design ABC. In addition, the goodness of the validation is here provided by: (a) the visual inspection of the Figure 1 that represent jointly the experimental and the theoretical outcomes, in the order: GFP, c-fos, DRD3 and glutamate; (b) for the fitting degree of both data sets, here computed by the determination coefficient (R^2), which varies in the interval [0,1]: the closer to the unit the determination coefficient is the better fitting degree of both data sets.

Observe also that Phases A of both experimental designs play the role of a control base-line: the observable differences between Phases A and Phases B and C (where the methylphenidate stimulus is provided) indicate that the stimulus produces an appreciable change.

Let us start with Case 1, corresponding to the pseudo-experimental design AB. Phase A of Case 1 is represented in Fig. 1 (a)-(d). Note that for this case, the responses to the quietness and isolation conditions of Phase A work as control base-line. On a hand, the experimental values change around a constant value such as it happens in Fig. 1(a) for the GFP or in Fig. 1(b) for the c-fos. On the other hand, Fig. 1(c) shows a slight inverted U-shape for the DRD3, and Fig. 1(d) a more stressed U-shape for the glutamate. However, the trends are different to those present in Phase B. In fact, besides, Phase B of Case 1 is represented in Figs. (f) – (i) as a consequence of a dose of 20 mg. Note that both the GFP (Fig. 1(f)) and the c-fos (Fig. 1(g)) present a stressed inverted U-shape dynamics, while the DRD3 dynamics (Fig. 1(h)) is oscillatory and the glutamate dynamics presents a slight inverted U-shape dynamics (Fig. 1(i)). All determination coefficients range between 0.85 and 0.97. Thus, the response model can be considered validated for Phase B of Case 1.

In order to validate with Case 2, corresponding to the experimental design ABC and Phase A of Case 2 is represented in Fig. 1 (j)-(m). Phase B of Case 2 is shown in Figs. Fig. 1 (o)-(r), illustrates the GFP, c-fos, DRD3 and glutamate dynamics as a consequence of a dose of 20 mg of

methylphenidate we proceed analogously to case 1 (using the same arguments). Let us remark that all determination coefficients range between 0.85 and 0.99. The response model can be considered validated for Phase B of Case 2. Similar arguments are used to validate the Phase C of Case 2, Fig. 1(s)-(v),that provides determination coefficients range between 0.82 and 0.99.

The corresponding optimal values of the model parameters for Phase B of Case 1, for Phase B Case 2 and Phase C of Case 2 are presented in Table 1. Note that those parameters corresponding to the stimulus equation have the same value for the GFP and for the three biological indicators.

6. Validation of the bridge model

The theoretical values provided by the bridge model, $E_i(t,y)$, are given by the numerical solutions of Eqs.18, 19 and 20, with the optimal parameter values obtained in the calibration process of the response model (Table 1). These numerical solutions have been obtained using the NDSolve function of MATHEMATICA 10.4. On a hand, the validation of the bridge model is provided by visual inspection: the joined representation of the experimental scores and the theoretical values $E_i(t,y)$ of the biological indicators versus the experimental values of the GFP. On other hand, the validation is supported by the corresponding determination coefficients of both sets of data. Note that this validation has only sense for Phase B of Case 1 and for Phases B and C of Case 2.

Consider Phase B of Case 1 and the corresponding optimal values of Table 1 to obtain the theoretical values by using the bridge model. Fig. 2 (a)-(d) present the joined results of the experimental biological indicators and theoretical values versus the GFP experimental values. Note that, both the visual inspection of the figures and the determination coefficients that range between R^2=0.85 and R^2=0.97, provide the validation of the bridge model for Phase B of Case 1. Similar arguments can be used to validate the bridge model for the Phase B of Case 2 with determination coefficients that range between R^2=0.85 and R^2=0.99 (see Fig. 2(e)-(g)) and Phase C of Case 2 determination coefficients that range between R^2=0.82 and R^2=0.99 (see Fig. 2(h)-(k)).

The general conclusion of this section is that the bridge model can be considered validated from the outcomes of both experimental designs.

7. Conclusions and discussion

The response model has been validated by calibration in the context of a previous (pilot) AB experiment and a subsequent ABC experimental design. As a consequence of getting the optimal parameter values for the response model, the presented bridge model has also been validated. Thus, it is confirmed that the GFP and the three biological indicators, c-fos, DRD3 and glutamate, vary jointly in response to a dose of a stimulating drug (methylphenidate). In addition, the validation of the bridge model in the context of both experimental designs provides the co-evolution of the GFP (mind) and the three biological indicators, c-fos, DRD3 and glutamate, (body). However, it seems obvious that future experimental designs might consider more subjects and more phases, due to the present study is centered on individuals, not in groups. The experimental designs of groups

would provide statistical significations, which would increase the consistency of the response and bridge models. Besides, other kinds of stimuli should be considered in alternative experimental designs, such as caffeine, alcohol, self-regulation therapy, etc., which would also consolidate the value of response and bridge models to study the body-mind problem.

In addition, let us stress that the bridge model is consequence of the assumption of the mathematical invariance principle, which determines the same mathematical structure to describe the dynamics of the GFP and the three biological indicators. Thus, here works the assumption of the general applicability in behavioral sciences of the differential models used by physics and other disciplines related with applied mathematics. This assumption has been demonstrated in the last centuries in science as a method to study successfully dynamics, complexity and nonlinearity. In fact, both the response and the bridge models have been demonstrated that are two successful mathematical tools to study the co-evolution of the GFP and the three biological indicators, as a consequence of a stimulus, such as a single dose of methylphenidate. Then, both models provide a new perspective to study the body-mind problem.

The new perspective has to be framed in practical applications in future. In fact, a concrete application of the bridge model would consist in being used to simulate changes in biology from the self-regulation therapy: those changes that would steer biology towards suitable dynamical states for the individual personality.

Note however that the present investigation is based on short term dynamics described by the response model. But the response model presented in [23] provides predictions at long term. A corresponding bridge model deduced under the invariance principle from the response model of [23] would be suitable to simulate changes in biology and personality at long term. This further bridge model would provide a tool to solve, for instance, problems of addiction from the double behavioral and biological perspective.

It is over understood by the authors that a definitive solution of the body-mind problem must consider the overall biology that underlies personality, which involves much more biological indicators than those here presented and their dynamical interrelationships, as well as their interaction with the stress system through the nervous system. In other words, a unified theory of the three levels of personality description: biological, physiological and psychological ones.

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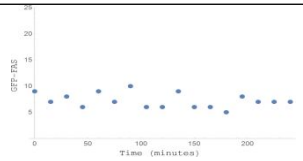
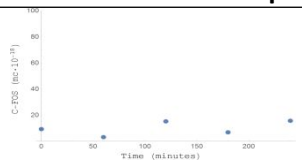
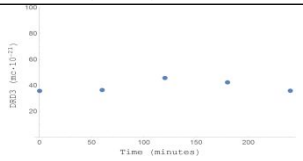
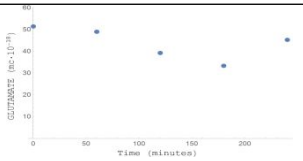
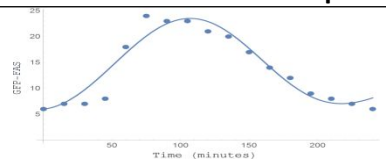
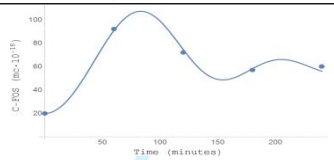
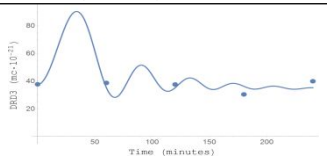
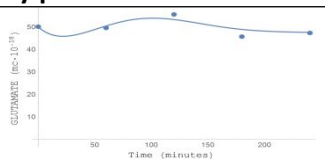
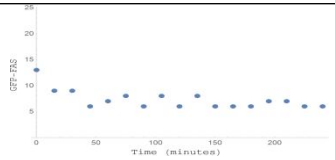
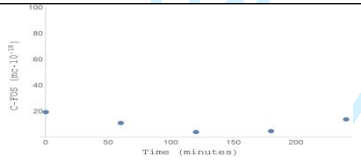
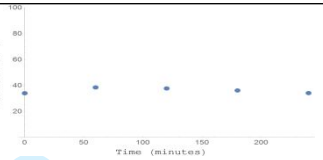
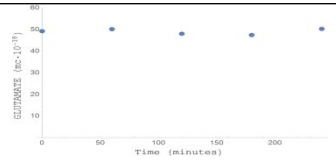
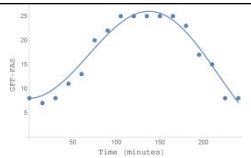
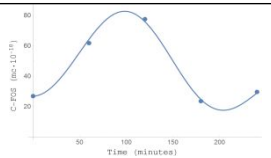
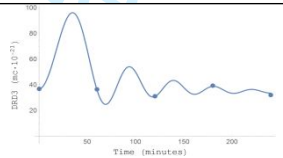
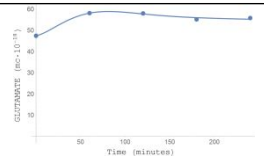
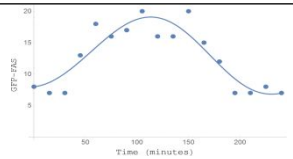
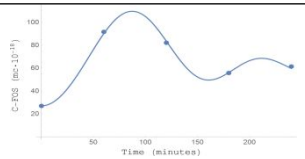
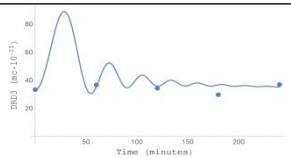
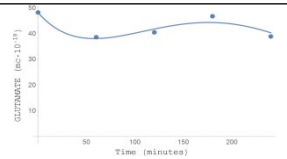
Design	CFP-FAS	C-FOS	DRD3	GLUTAMATE
PHASE A. CASE 1. **Experimental values (dots).**				
AB.	 (a)	 (b)	 (c)	 (d)
PHASE B. CASE 1. **Experimental values (dots) and theoretical values (curve). Dose of 20 mg of methylphenidate.**				
AB.	 (f) R^2=0.91.	 (g) R^2=0.97.	 (h) R^2=0.93	 (i) R^2=0.85
PHASE A. CASE 2. **Experimental values (dots) corresponding to the pseudo-experimental design AB.**				
ABC.	 (j)	 (k)	 (l)	 (m)
PHASE B. CASE 2. **Experimental values (dots) and theoretical values (curve). Dose of 20 mg of methylphenidate.**				
ABC.	 (o) R^2=0.97.	 (p) R^2=0.99.	 (q) R^2=0.95.	 (r) R^2=0.85.
PHASE C. CASE 2. **Experimental values (dots) and theoretical values (curve). Dose of 40 mg of methylphenidate.**				
ABC.	 (s) R^2=0.83.	 (t) R^2=0.99.	 (u) R^2=0.99.	 (v) R^2=0.82.

Figure 1 Validation of the response and bridge model.

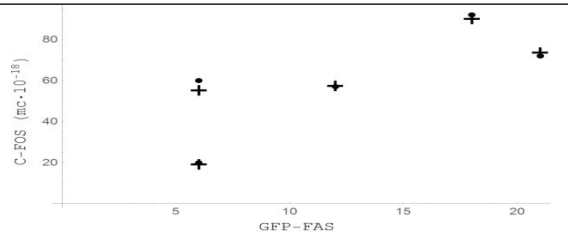
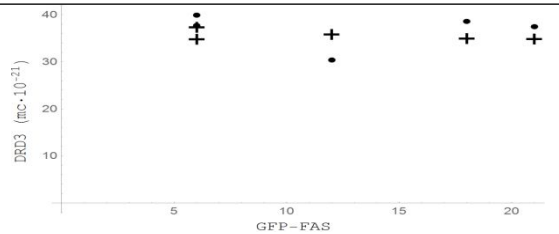
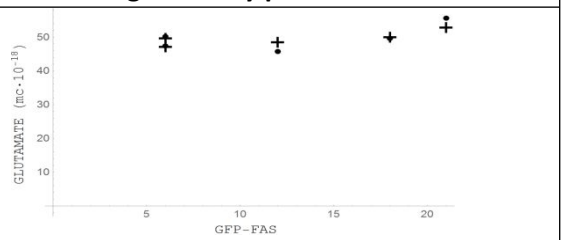
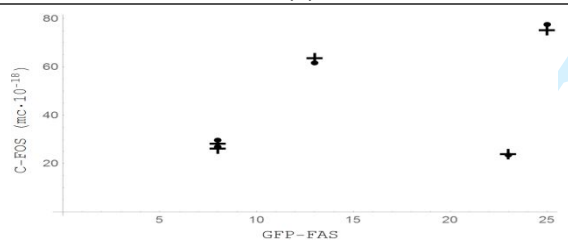
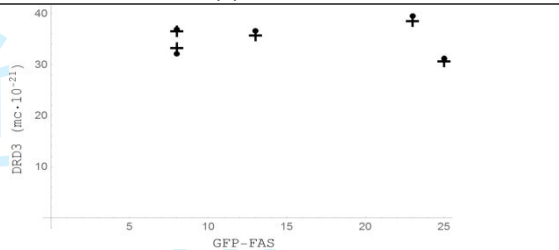
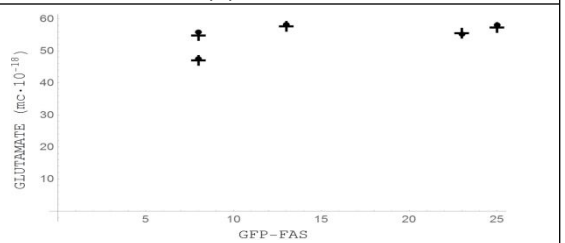
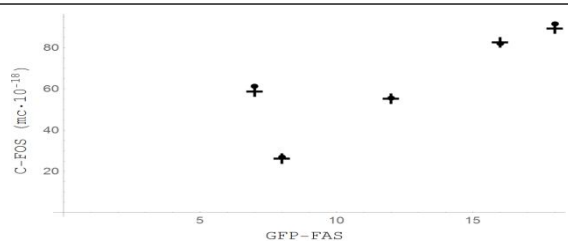
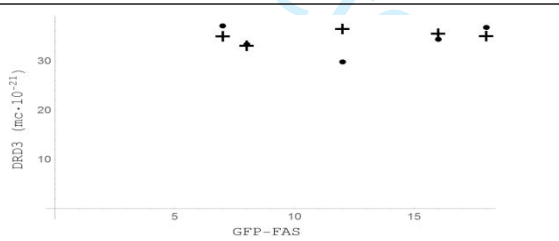
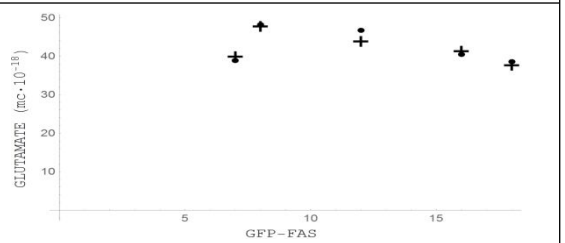
Design	***PHASE B. CASE 1*. Experimental values (dots) and theoretical values (crosses). Dose of 20 mg of methylphenidate**		
AB.	 (a) R^2=0.97.	 (c) R^2=0.94.	 (d) R^2=0.85.
ABC.	 (e) R^2=0.99.	 (f) R^2=0.95.	 (g) R^2=0.85.
***PHASE C. CASE 2.* Experimental values (dots) and theoretical values (crosses). Dose of 40 mg of methylphenidate.**			
ABC.	 (h) R^2=0.99.	 (j) R^2=0.99.	 (k) R^2=0.82.

Figure 2 Comparasion between CFP and FAS. Different cases and doses

Design AB. PHASE B. CASE 1. Dose of 20 mg of methylphenidate.				
Parameters	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	2.0000e+001	2.0000e+001	2.0000e+001	2.0000e+001
Inhibitor effect delay (T_i)	1.0213e+002	4.3812e+001	3.0735e+001	3.6923e+001
Assimilation rate (α)	3.2861e-003	3.2861e-003	3.2861e-003	3.2861e-003
Distribution rate (β)	8.8380e-004	8.8380e-004	8.8380e-004	8.8380e-004
Homeostatic control power (A_i)	4.9064e-003	6.3018e-004	4.0129e-003	1.7164e-002
Tonic level (B_i)	1.0924e+001	1.4871e+001	1.6519e+001	2.3570e+001
Excitation effect power (P)	1.3322e+000	1.4456e+001	6.3232e+001	8.5710e+000
Inhibitor effect power (Q_i)	1.2676e-005	2.8545e-005	2.3233e-004	8.4998e-006
Design ABC. PHASE B. CASE 2. Dose of 20 mg of methylphenidate.				
	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	2.0000e+001	2.0000e+001	2.0000e+001	2.0000e+001
Inhibitor effect delay (Ti)	1.7473e+002	8.2863e+001	3.1139e+001	1.1166e+001
Assimilation rate (α)	5.3711e-003	5.3711e-003	5.3711e-003	5.3711e-003
Distribution rate (β)	1.5732e-003	1.5732e-003	1.5732e-003	1.5732e-003
Homeostatic control power (Ai)	2.6764e-004	0	2.8734e-004	1.2631e-002
Tonic level (Bi)	4.6680e+000	2.0365e+001	1.8213e+001	5.3462e+001
Excitation effect power (P)	2.4243e-001	6.1950e+000	4.4131e+001	1.1024e+001
Inhibitor effect power (Qi)	8.4485e-006	5.7396e-006	1.2699e-004	6.2781e-006
Design ABC. PHASE C. CASE 2. Dose of 40 mg of methylphenidate.				
	GFP dynamics	C-FOS	DRD3	GLUTAMATE
Methylphenidate dose (M)	4.0000e+001	4.0000e+001	4.0000e+001	4.0000e+001
Inhibitor effect delay (Ti)	9.1556e+001	4.7736e+001	2.4158e+001	9.8056e+002
Assimilation rate (α)	1.0778e-003	1.0778e-003	1.0778e-003	1.0778e-003
Distribution rate (β)	7.4257e-004	7.4257e-004	7.4257e-004	7.4257e-004
Homeostatic control power (Ai)	1.7457e-003	0	5.3887e-003	1.4485e-002
Tonic level (Bi)	1.6158e+001	2.5438e+001	8.4389e+000	1.8165e+001
Excitation effect power (P)	1.6580e+000	3.1705e+001	7.2391e+001	2.7192e+000
Inhibitor effect power (Qi)	9.4120e-006	2.0085e-005	1.2778e-003	1.3752e-006

Table 1 . Optimal values of the response model for different cases.