*Dedicated to Prof. P.T. Frangopol on the occasion of his 75th anniversary*

# Rebalancing $Na^+$ and $K^+$ Ionic Fluxes in Dopaminergic Neurons

**SORINEL A. OPRISAN***
Department of Physics and Astronomy, College of Charleston, Charleston, SC 29424

*The ionic balance of living cells is maintained by Na/K ATPas pump. We found that the voltage dependence of the pump is not essential to maintain cellular homeostasis. We carried extensive numerical simulations in order to calibrate a realistic single-compartment Hodgkin-Huxley neural model of dopaminergic neuron. Bifurcation analyses of the computational model suggested that the half-activations of both $Na^+$ and $K^+$ ions involved in Na/K pump at the onset of action potentials are slightly shifted toward larger values in the absence of voltage dependence of Na/K pump. In addition, a voltage-independent Na/K pump is more stable and less sensitive to membrane potential perturbations. The model assumes that the internal $Na^+$ and external $K^+$ concentrations are constant.*

*Keywords: Bifurcation diagram, ionic balance, dopaminergic neurons*

Excitability of the living cells is the property that allows them to sense and adapt to environmental changes. Excessive neural excitability cold lead to physiopathologies such as epilepsy [1-3]. Autoregulation of the neuronal excitability [4, 5] could involve calcium-dependent $K^+$ conductances[6], the electrogenic Na/K pump, slow inactivation of Na conductances [7] etc. Strong experimental evidences show that electrogenic Na/K pump is responsible for rhythm generation in invertebrate[8], brain stem motoneurons [9], and dopaminergic neurons [10]. In many diseases or in a physiological emergency, dysfunction of the Na/K pumps is due to either lack of ATP or the low density of the pump proteins within the cell membrane [11]. Physical manipulation of the pump molecules has become a central target for therapeutic purposes. Experimental blockade of the electrogenic Na/K pump by strophanthidin disrupted the rhythm of the neural networks by decreasing the interburst interval duration and increasing the rate of asynchronous "background" activity.

*Model and results*

We investigated the homeostatic effect of Na/K-ATPas pump on a single-compartment Hodgkin-Huxley (HH)-type parallel conductance membrane model mimicking the behaviour of dopaminergic neurons. The basic mathematical model was published elsewhere [2, 3] and in this letter we discuss the effect of adding an electrogenic Na/K-ATPas pump to the above-mentioned mathematical model. The pump extrudes three $Na^+$ ions out of the cell via the exchange of two $K^+$ ions and consumption of one ATP in each pumping cycle [12, 13]. The electrical block of a HH model is given by one equation for the membrane potential, and additional equations for ionic currents that are responsible for potential change. The chemical block of a HH model is given by equations describing the kinetics of intracellular concentrations of calcium, sodium and potassium, extracellular potassium, the kinetics of calcium complex formation with cytosolic ligands, etc.

In our numerical model, the Na/K-ATPas pump was modeled as a product of three factors $I_{Na/K\ pump} = I_{max}\, a(V)\, b([Na]_i)\, c([K]_o)$, where $I_{max}$ is the maximum pump current, $a(v) = (v+150)/(v+200)$ is a voltage-dependent factor, $b([Na]_i) = 1/(1+(K_{m\,Na}/[Na]_i)^{n_{Na}})$ summarizes the effect of internal sodium concentration $[Na]_i$ and is described by a Hill equation with the half-activation $K_{m\,Na}$ and Hill's exponent $n_{Na} = 3/2$, $c([K]_o)$ $1/(1+(K_{m\,K}/[K]_o)^{n_K})$ summarizes the effect of external potassium concentration

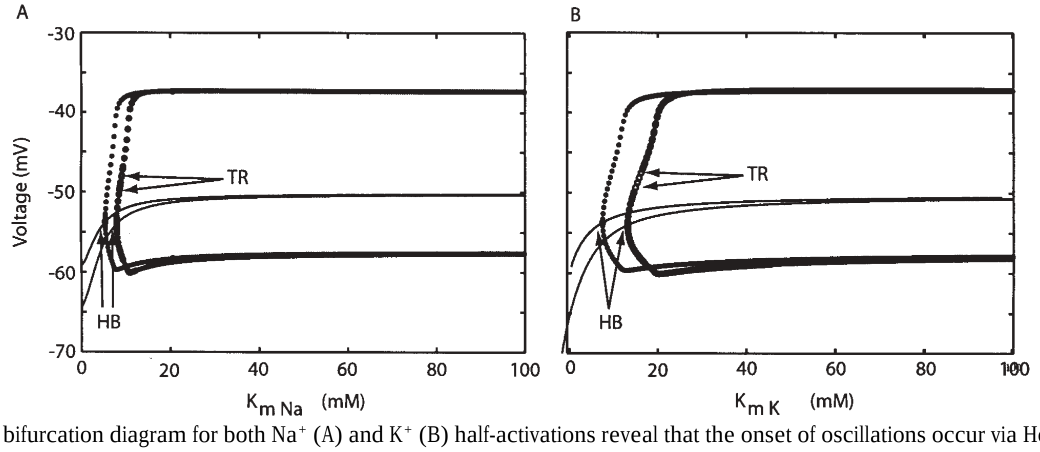


Fig. 1. The bifurcation diagram for both $Na^+$ (A) and $K^+$ (B) half-activations reveal that the onset of oscillations occur via Hopf bifurcations (HB) from unstable steady-states when the Na/K-ATPas half-activation concentration is high enough to compensate for outward potassium currents. Except for a very limited range of half-activations near the HB point, the voltage-dependent term (blue trace) makes no contribution to overall firing amplitude. A peculiar feature of voltage-dependent Na/K ATPas pump is the torus bifurcation (TR) that occurs immediately after the HB. This happened because the stable periodic oscillation emerging at HB has narrow window of instability due to the voltage-dependent Na/K pump and switches to a quasiperiodic oscillation.

* email: soprisan@yahoo.com

$[K]_o$ and is described by a Hill equation with the half-activation $K_{m\,K}$ and Hill's exponent $n_K = 1$. We used the freely available XPPAUT package [14] to investigate the stability of the firing pattern for different values of half-activations for both $Na^+$ and $K^+$ ions involved in Na/K ATPas pump. The bifurcation diagrams (fig. 1) show that the peak-to-peak membrane potential is almost constant for a wide range of half-activations, except for a narrow region around the Hopf bifurcation (HB) point. Furthermore, the voltage-dependence of Na/K ATPas pump has only a mild effect on the overall firing pattern of dopamine neurons by shifting the HB point and the onset of oscillations at a higher level of half-activation to compensate for the decrease in the current pump due to voltage-dependence. For example, $K_{m\,Na}$ was shifted from 5.334 mM in the absence of a voltage-dependent activation to 8.001 mM (fig. 1A) and $K_{m\,K}$ was shifted from 7.556 mM to 13.180 mM (fig. 1B). The voltage dependence of Na/K pump also induces a narrow unstable region immediately following the HB due to a significant increase in pump activity during the depolarized phase.

## Conclusions

Na/K ATPas pump plays an essential role in maintaining the ionic balance of living cells. Our numeric simulations showed that the voltage dependence of Na/K pump is not essential in ensuring cellular homeostasis. Our results also suggested that the effect of Na/K pump strongly depends on both the $[Na]_i$ and $[K]_o$ concentrations, which assumed constant values. However, a more detailed analysis including material balances for both $Na^+$ and $K^+$ ions, similar to calcium balance included in our model, is necessary.

*Acknowledgments: This work was supported by a Research and Development grant from the College of Charleston.*

## Reference

1.AMINI, B., W.CLARK JR.,J., CANAVIER,C.C., J. Neurophysiol., 1999, 82, p. 2249
2. CARMEN, C.C., OPRISAN, S.A., CALLAWAY, J., JI, H., SHEPARD,P.D. , J Neurophysiol., 2007, 98, p. 3006
3.. OPRISAN, S.A, Rev. Roum. Chem., 2008, (in press)
4.DARBON, P., SCICLUNA, L., TSCHERTER, A., STREIT, J., Eur. J. Neurosci., 2002, 15,p. 671
5. DARBON, P., TSCHERTER,A., YVON, C., STREIT, J., J. Neurophysiol., 2003, 90, p. 3119
6.EL MANIRA, A., TEGNER, J., GRILLNER,S., J. Neurophysiol., 1994, 72, p. 1852
7. FLEIDERVISH, I.A., FRIEDMAN, A., GUTNICK, M.J., J. Physiol., 1996, 493, p. 83
8. TSAI,M.C., CHEN, Y.H., Comp. Biochem. Physiol., 1995, 111, p. 131
9. DEL NEGRO, C.A., HSIAO,C.F., CHANDLER, S.H. , J. Neurophysiol., 1999, 81, p. 1478
10. SHEN, K.Z., JOHNSON, S.W., J. Physiol., 1998, 512, p. 449
11. CLAUSEN, T., T, Clin. Sci., 1998, 95, p. 3
12. ROSE, A.M., VALDES Jr, R., Clin. Chem., 1994, 40, p. 1674
13.SULMAN, T., KATSNELSON, L.B. , SOLOVYOVA, O., MARKHASIN, V..S. Bull. Math. Biol., 2008, 70, p. 910
14. ERMENTROUT, B., Simulating, Analyzing, and Animating Dynamical Systems: A Guide to XPPAUT for Researchers and Students, Soc. for Industr. & Appl. Math, Philadelphia, 2002

Manuscript received: 20.08.2008