

Research Paper: Investigating the Cocaine-induced Reduction of Potassium Current on the Generation of Action Potentials Using a Computational Model



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ABSTRACT

Introduction: Drugs of abuse, such as cocaine, affect different brain regions and lead to pathological memories. These abnormal memories may occur due to changes in synaptic transmissions or variations in synaptic properties of neurons. It has been shown that cocaine inhibits delayed rectifying potassium currents in affected brain regions and can create pathological memories.

This study investigates how the change in the conductance of delayed rectifying potassium channels can affect the produced action potentials using a computational model.

Methods: We present a computational model with different channels and receptors, including sodium, potassium, calcium, NMDARs, and AMPARs, which can produce burst-type action potentials. In the simulations, by changing the delayed rectifying potassium conductance bifurcation diagram is calculated.

Results: By decreasing the potassium current for a fixed stimulatory signal, burst-type action potentials can be generated. In the following and with a further reduction of potassium conductance, produced action potentials exhibit non-linear and even chaotic behaviors.

Conclusion: Results show that for a specific range of potassium conductance, a chaotic regime emerges in produced action potentials. These chaotic oscillations may play a role in inducing abnormal memories.

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Highlights

- Cocaine consumption reduces the potassium current in affected cells.
- Decreasing the potassium currents elicits burst action potentials.
- Produced bursts might have chaotic behaviors.
- Chaotic oscillations might be related to the toxic effects of cocaine.

Plain Language Summary

Drugs of abuse such as cocaine can manipulate brain circuits and may form some pathological memories. These memories can lead to long-term addiction. Furthermore, these drugs also can have toxic effects on the cells. Researchers are looking for the mechanisms that can lead to abnormal memories and toxic effects of drugs. It seems that an efficient mechanism that can be used by drugs of abuse is the manipulation of potassium currents in the affected cells. Here, in a computational model, we have shown that changes in the conductance of delayed rectifying potassium channels can lead to nonlinear and even chaotic behaviors in the produced action potentials. These behaviors might have a role in drug toxic effects.

1. Introduction

Addiction is a chronic disease that has various negative consequences. Cocaine consumption is one of the pervasive forms of addiction. The use of drugs, such as cocaine, can lead to maladaptive behavioral changes. Many researchers have shown that these changes are due to the intervention of drugs in the plasticity mechanism of the brain (Nestler, 2001; Kauer, & Malenka, 2007; Lüscher 2013; Kutlu, & Gould 2016; Borjkhani, Bahrami, & Janahmadi, 2018; Borjkhani, et al., 2018; Preston, Brown, & Wagner, 2019). Some researchers consider that drugs of abuse can form a pathological memory, called the memory of addiction (Boening 2001; Kelley 2004; Nestler, 2013).

Among the involvement of different brain regions in the addiction process, the hippocampus has an integral role in forming addiction memories and triggering relapse during withdrawal times (Caffino, et al., 2014; Kutlu, & Gould, 2016; Preston, et al. 2019). It has been shown both empirically and computationally that one reason for the formation of addiction memory is the increased excitability of neurons (Cohen, Doze, & Madison, 1992; Kauer, & Malenka 2007; Borjkhani, Mahdavi, & Bahrami, 2014; van Huijstee & Mansvelde 2015; Shukla, et al. 2017; Borjkhani, et al. 2018; Borjkhani, et al. 2018a; Borjkhani, et al. 2018b).

Excitability of the neurons can be changed by drug intervention in N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors mediated currents that some researchers investigated (Trujillo 2002; Bao, Kang et al., 2007; Kauer, & Malenka 2007; Zweifel, Argilli, E., Bonci, & Palmiter, 2008; Zachariou, Alexander, Coombes, & Christodoulou 2013; Borjkhani, et al. 2018; Borjkhani, et al. 2018). Meanwhile, the missing issue is the role of potassium currents in changing cell excitabilities. It has been observed that the consumption of cocaine increases the excitability of the hippocampal neurons by inhibiting the potassium current (Chen, Lin, Lin, & Tsai, 2006). Cocaine consumption provokes action potential bursts in neurons (Chen, et al., 2006). Moreover, it has been suggested that the emergence of the burst is associated with cocaine's inhibitory effects on the delayed rectifying K current (Chen, et al., 2006). Therefore, one of the mechanisms by which cocaine changes neurons' excitabilities and innervates in memory formation is the reduction of potassium current. So, based on these observations, we want to computationally investigate potassium current reduction affects the produced action potentials in the hippocampus. This research can reveal new dimensions of the formation of cellular addiction.

In the next section, the implemented computational model is introduced. Then the simulation results are presented, and, finally, potential applications of the proposed model are discussed.

2. Methods

To analyze the cocaine effects on action potential generation in hippocampal neurons, we used a modified version of the ‘Hodgkin–Huxley style’ formulation (Hodgkin & Huxley, 1952). The equation denoting voltage variation of the neuron with ionic current equations is as follows:

$$1) \quad dv-dt = -(I_{Na} + I_{Nap} + I_{Kdr} + I_A + I_M + I_{Ca} + I_C + I_{sAHP} + I_L) - I_{AMPA} - I_{NMDA}$$

Here, I_{Na} is the transient sodium current, I_{Nap} denotes the persistent sodium current, I_{Kdr} shows the delayed rectifier potassium current, I_A demonstrates the A-type potassium current, I_M exhibits the

muscarinic-sensitive potassium current, I_{Ca} illustrates the High-voltage calcium current, I_C describes the

fast calcium-activated potassium current, I_{sAHP} displays the slow calcium-activated potassium current,

I_L indicates the leak current, I_{AMPA} represents the AMPAR mediated current, and I_{NMDA} refers to the NMDAR mediated current.

Transient sodium current (I_{Na}) can be described using the following equations (Golomb, Yue, & Yaari., 2006):

$$2) \quad I_{Na}(V,h) = 35 * m_{\infty}^3(V) * h(V-55)$$

$$m = m_{\infty}(V)$$

$$h = \frac{[h_{\infty}(V)-h]}{h_{\infty}(V)} \quad d\phi$$

$$dt \quad \tau$$

$$\tau_h(V) = 0.1 + 0.75(1 + \exp(-\frac{V+40.5}{-6})) - 1$$

Here, m and h are gating variables and τ_h is the time constant. Persistent sodium current can be described by the following equation (Golomb, et al., 2006):

$$3) \quad I_{Nap}(V) = 0.1 * p_{\infty}(V) * (V-55)$$

The delayed rectifier potassium current (I_{Kdr}) can be represented by the following equations (Golomb, et al., 2006):

$$4) \quad I_{Kdr}(V,n) = g_{Kdr} * n^4 * (V+90)$$

$$dt = \frac{\phi[n_{\infty}(V)-n]}{(V)} \quad dn$$

$$\tau_h(V) = 0.1 + 0.5(1 + \exp(-\frac{V+27}{-15})) - 1$$

Here, n is the gating variable and $g_{Kdr} = 6$ mS/cm² is the default conductance of the channel. The A-type potassium current (I_A) can be demonstrated by the following equations (Golomb, et al., 2006):

$$I_A(V,b) = 1.4 * a_{\infty}^2(V) * b * (V+90)$$

$$a = a_{\infty}(V)$$

$$dt = \frac{[b_{\infty}(V)-b]}{15} \quad db$$

The muscarinic-sensitive potassium current (I_m) is denoted by the below equation (Golomb, et al., 2006):

$$6) \quad I_m(V,z) = 1 * z * (V+90)$$

$$dt = \frac{[z_{\infty}(V)-z]}{1} \quad dz$$

The High-voltage calcium current (I_{Ca}) can be shown by the following equation (Golomb, et al., 2006):

$$7) \quad I_{Ca}(V,r) = 0.2 * r^2 * (V-120)$$

$$dt = \frac{[r(V)-r]}{1} \quad dr$$

The fast calcium-activated potassium current (I_c) is described by the following equation (Golomb, et al., 2006):

$$8) \quad I_c(V,c) = 10 * d_{\infty}([Ca^{2+}]_i) * c * (V+90)$$

$$dt = \frac{[c_{\infty}(V)-c]}{3} \quad dc$$

$$d_{\infty}([Ca^{2+}]_i) = (1 + 6[Ca^{2+}]_i)^{-1}$$

Here $[Ca^{2+}]_i$ is the calcium concentration in the neuron; the slow calcium-activated potassium current (I_{sAHP}) can be shown by this equation (Golomb, et al., 2006):

$$9) \quad I_{sAHP}(V,q) = 5 * q * (V+90)$$

$$dt = \frac{[q_{\infty}([Ca^{2+}]_i)-q]}{450} \quad dq$$

$$q_{\infty}([Ca^{2+}]_i) = (1 + 2^4[Ca^{2+}]_i^4)^{-1}$$

The leak current (I_L) can be represented by this formula (Golomb, et al., 2006):

$$I_L = 0.05 * (V + 70)$$

This equation can show the dynamics of calcium concentration inside the neuron:

$$11) \frac{d[Ca^{2+}]_i}{dt} = -0.13 I_{Ca} - 0.012 I_{NMDA} - 0.0012 I_{AMAP} - [Ca^{2+}]_i / 13$$

The AMPA current (I_{AMAP}) is modeled by the following formula (Destexhe, Destexhe, Mainen, & Sejnowski 1998; Borjkhani, et al., 2018):

$$12) I_{AMAP} = 0.35 * m_{AMPA} * (V - 55)$$

$$\frac{dm_{AMPA}}{dt} = \alpha_{AMPA} \cdot G_{st} \cdot (1 - m_{AMPA}) - \beta_{AMPA} m_{AMPA}$$

, where m_{AMPA} is the gating variable of the receptor, $\alpha_{AMPA} = 1.1$ mM/ms and $\beta_{AMPA} = 0.67$ mM/ms are the opening and closing rate of the receptor, respectively, and G_{st} is the synaptic glutamate or the stimulatory signal which activates the receptor.

The NMDA current (I_{NMDA}) can be represented by the following formula (Destexhe, et al., & Sejnowski 1998; Borjkhani, et al., 2018):

$$13) I_{NMDA} = (1 + g_{VD}) \cdot m_{NMDA} \cdot M \cdot g \cdot (V - 55)$$

$$\frac{dm_{NMDA}}{dt} = \alpha_{NMDA} \cdot G_{st} \cdot (1 - m_{NMDA}) - \beta_{NMDA} m_{NMDA}$$

$$Mg = 1 / (1 + (-\frac{[Mg^{2+}]_0}{3.75}) * \exp(-0.062 * V))$$

$$\frac{dg_{VD}}{dt} = (k(V - V_0) - g_{VD}) / \tau g$$

Here, m_{NMDA} is the gating variable of the receptor, Mg , denotes the dynamics for Mg^{2+} blocking of the receptor, $[Mg^{2+}]_0 = 2$ mM is the concentration of Mg^{2+} in the extracellular fluid, g_{VD} is the receptor's conductance dependent to the voltage, $k = 0.0007$ and $V_0 = -100$ mv are constants, and $\tau g = 0.05$ ms is a time constant. $\alpha_{NMDA} = 0.14$ Mm/ms and $\beta_{NMDA} = 0.03$ mM/ms are the opening and closing rates of the receptor.

The following formula can describe the activation function of gating variables in the equations:

$$14) x_{\infty}(V_{post}) = (1 + \exp(-(V - \theta_x) / \sigma_x))^{-1}$$

, where x can be replaced by $x = m, h, n, a, b, z, p, r, c$, and the related parameters are $\theta_m = -30$ and $\sigma_m = 9.5$, $\theta_n = -35$ and $\sigma_n = 10$, $\theta_h = -45$ and $\sigma_h = -7$, $\theta_a = -50$ and $\sigma_a = 20$, $\theta_b = -80$ and $\sigma_b = -6$, $\theta_z = -39$ and $\sigma_z = 5$, $\theta_p = -41$ and $\sigma_p = 3$, $\theta_r = -20$ and $\sigma_r = 10$, and finally $\theta_c = -30$ and $\sigma_c = 7$.

Here the units for the voltages are millivolts.

3. Results

Simulation results are presented in this section. All simulations have been performed in Matlab 2018a software. A stimulatory signal (assumed to be the glutamate) with an amplitude of 0.1 mM and a frequency of 10 Hz with a pulse duration of 10 ms affects the AMPARs and NMDARs (G_{st} in equations 12 and 13). The stimulatory signal is shown in Figure 1.

Since cocaine dose-dependently attenuates the potassium current in empirical observations (Chen, et al., 2006), in the simulations, the conductance of potassium current gradually increases from 0 to 10, and the bifurcation diagram is shown in Figure 2. Here, by changing the conductance, the peaks of the action potentials are calculated. Between 2 to 8 values of the delayed rectifier potassium conductance (g_{kdr}), the model has multi-stability, and the voltage has several peak values. These multi-peaks may represent a chaotic behavior. Further decrease of the conductance from 2 or increase of the conductance from 8 leads to semi-stable peak values for generated action potentials.

For further analysis, action potentials for different values of g_{kdr} and their related phase spaces are calculated and represented through Figures 3-7. Phase spaces are calculated by plotting the V_{n+1} against V_n .

Here V_n and V_{n+1} are the values of the action potentials at the time of n and $n+1$, respectively. Figure 3 shows the produced action potentials and related phase space for $g_{kdr} = 0.01$. It can be seen that regular spiking patterns exist, and reconstructed space denotes a limit cycle.

The left panel illustrates the produced action potentials, and the right panel the related phase space.

By increasing the conductance to 1 (Figure 4.), the firing frequency increases, and spiking patterns can be seen here. The produced action potentials follow the fre-

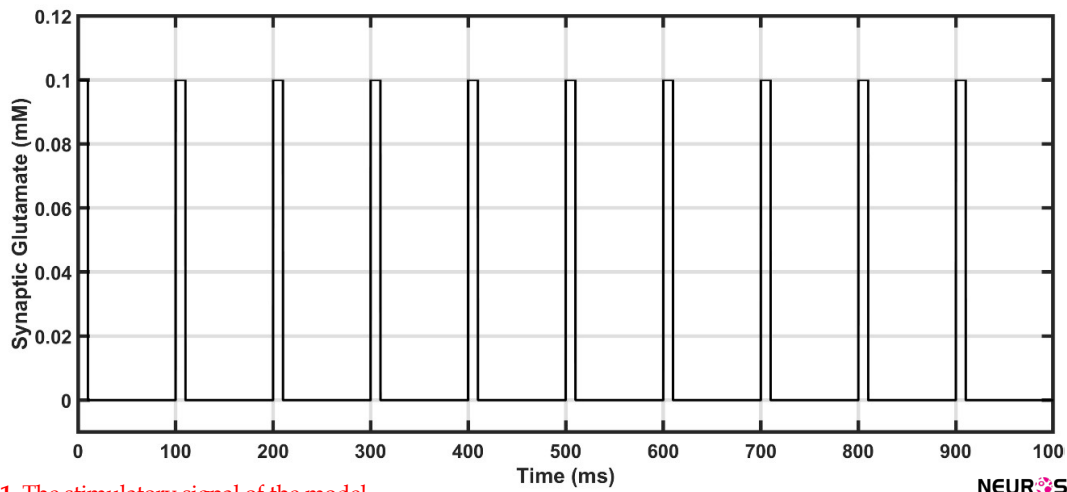


Figure 1. The stimulatory signal of the model

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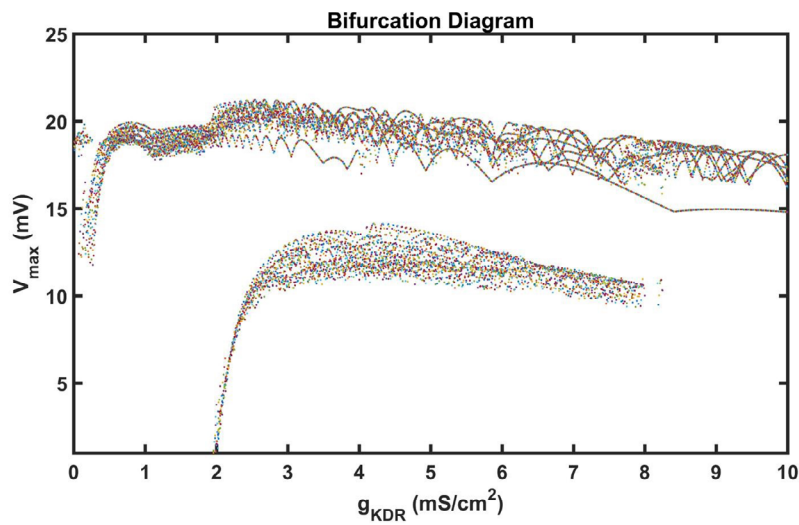


Figure 2. The peak values of the generated action potentials for different sets of g_{Kdr} (bifurcation diagram)

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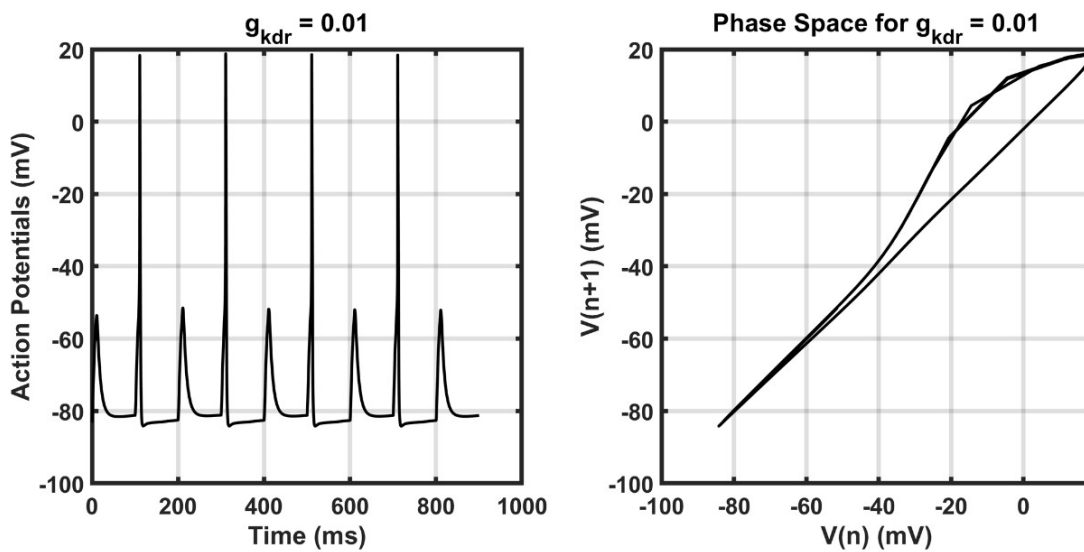


Figure 3. Produced action potentials and reconstructed phase space for $g_{Kdr} = 0.01$

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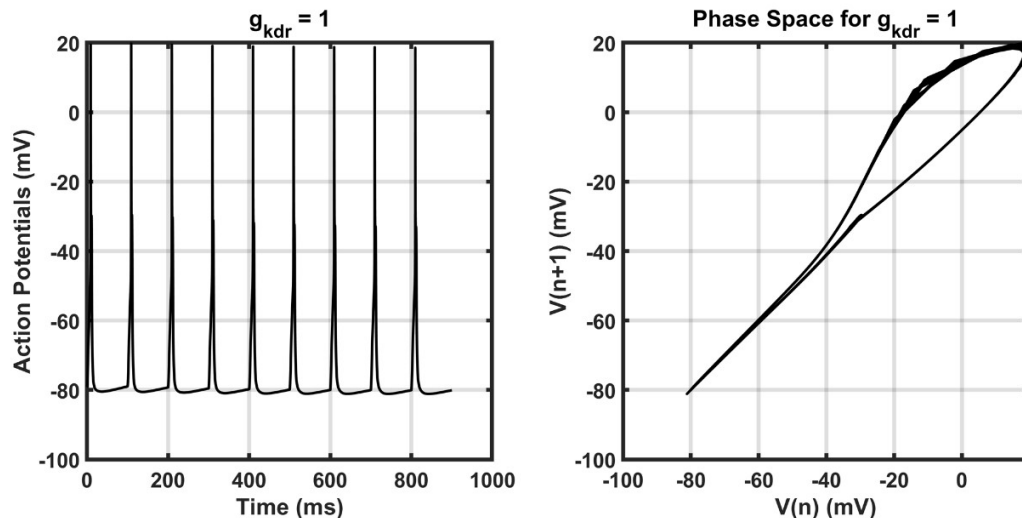


Figure 4. Produced action potentials and reconstructed phase space for $g_{kdr} = 1$

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quency of the stimulatory signal. Furthermore, the phase space demonstrates a normal limit cycle.

The left panel denotes the produced action potentials, and the right panel shows the related phase space.

By changing the conductance to the $g_{kdr}=4$, burst-type action potentials emerge (Figure 5). The reconstructed phase space of the signal shows that the chaotic regime appears. As seen, the generated potentials are different. Some of the potentials are single spikes, and some have burst. Also, the phase space shows that multiple limit cycles emerge that may show chaotic behaviors.

The left panel denotes the produced action potentials, and the right panel the related phase space.

By increasing the conductance (g_{kdr}) to 6, more irregularities emerge in the generated action potentials (Figure 6). These behaviors may represent chaotic behavior or may lead to chaos.

The left panel shows the produced action potentials, and the right panel the related phase space.

Figure 7 shows the action potentials and reconstructed phase space for $g_{kdr} = 10$. It can be seen that chaotic oscillations diminish, and regular spiking patterns emerge again. In this case, we see the regular

The left panel denotes the produced action potentials, and the right panel the related phase space.

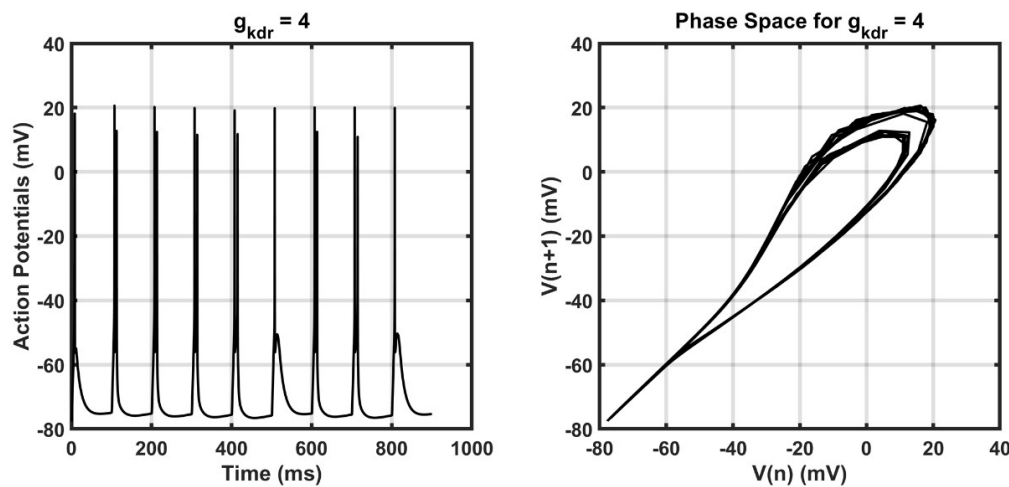


Figure 5. Produced action potentials and reconstructed phase space for $g_{kdr} = 4$

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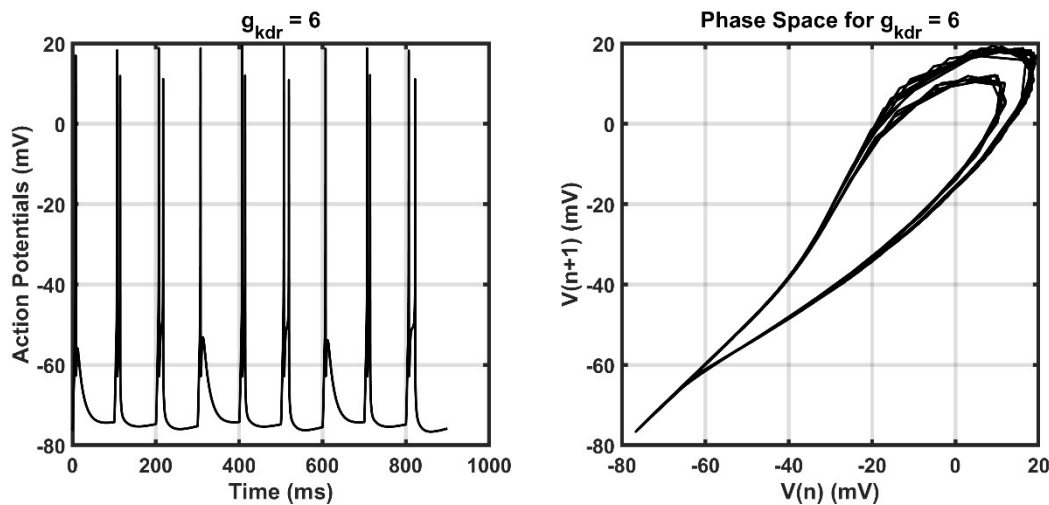


Figure 6. Produced action potentials and reconstructed phase space for $g_{kdr} = 6$

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4. Discussion

Despite many studies in addition, lots of questions have remained unanswered. Cocaine interacts with several transporters, receptors, and channels (Kobayashi, Nishizawa, Iwamura, & Ikeda, 2007). In this paper, the effect of reducing the conductivity of potassium channels (which can be due to the consumption of cocaine) in the generation of action potentials was investigated. For this purpose, a computational model was used that could generate the burst-type action potentials. The study of potassium current is critical because, in some experimental research, this current is affected by the consumption of cocaine. It has been shown that cocaine consumption blocks the calcium-dependent K^+ channel in the hippocampus neurons. Besides, it has been suggested that cocaine is related to the blocking of Ca^{2+} -dependent K^+ channels that may broaden the action potential and

cause repetitive firing of neurons (Premkumar, 2005). In addition to demonstrating this empirical finding using a computational model, we state that chaotic behaviors are also observed in the process of reducing potassium current. Besides that, decreasing the potassium currents in simulations elicits burst action potentials reported in empirical experiments (Chen, et al., 2006).

The simulation results show that by decreasing the potassium current for a fixed stimulatory signal, burst-type action potentials can be generated. With a further reduction of potassium conductance, produced action potentials exhibit non-linear and even chaotic behaviors. The appearance of chaotic patterns has been seen in many diseases and can contribute to forming abnormal and addictive memories, which requires further studies, both in computational and empirical research. The fact that cocaine inhibition of GIRK (the G protein-coupled

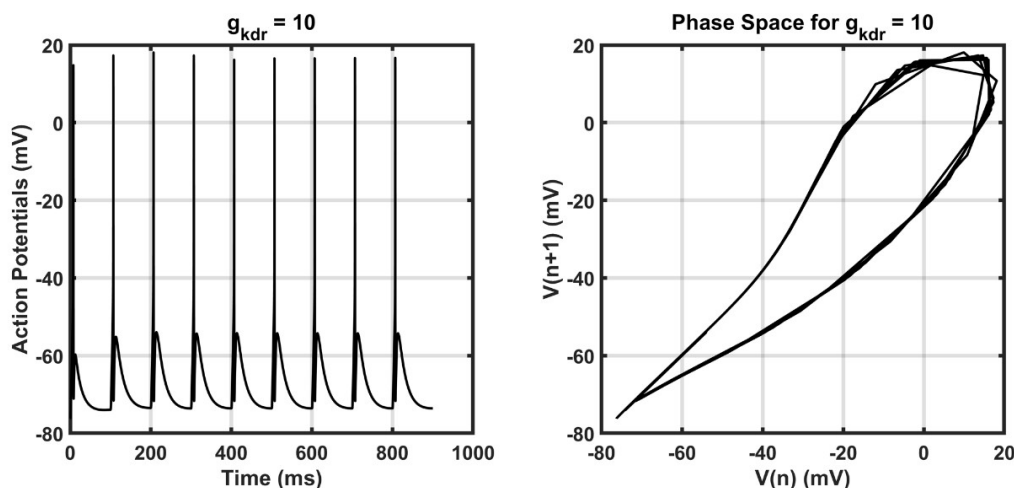


Figure 7. Produced action potentials and reconstructed phase space for $g_{kdr} = 10$

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inwardly-rectifying potassium) channels may involve in its toxic effects (Kobayashi, et al., 2007) can relate to emerging chaotic oscillations which were observed in the simulations. Since cocaine has diverse harmful effects such as seizures, cardiac arrhythmias, and sudden death (Lathers, Tyau, Spino, & Agarwal, 1988; O'leary and Hancox 2010), and the potassium channels play an essential role in creating these obstacles, the proposed model can help the researchers investigate these effects, too.

Ethical Considerations

Compliance with ethical guidelines

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflicts of interest.

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