Dynamical System Approach in Modeling Addiction

Selin Metin and N. Serap Şengör

Abstract A computational model combining reinforcement learning approach with an action selection (A-S) module is proposed to initiate a model for addiction. The A-S module is realized as a nonlinear dynamical system. The reinforcement mechanism adapts the parameters of the A-S module till the acquisition of nicotine addiction is set up. The interpretation of the parameters from the point of view of neuroscience is given and in order to investigate the dynamical behavior of A-S module, its bifurcation diagram is obtained. The result obtained encourages expanding the model to include the role of limbic structures on acquisition of addiction further.

1 Introduction

The interaction between limbic and cortical structures has been considered in explaining a large spectrum of cognitive processes including the addiction [1, 2, 3]. In this work, an initiate model of addiction based on the interactions of limbic and cortical structures is proposed. The model is influenced from a computational model of A-S through reinforcement learning [4] and nicotine addiction [5]. While the model is capable of revealing the effect of limbic system on addiction, it needs to be developed further to include the overall influence of limbic structures.

The main idea is to use dynamical systems approach in modeling a cognitive process, thus the behavior of A-S module is explained using bifurcation

Selin Metin
Istanbul Technical University, Electrical and Electronics Engineering Faculty, Maslak 34469, Istanbul, Turkey, e-mail: selinmetin@gmail.com

N. Serap Şengör
Istanbul Technical University, Electrical and Electronics Engineering Faculty, Maslak 34469, Istanbul, Turkey, e-mail: sengorn@itu.edu.tr

diagrams obtained by XPPAUT, while the addiction process is simulated with an m-file in MATLAB.

In the next section a brief summary of neural mechanisms considered in obtaining the model is given. In section 3, first the proposed model is introduced, then the behavior of A-S module is investigated and the simulation results are discussed. In the conclusion, how the proposed initiate model can be developed is discussed.

2 Neural Mechanisms of Addiction

Rewards are sensed as "making experiences better", and are therefore desired and pursued [6]. The behavior frequency, which lead to rewards, are increased by positive reinforcement. Addiction is a behavioral disorder characterized by compulsive drug seeking and repeated relapses into drug use [7]. It is thought that some irreversible modifications in the neural structures and/or synaptic plasticity cause addiction. Rewards in the form of drugs are experienced as more valuable compared to other rewards, thus they cause the addict's life's goal to become compulsive seeking and focusing on obtaining drugs.

The most effective neurotransmitter in addiction mechanism is dopamine (DA). The neural basis of the drug rewarding is the mesolimbic DA system. The value of the possible choices based on the reward gains of the past actions is stored in the memory. The organisms use this stored information to predict the results of each possible action as reward or punishment. An error is computed by comparing the outcome of the action and the reward gain of the prediction. DA is supposed to code this error and shape the future actions in order to increase reward gain [6]. The midbrain DA systems have important roles in motor and reward systems as well as in higher order functions such as cognition and memory [8].

There are two resources of DA secretion especially important for actions based on reward evaluation (Figure 1.): the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) [9]. The DA neurons in the VTA project to the limbic forebrain (nucleus accumbens, amygdala, hippocampus) and the prefrontal cortex (PFC).The DA neurons in the SNc, project to the dorsal striatum (caudate and putamen) [6]. All of these structures, except the nucleus accumbens (NA), have excitatory glutamatergic connections with the VTA which have a key role in VTA cell firing. Alterations in the mesocortical DA system and its glutamatergic feedback loop causes compulsive drug seeking and may trigger relapses into drug using [7].

Information obtained by rewards is important especially in reinforcement learning, and helps deciding between actions [9]. Natural rewards and addictive substances have similar effects on behaviors by increasing the synaptic DA level in NA [10]. Natural rewards and addictive substances have similar effects on behaviors by increasing the synaptic DA level in NA. Amygdala and

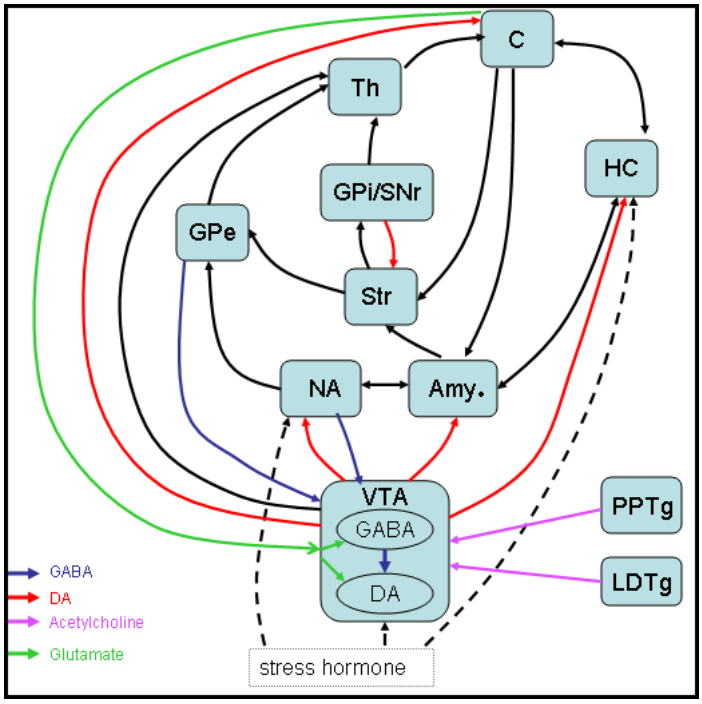

Fig. 1 The mesolimbic dopamine subsystem. Red, green, blue and purple arrows show DA, glutamate, GABA, and acetylcholine secretion paths, respectively. Amy., amygdala; C, cortex; GPe, globus pallidus externus; GPi/SNr, globus pallidus internus/substantia nigra pars compacta; HC, hippocampus; LDTg, lateral dorsal tegmental nucleus; NA, nucleus accumbens; PPTg, pedunculopontine tegmental nucleus; Str, dorsal striatum; Th, thalamus; VTA, ventral tegmental area.

the PFC, along with NA, have important roles in the evaluation of rewards and the constitution of memories related with the rewards. The DA release in NA relates the positive features of a goal with motivation and thus has a critical role in the formation of reward-related behaviors. In other words, DA is not required for reward-related learning, but is necessary for motivational behaviors leading to reward gain. Exposure to a stress factor has similar effects on excitatory synapses in VTA by enhancing afferent inputs to midbrain DA cells [11].

The information about the efficient actions in reward gain is stored in dorsal striatum. The striatum is part of the circuit involved in learning based on current rewards to guide the future actions. The dorsal striatum, particularly the caudate nucleus, is involved in social learning [9]. The PFC guides the organism successfully to a goal as well as it inhibits actions causing harm. The DA release in NA, PFC, amygdala, and dorsal striatum identifies the motivational importance and value of certain experiences. However, the DA

neurons in the VTA do not have such a role. They serve as the triggering source of the mesolimbic DA system.

The property of addictive drugs stimulating DA transmission is specific. Non-psychostimulant drugs such as morphine and nicotine stimulate DA transmission in the nucleus accumbens shell (NAs). However they do not increase DA transmission in the medial PFC (mPFC) where mesocortical DA neurons terminate [12]. Abusive drugs including nicotine, morphine, and cocaine stimulate DA transmission in NAs, so they increase the activity of intrinsic and afferent neural input [12]. Adaptive changes in DA transmission cause non-associative, long-lasting, and eventually irreversible modifications (sensitization to DA) in the DA system, resulting in addiction [10].

The principal excitatory inputs to the VTA DA neurons are glutamatergic projections from the PFC which synapse on DA and γ-aminobutyric acid (GABA) neurons in the VTA, modulating their activity. The main inhibitory inputs to the VTA are GABAergic and project from NA and ventral pallidum (VP). Cholinergic projections to the VTA come from pedunculopontine tegmental nucleus (PPTg) and lateral dorsal tegmental nucleus (LDTg) of the brain stem (Figure 1). Acute effects of nicotine in the VTA affect GABA neurons in the VTA, leading to a long-lasting excitation of the DA neurons through lack of inhibition [13, 14, 15]. Desensitization due to nicotine exposure inhibits VTA GABA neurons so DA neurons in the VTA receive less inhibitory input resulting increased firing of DA neurons [14].

The model we proposed in this work focuses on the cortico-striato-thalamic A-S circuit triggered by the DA secretion from the VTA. The basal ganglia structures GPe, GPi/SNr, and striatum together with PFC and thalamus are taken into account in the action-selection circuit. Although amygdala and hippocampus play critical roles in learning reward-related behaviors, they are not considered in the present model to reduce complexity. Also, some inputs of the VTA (PPTg, LDTg) are not included in the model due to the same reason.

3 A Computational Model for Nicotine Addiction

Nicotine addiction, like all other kinds of abusive substance addictions, develops with the malfunctioning of the reward mechanism. Nicotine effects the VTA DA signaling, which in turn modify the glutamatergic processes responsible in learning. The behavioral choices depend on the learned situations, in nicotine addiction this choice is in favor of obtaining more nicotine. Continuous exposure to nicotine causes behavioral choice modified by DA to become rigid, resulting in addiction. The proposed model captures this property through reinforcement learning which adapts a parameter that denotes the effect of VTA DA signaling on action selection.

3.1 The Proposed Model

In this work the approach proposed in [5] for nicotine addiction is combined with the goal-directed A-S system proposed in [4]. The model has two parts: a DA signaling module which is triggered by nicotine presence and an action-selection module. As in [5], the effect of DA is demonstrated by a DA module which is represented by a difference equation in order to model the dynamic behavior of the process (1):

$$u_{DA}(k+1) = u_{DA}(k) + mu_{DA}(-u_{DA}(k) + s_{DA}(ri, ni)) \tag{1}$$

The activation function s_{DA} is a sigmoidal function given as (2):

$$s_{DA}(ri, ni) = 0.5(1 + \tanh(ni * ri - \theta_{DA})) \tag{2}$$

ni is nicotine uptaking and θ_{DA} is the threshold setting the minimum tonic DA. We take $\theta_{DA} = 0.1 * ni$. ri is the reward signal initiated by nicotine. The nicotine signal is taken as $ni = 0.1$. mu_{DA} is the learning rate in the DA subsystem.

Previous works by [16, 17, 18, 19] suggest A-S models for the cortico-basal ganglia-thalamic loop. In our action-selection module, module which is acquired from [4], there are two components: premotor and motor loops which model the dynamical system of cortex-basal ganglia-thalamus (C-BG-TH) loops. The relevant equations for premotor and motor loops, respectively, are (4) and (5):

$$\begin{aligned}
p_{pm}(k+1) &= f(\lambda p_{pm}(k) + m_{pm}(k) + W_{c_{pm}} I(k)) \\
m_{pm}(k+1) &= f(p_{pm}(k) - d_{pm}(k)) \\
r_{pm}(k+1) &= W_{r_{pm}} f(p_{pm}(k)) \\
n_{pm}(k+1) &= f(p_{pm}(k)) \\
d_{pm}(k+1) &= f(W_{d_{pm}} n_{pm}(k) - r_{pm}(k))
\end{aligned} \tag{3}$$

$$\begin{aligned}
p_m(k+1) &= f(\lambda p_m(k) + m_m(k) + \beta p_{pm} + \text{noise}) \\
m_m(k+1) &= f(p_m(k) - d_m(k)) \\
r_m(k+1) &= W_{r_m} f(p_m(k)) \\
n_m(k+1) &= f(p_m(k)) \\
d_m(k+1) &= f(W_{d_m} n_m(k) - r_m(k))
\end{aligned} \tag{4}$$

The variables $p_{pm/m}$, $m_{pm/m}$, $r_{pm/m}$, $n_{pm/m}$, $d_{pm/m}$ stand for vectors corresponding to cortex, thalamus, striatum, subthalamic nucleus, and globus pallidus interna/substantia nigra pars reticulate constituents of premotor and motor loops, respectively. The dimensions of these vectors are determined by

the number of action choices. For nicotine addiction, two actions are considered, "smoke" and "not smoke", so the dimension of the system as a whole is 20. Just like in [4], the A-S module decides on an action outcome by evaluating the value of the presented stimuli. However, if the reward signal generated for that stimulus is disappointing, a random response is generated. To enable randomness, a noise signal is added to the motor loop. The premotor part completes the evaluation and determines possible actions and then the motor part decides on one of these possibilities by acting as a fine discriminator. The sensory stimulus denoted by I, affects the premotor constituent of cortex and the output of this loop modulates the motor constituent of cortex, resulting in the action. For nicotine addiction model at this level this sensory stimulus is considered to be neutral and a 2-dimensional vector with same small component values is considered.

The nonlinear function is sigmoid and given as (5):

$$f = 0.5(1 + \tanh(a(x - 0.45))) \tag{5}$$

$W_{d_{pm/m}}$ adds the diffusive effect of subthalamic nucleus and is a symmetrical matrix. The diagonal matrix $W_{r_{pm}}$ represents the effect of ventral striatum (nucleus accumbens) on dorsal striatum (caudate nucleus and putamen). The representation of sensory stimulus is formed by the matrix $W_{c_{pm}}$. The adaptation of weights $W_{c_{pm}}$ and $W_{r_{pm/m}}$ is done as below (6):

$$W_{c_{pm}}(k+1) = W_{c_{pm}}(k) + \eta_c \delta(k) p_m(k) I(k)^{'} \tag{6}$$

$$W_{r_{pm}}(k+1) = W_{r_{pm}}(k) + \eta_r((\overline{U_{DA}} + ni)(U_{DA} - \theta_{w_{DA}})^{'}(p_m(k) - \theta))^{'} f(p_m(k)) r_m(k) \tag{7}$$

The factors are the phasic DA activitiy U_{DA}, running average of 10 steps is denoted as in [5] by $\overline{U_{DA}}$. Thresholds for U_{DA} and p_m, respectively are θ_{DA} and θ, and are taken as 0.1 times their respective signal. The learning rate η is taken as 0.1. The variable δ represents the error in expectation and is calculated as (8):

$$\delta(k) = ri(k) + \mu V(k+1) - V(k) \tag{8}$$

The evaluation of the A-S based on the cortex input and the corresponding reward is given as the value signal (9):

$$V(k) = (W_v + \text{base}) I(k) \tag{9}$$

Here, W_v is a row vector and the term *base* is a row vector with identical entries. An expectation signal based on the value signal is generated which, together with ri, gives rise to the error δ. The error signal represents the modulating role of the neurotransmitters and modulates the behavior of dorsal striatum stream via $W_{r_{pm}}$. The error signal strengthens the representation of the sensory input via $W_{c_{pm}}$ and updates the value of stimuli via W_v (10):

$$W_v(k+1) = W_v(k) + \eta_v \delta(k) I(k)^{'} \tag{10}$$

3.2 Dynamics of Action Selection Module

The effect of the modification of $W_{r_{pm}}$ on the premotor system is demonstrated with the bifurcation diagrams. In order to explain explicitly what is going on during the operation of the model, one set of parameter values are considered below. Only cortex component, p_{pm}, is taken into account because it drives the motor loop.

Before learning begins, the randomly selected weight matrices are given below:

$$W_{r_{pm}} = \begin{bmatrix} 0.5061 \\ 0.5061 \end{bmatrix}, W_{c_{pm}} = \begin{bmatrix} 0.5410 & 0.1935 \\ 0.3310 & 0.4624 \end{bmatrix}, W_v = \begin{bmatrix} 0.0185 & 0.0176 \end{bmatrix} \tag{11}$$

Using these weights with parameters taken as $I = 0.1$, $W_{d_{pm}}$ as a 2 by 2 matrix composed of 0.5's, $\lambda = 0.5$, $a = 3$ the following fixed points (1) are obtained for the premotor system.

Table 1 The fixed points obtained before the weight matrices are adjusted by learning. In the right columns the eigenvalues of the linearized system at these fixed points are shown.

	Equilibrium point	Eigenvalues				
p_{pm_1}	0.9982	0.06	-0.05	0 + i 0.02	0 - i 0.02	0
p_{pm_2}	0.9981	0.06	-0.06	0 + i 0.02	0 - i 0.02	0

The first five component values of the equilibrium point are given in Table 1 and it can be followed that this equilibrium point is stable.

The bifurcation diagrams drawn at this point according to W_r parameter are given in Figure 2. The labeled points in the diagrams show the bifurcation points and are listed in Table 2. At the point with label 4 in the diagram there is a Hopf bifurcation.

Table 2 Bifurcation values of p_{pm} according to W_r parameter before learning (TY: type of bifurcation, LAB: label, EP: End Point, LP: Limit Point Bifurcation, HB: Hopf Bifurcation)

TY	LAB	W_{r_1}	p_{pm_1}	TY	LAB	W_{r_2}	p_{pm_2}
EP	1	0.5	0.9981	EP	1	0.5	0.9981
EP	2	2.32	0.9983	EP	2	2.15	0.9983
LP	3	-0.046	0.816	LP	3	-0.04	0.827
HB	4	-0.045	0.735	HB	4	-0.23	0.305
EP	5	-2.24	0.133	EP	5	-2.09	0.128

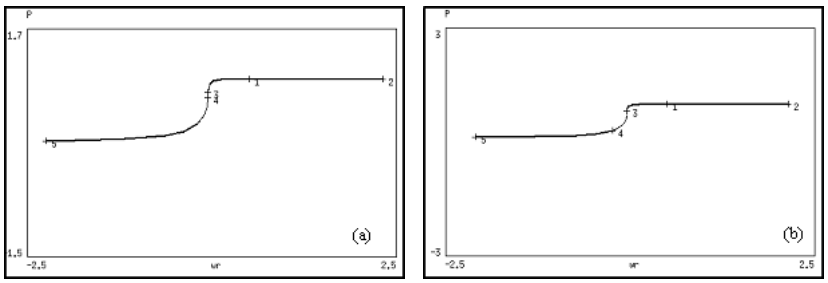

Fig. 2 Bifurcation diagrams of p_{pm} according to W_r parameter before learning begins. a) Bifurcation diagram for p_{pm_1} b) Bifurcation diagram for p_{pm_2}

After the learning ends the weight matrices become:

$$W_{r_{pm}} = \begin{bmatrix} 1 \\ 0.7018 \end{bmatrix}, W_{c_{pm}} = \begin{bmatrix} 1.1855 & 0.8380 \\ 0.2518 & 0.3833 \end{bmatrix}, W_v = \begin{bmatrix} 0.5409 & 0.5409 \end{bmatrix} \quad (12)$$

The fixed points for the above parameters are given in Table 3. With the above parameters the bifurcation diagrams in Figure 3 are obtained. The labeled points in the diagrams show the bifurcation points and are listed in Table 4. At the points with label 3 and 4 in the diagram there is a Hopf bifurcation. The time-domain solutions of p_{pm} obtained in the stable and unstable regions are shown in Figure 4.

Table 3 The fixed points obtained after the weight matrices are adjusted by learning. In the right columns the eigenvalues of the linearized system at this fixed points are shown.

	Equilibrium point	Eigenvalue				
p_{pm_1}	0.9989	0.05	-0.05	0 + i 0.04	0 - i 0.035	0
p_{pm_2}	0.9981	0.07	-0.07	0 + i 0.05	0 - i 0.05	0

Table 4 Bifurcation values of p_{pm} according to W_r parameter after learning (TY: type of bifurcation, LAB: label, EP: End Point, LP: Limit Point Bifurcation, HB: Hopf Bifurcation)

TY	LAB	W_{r_1}	p_{pm_1}	TY	LAB	W_{r_2}	p_{pm_2}
EP	1	1	0.9989	EP	1	0.7018	0.9981
EP	2	2.03	0.9989	EP	2	2.224	0.9982
HB	3	-0.116	0.695	LP	3	-0.032	0.712
HB	4	-0.782	0.298	HB	4	-0.177	0.313
EP	5	-2.247	0.211	EP	5	-2.182	0.12

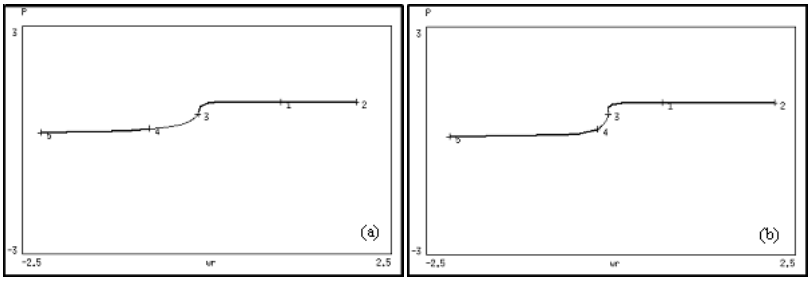

Fig. 3 Bifurcation diagrams of p_{pm} according to W_r parameter after learning is completed. a) Bifurcation diagram for p_{pm_1} b) Bifurcation diagram for p_{pm_2}.

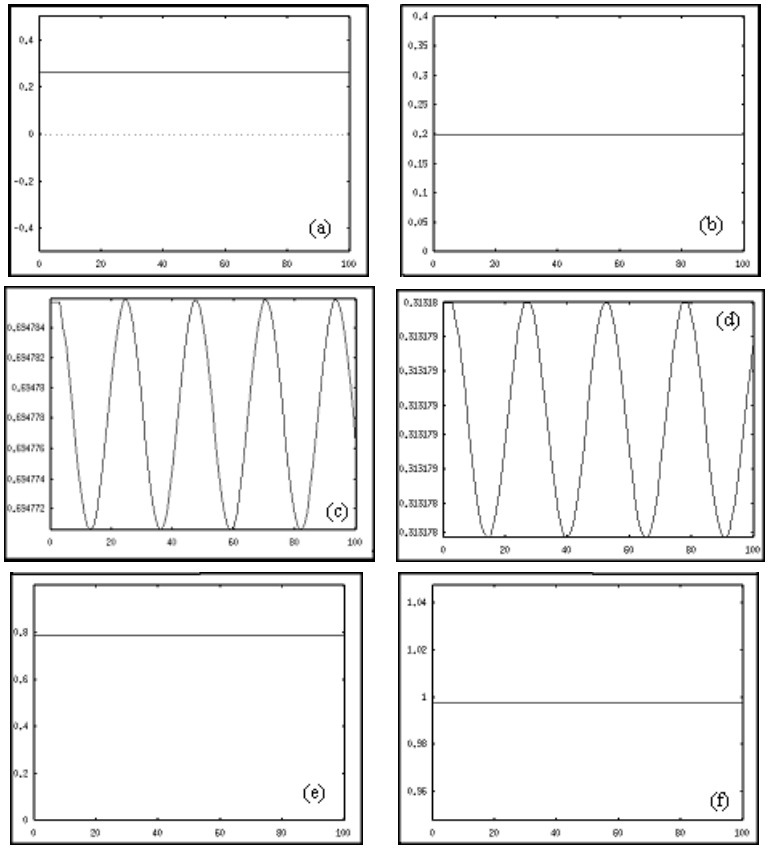

Fig. 4 Time domain solutions of p_{pm} (a) $W_{r_1} = -1.022$, $p_{pm_{10}} = 0.2673$ (b) $W_{r_2} = -0.4183$, $p_{pm_{20}} = 0.2006$ (c) $W_{r_1} = -0.1156$, $p_{pm_{10}} = 0.6948$ (d) $W_{r_2} = -0.1773$, $p_{pm_{20}} = 0.3132$ (e) $W_{r_1} = -0.1008$, $p_{pm_{10}} = 0.7879$ (f) $W_{r_2} = 0.317$, $p_{pm_{20}} = 0.9975$.

When the bifurcations diagrams before and after learning are observed, the most important difference is the unstable parameter range. It is larger in after learning than the before learning. The parameter values corresponding to unstable region and Hopf bifurcation evoke the "exploration" process while the parameter values giving rise to stable equilibrium points correspond to an action selected. If both components of the variable corresponding to cortex component have almost same value near one or zero, than no choice between possible actions is given, but if the value of one component is bigger than the other, a choice is established.

3.3 The Simulation Results

To investigate the appropriateness of the proposed model the response to nicotine uptaking explained in [5] is considered. The reward delivered at the end of each smoking decision is taken as 1, and for each nonsmoking decision is taken as -1. After 20 smoking decisions the system is considered to have become an addict. Once 20 succesive decisions are "smoking", the system is considered to model an addict.

When the solution of the nonlinear discrete time system is settled to a stable equilibrium, the action selected by the A-S module is determined by calculating the solution of p_m. The value function V and the error function δ are calculated and using these functions the weight matrices $W_{c_{pm}}$, $W_{r_{pm}}$, and W_v are updated. The simulation stops if the smoking action is selected successively for 20 times.

The parameter values used in the simulation are $\lambda = 0.5$, $\beta = 0.03$, $a = 3$, $\mu_{DA} = 0.1$, $\eta_c = 0.1$, $\eta_r = 0.1$, $\eta_v = 0.1$ and base= 0.2. The initial values of the weight matrices W_c and W_v are generated randomly with small positive real numbers. The initial value of the diagonal matrix $W_{r_{pm}}$ is ones. During updating the matrix values,$W_{c_{pm}}$ and $W_{r_{pm}}$ are normalized. The matrices $W_{d_{pm/m}}$ and W_{r_m} are composed of 0.5's and they are constant. The noise signal is generated as a very small random number. The action outputs are coded as [1 0]' for smoking, [0 1]' for nonsmoking, and [1 1]' and [0 0]' for indecisive behaviors.

During the operation, if the learning takes less than 120 steps, it is considered to be successful, in other words addiction occurs. Otherwise the system is not considered as an addict because too long step size means that addictive behavior is not learned. In 20 successive runs the model completed the task on average 63 trials with a standard deviation of 48.8542. The final matrices for a successful trial when addiction is set up are given as follows:

$$W_{r_{pm}} = \begin{bmatrix} 0.9495 \\ 1 \end{bmatrix}, W_{c_{pm}} = \begin{bmatrix} 0.5182 & 0.5205 \\ 0.2883 & 0.1202 \end{bmatrix} \tag{13}$$

In Figure 5, the change in the value of δ is given for one run. δ remains constant if the same choice is made successively, changes otherwise and as learning takes place its value approaches zero.

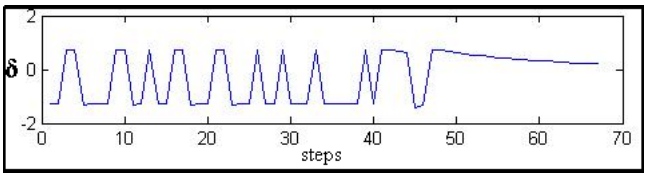

Fig. 5 The difference in δ

4 Discussion and Conclusion

Reinforcement learning and opponent processes have important roles in abusive drug addiction. To represent the effects of these processes, the phasic and persistent modifications of nicotine in DA pathways and its administration of the plasticity of the corticostriatal A-S circuits are modeled in [5]. The model is composed of two modules working based on the effects of nicotine. The first module is the A-S circuit, and the second module is the dopamine signaling module which administers the action selections according to its outputs.

In this work a model of nicotine addiction based on an A-S module is proposed. This module is composed of two components, A-S part corresponds to the dorsal stream responsible for behavioral choices and the second part corresponds to the ventral stream responsible for evaluation and modulates the action selection. Thus, the A-S module, unlike the one in [5] is capable of revealing reinforcement learning. The A-S circuit is realized as an interconnected nonlinear dynamical systems corresponding to premotor and motor loops and performs competitive learning guided by action evaluation. The bifurcation diagrams given demonstrate the effectiveness of the proposed model especially for exploration.

This work supports the idea that addiction like goal-directed behavior may arise from the interaction between the cortico-striato-thalamic loops integrated with limbic structures. Modeling these loops as nonlinear dynamical systems enables a realistic simulation of reinforcement learning in neural structures. The neural mechanisms of addiction are complicated and the reasons that lead to addiction are not only molecular (nicotine, etc.), but also social and psychological. Our model reduces the complex network of the cortex-thalamus-basal ganglia-hippocampus-amygdala-VTA and considers only DA as the dominant neurotransmitter in addiction. We emphasize reinforcement learning as the major process underlying addiction, however

future work should also consider other psychological processes and other relevant neurotransmitters as well.

References

1. Everitt, B.J, Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P., Robbins, T.W. (1999) Associative Processes in Addiction and Reward The Role of Amygdala-Ventral Striatal Subsystems. Ann. New York Aca. Sci., 877, 412–438
2. Cardinal, R.N., Everitt, B.J (2004) Neural and psychological mechanisms underlying appetitive learning: links to drug addiction. Cur. Opi. Neurobio., 14, 156–162
3. Fudge, J.L., Haber, S.N., McFarland, N.R. (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. The Jour. Neuroscience 20, 2369–2382
4. Sengor, N.S., Karabacak, O., Steinmetz, U. (2008) A Computational Model of Cortico-Striato-Thalamic Circuits in Goal-Directed Behavior. LNCS 5163, Proceedings of ICANN 328-337
5. Gutkin, B.S., Dehaene, S., Changeux, J.P. (Jan 24, 2006) A Neurocomputational Hypothesis for Nicotine Addiction. PNAS **103** no.4 1106–1111,
6. Hyman, S.E., Malenka, R.C., Nestler, E.J. (2006) Neural Mechanisms of Addiction: The Role of Reward-Related Learning and Memory. Annual Review of Neuroscience. **29** 565–598
7. Spanagel, R., Heilig, M. (December 2005) Addiction and Its Brain Science. Addiction **100** no.12, 1813–1822
8. Koob, G.F., Le Moal, M. (2001) Drug Addiction, Dysregulation of Reward, and Allostasis. Neuropsychopharmacology **24** no.2 97–129
9. Delgado, M.R. (2007) Reward-Related Resposes in the Human Striatum. Annals of the New York Academy of Sciences, **1104** 70–88
10. Di Chiara, G. (2000) Role of Dopamine in the Behavioural Actions of Nicotine Related to Addiction. European Journal of Pharmacology **393** 295–314
11. Saal, D., Dong, Y., Bonci, A., Malenka, R. (2003) Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron, 37 n.4, 577–582
12. Di Chiara, G. (1999) Drug addiction as dopamine-dependent associative learning disorder. European Journal of Pharmacology **375** 13–30
13. Laviolette, S. R., van der Kooy, D. (2004) The Neurobiology of Nicotine Addiction: Bridging the Gap from Molecules to Behaviour. Nature Rev. Neurosci. **5** 55–65
14. Mansvelder, H.D., McGehee, D.S. (2002) Cellular and Synaptic Mechanisms of Nicotine Addiction. J. Neurobilogy, vol. 53 606–617
15. Grace, A.A., Floresco, S.B., Goto, Y., Lodge, D.J. (2007) Regulation of Firing of Dopaminergic Neurons and Control of Goal-Directed Behaviors. Trends in Neurosciences, vol.30 no.5 220–227
16. Taylor, N.R., Taylor, J.G. (2000) Hard-wired Models of Working Memory and Temporal Sequence Storage and Generation. Neural Networks, 13 201–224
17. Taylor, J.G., Taylor, N.R. (2000) Analysis of Recurrent Cortico-Basal Ganglia-Thalamic Loops for Working Memory. Biological Cybernetics, 82 415–432
18. Gurney, K., Prescott, T.J., Redgrave, P. (2001) A Computational Model of Action Selection in the Basal Ganglia I: A New Functional Anatomy. Biological Cybernetics, 84, 401–410
19. Gurney, K., Prescott, T.J., Redgrave, P. (2001) A Computational Model of Action Selection in the Basal Ganglia II: Analysis and Simulation of Behaviour. Biological Cybernetics, 84, 411–423