Identification and Control of Intrinsic Bias in a Multiscale Computational Model of Drug Addiction

Yariv Z. Levy
University of Massachusetts
Department of CS
Amherst, MA 01003, USA
+1 (413) 545-2744
ylevy@cs.umass.edu

Dino Levy
New York University
Center for Neural Science
New York, NY 10003, USA
+1 (212) 998-3904
dino.levy@nyu.edu

Jerrold S. Meyer
University of Massachusetts
Department of Psychology
Amherst, MA 01003, USA
+1 (413) 545-2168
jmeyer@psych.umass.edu

Hava T. Siegelmann
University of Massachusetts
Department of CS
Amherst, MA 01003, USA
+1 (413) 545-2744
hava@cs.umass.edu

ABSTRACT

Personalized medicine is rapidly evolving with the objective of providing a patient with medications based on the "use of genetic susceptibility or pharmacogenetic testing to tailor an individual's preventive care or drug therapy" [1]. It is reasonable to foresee that this domain will incorporate sources of biological knowledge other than genetics including computational modeling of diseases. For this purpose, a critical issue is how to identify and control systematic biases that may arise. In this paper, a multiscale computational model of drug addiction is presented and the interpretations of the simulated behavioral profiles of a virtual subject are discussed. These outcomes are analyzed using mathematical analytical techniques with particular attention directed to minimization of systematic biases. The simulations exemplify how a structural analysis of the model, prior to the actual simulations, may benefit the overall framework in terms of accuracy. While this paper focuses on an equation-based model for drug addiction, a similar methodology could be applied to other types of computational models for other diseases.

Categories and Subject Descriptors

I.6.6 [**Simulation and Modeling**]: Simulation Output Analysis

General Terms

Experimentation, Measurement, Performance, Standardization.

Keywords

Drug Addiction, Dynamical System, High Dimensionality, Multiscale Modeling, Sensitivity Analysis.

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1. INTRODUCTION

Computational models of complex systems should encompass pertinent features without introducing bias towards a particular outcome. This issue can be very challenging, especially when parametric variables in the simulation lock the whole system leading to a biased result not representative of the system's real characteristics and properties.

In many disciplines, the study of complex systems can benefit from techniques used in signal processing, statistics, and dynamical systems. In image analysis studies, for example, techniques of mutual information and cross-correlation are used to match a set of images to a reference image [10], and in neuroscience such techniques are used to synchronize the topography of the brain's activities in schizophrenia [3], to understand the pathophysiology dysfunction in that disease [6], and to uncover and understand nonlinear coordination in the cardiorespiratory system [9].

In neuroscience, the large amounts of pertinent experimental data and high degree of complexity require detailed attention when building a mathematical framework. A multi-dimensional dynamic system model could fail to identify and take proper account of parameters, and may heavily bias the computational framework leading to an erroneous end result. Some models are extremely complex, but simplification of the underlying equations will lose their properties. Massive computation could potentially be used to investigate the effects of the model's parameters, but the main bottlenecks in this case are the availability of the computational power and time needed for such a task. A more practical approach may reside within a Sensitivity Analysis (SA) framework, "the study of how the variation (uncertainty) in the output of a mathematical model can be apportioned, qualitatively or quantitatively, to different sources of variation in the input of a model" [11].

The present investigation proposes a relatively simple yet potentially pertinent SA methodology to further understand the outcome of a complex system and minimize innate bias that may occur during the model's development. This approach is illustrated for the particular case of a theoretical multiscale model of drug addiction which was recently developed [4].

2. DRUG ADDICTION MODEL

A multiscale computational model of drug addiction was recently developed that integrates elements of neuropsychology, cognition, and behavior to simulate and predict whether a virtual subject will tend toward healthy or maladaptive drug-seeking behavior [4]. The essential features of this model are illustrated in Fig. 1. The overall output G(t) is the likelihood of drug-seeking behavior.

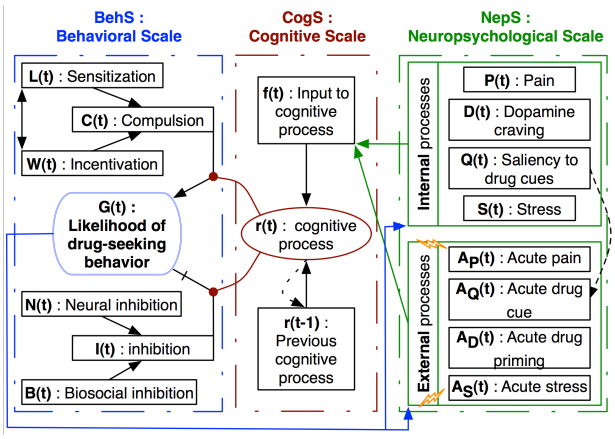

Figure 1. Computational model of drug addiction including Behavioral, Cognitive, and Neuropsychological Scales [4].

The neuropsychological scale of the model represents the ongoing cortical activity of the virtual subject. This scale comprises continuous "internal" processes and discrete "external" processes. The internal processes are progressive and include drug-related pain P(t), dopamine craving D(t), drug associated stress S(t), and saliency to drug cues Q(t). The comportment of these processes relies on the value of the model output G(t). The external processes are distinct events which may occur with a certain probability. If triggered, these processes have an acute effect, limited in time and variable in intensity. Such external processes include acute pain $A_P(t)$, acute drug cue $A_Q(t)$, acute drug priming $A_D(t)$, and acute stress $A_S(t)$. Both internal and external processes are weighted and summed at the cognitive scale by the process f(t):

$$f(t) = \left[-\omega_S S(t) + \omega_P P(t) - \omega_D D(t)\right] + \left\{\omega_A\left[-A_S(t) + A_P(t) - A_D(t)\right] - \omega_Q Q(t)\right\} \quad (1)$$

where ω_i are weights for the different processes. The value of f(t) is used to compute the cognitive rationality process r(t):

$$r(t) = \frac{1}{2}\tanh\left(\alpha \cdot r(t-1) + \beta \cdot f(t) + \gamma\right) + \frac{1}{2} \quad (2)$$

where α, β, and γ are constants. The cognitive rationality process regulates the competition between the compulsion process C(t) and the inhibition process I(t). These processes define the likelihood of drug-seeking behavior G(t), the model output, according to the relationship:

$$G(t) = -C(t)\left(1 - r(t)\right) + I(t)r(t) \quad (3)$$

A higher compulsion C(t) is more likely to express maladaptive behavior in the virtual subject, whereas a higher inhibition I(t) is more likely to express healthy behavior. Detailed descriptions and computational definitions for these processes are presented in [4].

A first attempt to analyze the outputs of this theoretical model considered averages, standard deviations, integrals of the function G(t) from its average, consistency of fluctuations for different virtual subject profiles, and convergence to attractors [5]. From this analysis, it was concluded that a person with more addictive tendencies has less fluctuation and flexibility in his/her drug-seeking behavior trajectory than a healthier person. The present study shows how an SA can be used to further understand the outcome of this complex system and minimize innate bias that may occur.

3. METHODS

3.1 Approach

The methodology proposed in this paper is a particular type of SA, namely a One Factor At a Time (OAT) screening technique. This OAT technique utilizes simulated results of the computational framework to evaluate how different values of the model's variables affect the overall simulation outcome one variable at a time [2,7]. First the model is repeatedly executed for different values of its parameters, and then the simulation outcomes are analyzed to determine the significance of a variable's value on the model's output.

Complex systems may require a large number of simulations to assess the effect of the variables on the model behavior. In this paper, it is shown how an early structural analysis prior to execution of the model can significantly reduce the number of simulations. The overall approach is illustrated in Fig. 2. Such an analysis can take advantage of inter-correlations existing between the real system and its mathematical description, and eventually provide a functional control, which may be refined after the model execution and analysis of the results. More specifically, this approach aims to integrate the system's phenomenological and mathematical aspects that have strong mutual relationships into a unique computational function. For this purpose, it may be adequate to consider the effect of a model's variable that is mathematically defined within a specific numerical interval. When this variable's value belongs to a particular subset of that numerical interval, analytical exploration may reveal systematic prejudice affecting the simulation outcomes. In this case, introduction of a functional control can reduce the size of the numerical interval. The functional control may be subsequently refined after the model execution based upon the outcomes.

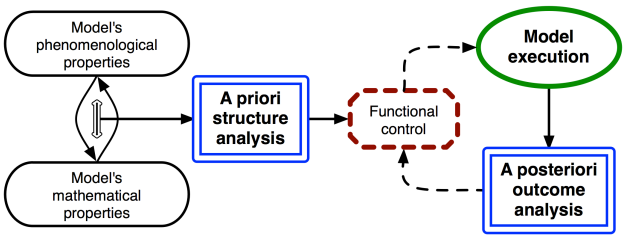

Figure 2. Structural analysis of the model is performed prior to its execution to create functional control of the variables.

A computational model should emulate a specific phenomenology and may require particular mathematical properties for this purpose. A structural analysis considering both of these factors and performed prior to the model's execution may help to control or reduce innate prejudices in favor or against a particular outcome of the model. For the drug addiction model described above, the a priori structural analysis is driven on the one hand by the involuntary but possible tendency to predispose the model's outcome toward a certain behavior, and on the other hand by the specificity of the functions which define the computations. More particularly, this model should be able to provide a control which allows the drug-seeking behavior trajectory (output of the model) to be flexible and able to fluctuate. The key sensitivity parameter in Eq. (2) is γ, so a functional control rule is needed to obtain appropriate values for this variable. Successive analyses of the results using selected signal processing tools are used to explore the effect of this control rule on γ and to show its benefits within the system.

3.2 Equation-based model structural analysis

It was previously found that the cognitive process r(t) may strongly affect the behavioral predisposition of a virtual subject in either facilitating or impeding healthy behavior [5]. Now we consider the procedures and simulation parameters to ensure that this process will not introduce any systematic bias to the model.

In Eq. (2), the values of α, β, and γ are constants, and f(t) is computed with respect to the internal and external processes. The hyperbolic tangent is a function in [-1,1], but after multiplying by 0.5 and adding 0.5, the hyperbolic tangent maps its inputs within the interval [0,1]. Therefore Eq. (2) can be rewritten as:

$$r(x) = \frac{1}{2}\tanh\left(\tilde{x} + \gamma\right) + \frac{1}{2} \quad \text{with} \quad \tilde{x} = \alpha \cdot r(t-1) + \beta \cdot f(t) \qquad (4)$$

For simplification, α and β are set equal to 1, and all the weights ω_i in the definition of the process f(t) are also set equal to 1. In this case, the values of $\tilde{x}$ belong to the interval [-5,3], since r(t-1) is in the interval [0,1], and the larger interval of f(t) is [-5,2]. For different values of γ, the function $y = 0.5 \cdot \tanh(x + \gamma) + 0.5$ moves horizontally. Positive values of γ slide the hyperbolic tangent value towards more negative values, whereas negative values move the function output towards more positive values.

The choice of the parameter γ in Eq. (2) can have a big influence on the process r(t), and consequently on the model output G(t). Unjustified low or high values of r(t) will force G(t) to be either too low or too high, respectively. In order to avoid such bias, the value of γ should not be arbitrarily chosen, but computed with respect to the parameters α, β, and all the weights ω_i in order to guarantee that the process r(t) is equal to 0.5 when the input to its hyperbolic function is equal to the middle value of the interval defining it. This condition requires that $\tanh(0.5 \cdot (Lb + Rb)) = 0$, where Lb is the left bound and Rb is the right bound of the hyperbolic tangent function input. For the example considered above where the interval of $\tilde{x}$ is [-5,3], the average value in the interval is -1 and γ should be set equal to 1 in order to satisfy that condition. More generally, for values of α, β, and all the weights ω_i not necessarily equal to 1, the choice of γ is given by:

$$\gamma = \frac{1}{2}\left[\alpha - \beta \cdot \left(\omega_S - \omega_P + \omega_D + \omega_A + \omega_Q\right)\right] \qquad (5)$$

Eq. (5) should be used to determine the unbiased value of γ, unless experimental evidence suggests otherwise.

4. RESULTS

In this section, some results are presented to illustrate the effect of γ on the model and how its value is selected. Two classes of simulations are tested each with three different γ values. The two classes of simulations are differentiated from each other by the value of the weighting factor ω_P in Eq. (1): $\omega_P = 0.55$ for class 1 and $\omega_P = 0.75$ for class 2. According to the model, a bigger value of ω_P causes a higher G(t). Both classes of simulations are computed and analyzed for different values of the parameter γ in Eq. (2). These include ad hoc values γ = 3.3 and γ = -1.3 for both classes of simulations, and also unbiased values γ = -0.49375 for class 1 and γ = -0.41875 for class 2 calculated from Eq. (5). Both classes of simulations refer to an 18 year old virtual subject who at the beginning of the simulation is addicted to a substance (e.g., alcohol or narcotics). Each class of simulation is composed of 100 simulated runs each with 720 time steps (the equivalent of 30 days). The means for each simulation over the 100 trials are presented in Fig. 3. Their corresponding standard errors are not included in this figure since the parameters of the simulations were specifically chosen to describe robust profiles with low standard errors.

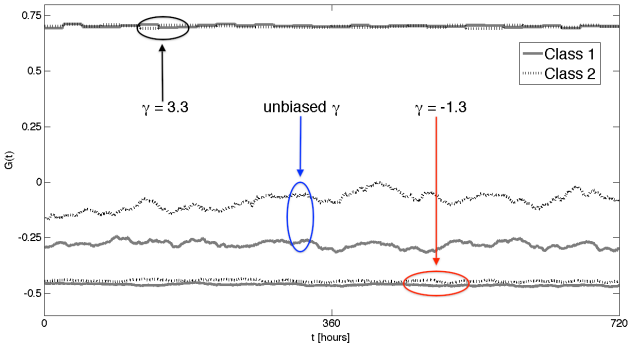

Figure 3. Output G(t) for the two simulation classes over 720 time steps with different values of γ.

4.1 Analysis of the results

The Pearson linear correlation coefficients between the two simulation classes for the three values of γ are [-0.2111, -0.1507, 0.3028] for γ = 3.3, the unbiased γ, and γ = -1.3, respectively. Despite very low correlations, the differences in their absolute values may suggest that the arbitrarily chosen values of γ give rise to behavioral profiles that are more nearly linear than the profile for which the parameter γ is computed from Eq. (5). Therefore using the unbiased values of γ may lead to simulated profiles having a weaker interdependence than those obtained using arbitrarily chosen values. The centered and not centered data (with respect to their means) showed the same Pearson coefficients.

The importance of time-dependant similarities between the two simulation classes is shown in Fig. 4 in terms of their cross-correlations and their normalized cross-correlations on the left- and right-hand sides, respectively. Simulations for γ = 3.3 have a notably higher maximum value of cross-correlation, whereas simulations achieved with the unbiased value of γ have a lower

maximum value. These magnitudes are not normalized and their comparison could lead to an inaccurate interpretation, but their symmetric characteristics are interesting: the graph on the right side of Fig. 4 suggests that for the two arbitrarily chosen values of γ, the similitude of the model outcome is symmetrical with respect to time. This relationship, which is difficult to see on the left graph, is less accentuated for those cases using the unbiased value of γ. For unbiased values of γ, the normalized cross-correlation is sometimes higher and sometimes lower than for simulations using very high or very low ad hoc γ values. This suggests that the profiles using an unbiased γ can express a more elaborated time dependent behavioral pattern than the ones using biased values.

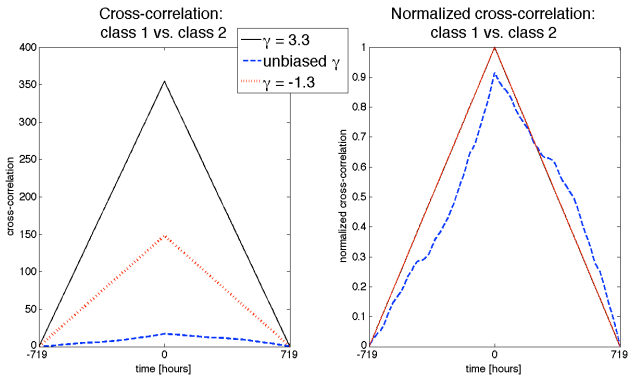

Figure 4. Cross-correlations and normalized cross-correlations between the two classes of simulations for each value of γ. Note that the normalized cross-correlation curves overlap for γ = 3.3 and γ = -1.3.

In order to further investigate the behavioral dissimilarity perceived between simulations using the unbiased γ, a number of 2 dimensional cross-correlations were conducted using the data from the single trials of each conducted simulation, not from their means as before. Fig. 5 shows the 2-D cross-correlations between the outcomes of class 1 and the outcomes of class 2 for each value of γ. The cross-correlation matrices in the first column were calculated using the raw data without any pretreatments. The cross-correlation matrices for data normalized with respect to themselves (local normalization) are presented in the middle column: every one of the 100 trials was subtracted from its own mean and divided by its standard deviation. Finally, the matrices for data normalized using the general mean and standard deviation of the whole simulation (global normalization) are presented in the third column.

The graphs in the first column using raw data show a clear disparity between the pattern expressed by the cross-correlation matrix using the unbiased γ and the others. On the one hand, the round shape motif becomes distorted, and on the other hand, accentuated horizontal irregularities are visible. For the data normalized with respect to themselves in the second column,, the unbiased γ simulations appear to have generally higher values of cross-correlation. Finally, for the data normalized with respect to the general mean and standard deviation in the third column, the simulations for γ = 3.3 and the unbiased γ both tend to show a pattern of horizontal lines.

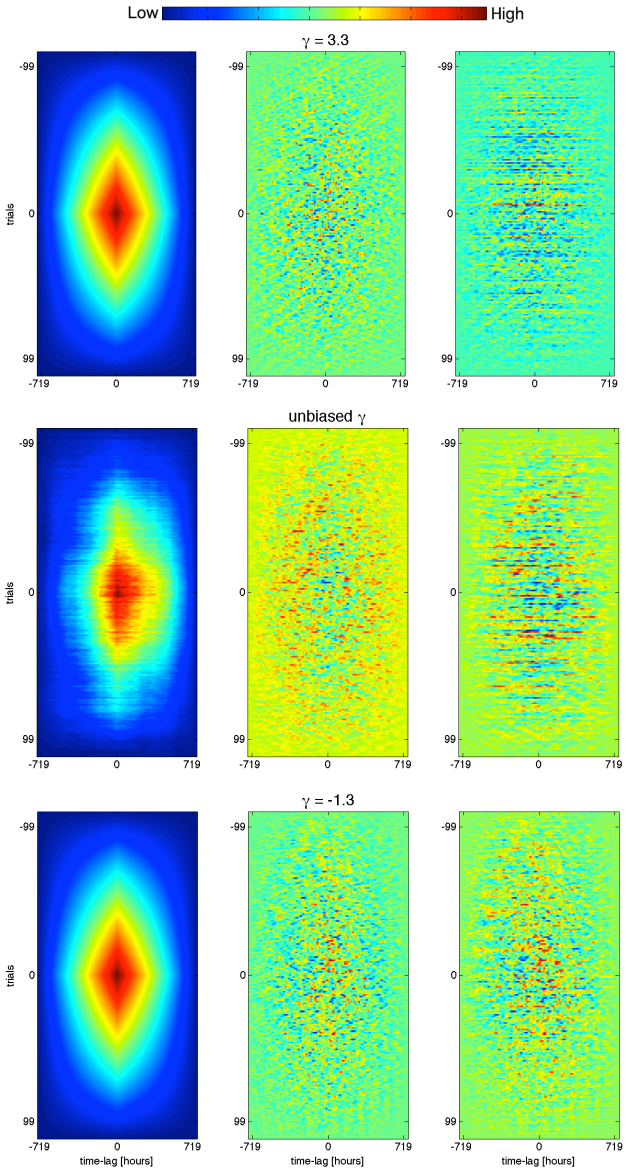

Figure 5. 2D cross-correlations matrices for simulation class 1 against simulation class 2 using raw data (column 1), local normalized data (column 2), and global normalized data (column 3).

5. CONCLUDING REMARKS

The analysis presented above shows how the selection of a single parameter among a large group of parameters can affect the end results of a dynamical system with high dimensionality. Analytical techniques were applied in order to evaluate how this parameter can intrinsically predispose the model towards a particular outcome. Two very similar simulated profiles related to the drug seeking behavior of a virtual subject were tested and compared against three values of the examined parameter.

From a mathematical standpoint, these exploratory results confirm the importance of properly selecting the value of a key parameter

prior to the execution of the simulations. The correlations show that controlled unbiased values of this parameter express a smaller linear dependency among their outcomes than uncontrolled values with bias. The cross-correlations provide additional insight regarding the potential effect of this key parameter. Stronger or weaker symmetrical evolutions of the cross-correlations reveal that unbiased simulations can express behavioral convergence and divergence over time which may not be obtained with biased simulations. Applying 2-D cross-correlations onto the simulated data normalized in different ways confirms the time dependant flexibility with unbiased simulations. By revealing distortions aligned with the time axis, the 2-D cross-correlations between unbiased experiments of raw and globally normalized data indicate the model's ability to express a variety of behavioral oscillations even when using very similar profiles. However, the discrepancies noted predominantly in the 2-D cross-correlation matrix of the raw data, but also discernible when using the locally normalized data, could be an indicator of the different tendencies that this model may express.

From a biological perspective, the present analyses, especially the 2-D cross-correlations, appear to provide indications about the behavioral evolution of a virtual subject in the context of addiction. For example, it is plausible to assume that the rounded shapes obtained from using the raw data might correspond to the oscillatory flexibility of a profile. This and other possible conjectures could benefit from a significantly higher set of experiments in order to reach the critical amount of behavioral diversity that this framework can express. The tools used to carry out the present exploratory analysis show great potential. Similar techniques are already successfully used in neuroscience to predict the electrical behavior of a neuron with respect to its genetic expression [12].

The methodology proposed in this paper utilizes a structural analysis prior to model execution using a global Sensitivity Analysis (SA) approach. While illustrated here for equation-based models, it should also be applicable to computational frameworks based upon non equation-based models. For example, it could be readily applicable to self-regenerating multi-agent systems whose agents act with respect to local rules to maintain self-health [8]. The agents in such a model follow particular protocols (replication, repair, self-death, etc.) which depend on the agent internal state and specific global probabilities. Some of these probabilities are subject to mathematical and biological constraints and could be appropriate candidates for structural analyses as proposed herein. Such analyses could lead to the definition of plausible numerical intervals for these probabilities before the actual execution of the model.

Computational models of complex systems can benefit from an early structural analysis. This method has been found to be especially beneficial in reducing the extent of computational investigations required to identify potential sources of systematic bias. However, the successful use of this method requires a good understanding of both the mathematical and physical properties of the system and its framework.

6. ACKNOWLEDGMENTS

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