Space State Approach to Study the Effect of Sodium over Cytosolic Calcium Profile

Shivendra Tewari

Department of Mathematics
Maulana Azad National Institute of Technology
Bhopal – 462 051, India

K. R. Pardasani

Department of Mathematics
Maulana Azad National Institute of Technology
Bhopal – 462 051, India
kamalraj@rediffmail.com

Abstract

Calcium is known to play an important role in signal transduction, synaptic plasticity, gene expression, muscle contraction etc. A number of researchers have studied cytosolic calcium diffusion but none have studied the effect of sodium over cytosolic calcium profile. Here in this paper we have developed a mathematical model which incorporates all the important parameters like permeability coefficient, calcium flux, sodium flux, external sodium, external calcium etc. Thus we can study dynamically changing calcium with respect to dynamically changing sodium. Further, we have used Space State approach for the simulation of the proposed model which is a novel technique in itself developed in the later part of the twentieth century.

Keywords: Cytosolic calcium, permeability coefficient, sodium flux, calcium flux

1 Introduction

Intracellular calcium is known to regulate a number of processes [13]. One of the most important processes is the process of signal transduction. Calcium acts as a switch in the process of signal transduction while converting electrical signal into

a chemical signal. Calcium helps in the mechanism of exocytosis by combining with synaptotagmin to release neurotransmitters [9]. There are a number of parameters that affect its mobility and concentration like channels, pumps, leaks etc. Further, Reuter and Seitz found that calcium extrusion in heart muscles is caused by the electrochemical sodium gradient across the plasma membrane. Blaustein also observed that the sodium gradient across the plasma membrane influences the intracellular calcium concentration in a large variety of cells via a counter transport of Na^+ for Ca^{2+} . The dependence of $\text{Na}^+ - \text{Ca}^{2+}$ electrochemical gradient has been studied by Sheu and Fozzard for sheep ventricular muscle and Purkinje strands. Thus, there is enough evidence that Na^+ is an important parameter to be considered when modeling cytosolic $[\text{Ca}^{2+}]$ concentration. Matsuoka *et al.* also found that $\text{Na}^+ - \text{Ca}^{2+}$ is the major mechanism by which cytoplasmic Ca^{2+} is extruded from cardiac myocytes [5, 8, 12, 15]. The mathematical models proposed so far have not incorporated the effect of Na^+ in their models [13, 3, 4]. Thus in this model we have incorporated the effect of dynamically changing Na^+ over dynamically changing Ca^{2+} . In this mathematical model we have incorporated Ca^{2+} influx, Na^+ influx, $\text{Na}^+ / \text{Ca}^{2+}$ exchange pump. Further, for the simulation of the proposed mathematical model we have used space state approach which gives us the privilege of obtaining analytical results but at the cost of linearising the given model. The results are used to show the effect of $\text{Na}^+ / \text{Ca}^{2+}$ exchange over intracellular Ca^{2+} and intracellular Na^+ .

2 The Mathematical Model

The mathematical model consists of a Ca^{2+} flux, Na^+ flux and a $\text{Na}^+ / \text{Ca}^{2+}$ exchange pump. The influx of Ca^{2+} and Na^+ currents is modeled using the famous *Goldman-Hodgkin-Katz* (GHK) current equation [2] while the third parameter $\text{Na}^+ / \text{Ca}^{2+}$ exchange pump is modeled using the free energy principle [1]. We have assumed a cytosol of radius 5 μm and thickness 7 nm. The proposed mathematical model can be framed using the following system of ordinary differential equations:

$$\begin{aligned} \frac{d[\text{Ca}^{2+}]}{dt} &= -\sigma_{\text{Ca}} - \sigma_{\text{NCX}} \\ \frac{d[\text{Na}^+]}{dt} &= -\sigma_{\text{Na}} - \sigma_{\text{NCX}} \end{aligned} \quad (1)$$

Along with the initial conditions,

$$[Ca^{2+}] = 0.1\mu M$$

$$[Na^+] = 12mM$$

Ca²⁺ and Na⁺ currents

The influx of Ca²⁺ and Na⁺ is modeled using the GHK equation:

$$I_s = \frac{P_s z_s^2 \left(\frac{V_m F^2}{RT} \right) ([S]_i - [S]_o \exp(-\frac{z_s V_m F}{RT}))}{(1 - \exp(-\frac{z_s V_m F}{RT}))} \quad (2)$$

here, 'S' is any ion in this case Ca²⁺ or Na⁺. All the parameters have their usual meanings and have values as stated in Table 1. The value of permeability constant of Ca²⁺ and Na⁺ is determined from the fact that conductance or permeability is equal to $\frac{D}{L}$ where D is the diffusion coefficient and L is the thickness of the membrane [2]. The diffusion coefficients were taken as from Stryer *et al.* [6] and membrane thickness is taken to be 7 nm [2]. Further, the inward current was taken to be negative and is converted into Molar / second using the faradays constant and using the fact that 1 L = 10¹⁵ μm³ before being substituted in equation (1).

$$\sigma_{Ca} = \frac{-I_{Ca}}{z_{Ca} F V}$$

where, all the parameters have their usual meanings and V is the volume of the cytosol. Similarly, we can calculate the net flux of Na⁺ ions from the Na⁺ channel.

Na⁺ / Ca²⁺ exchange

The Na⁺ / Ca²⁺ exchange pump is known as the most important mechanism of Ca²⁺ extrusion [15]. This exchange is modeled by equating the electrochemical gradient of both the ions,

$$\Delta_{Ca} = RT \log\left(\frac{Ca_i}{Ca_o}\right) + z_{Ca} F V_m \quad (3)$$

Similarly, we can frame for electrochemical gradient of Na⁺ (Δ_{Na}). The pump is assumed to be electrogenic in nature as one Ca²⁺ leaves the cytosol for intake of three Na⁺ ions. Thus,

$$\Delta_{Ca} = 3\Delta_{Na} \quad (4)$$

Using equation (4) and solving we can obtain the required relation for $\text{Na}^+ / \text{Ca}^{2+}$ exchange, given in the following equation:

$$\begin{aligned} \sigma_{NCX} &= Ca_o \left(\frac{Na_i}{Na_o} \right)^3 \exp\left(\frac{FV_m}{RT}\right) \\ \bar{\sigma}_{NCX} &= Na_o \left(\frac{Ca_i}{Ca_o} \right)^{1/3} \exp\left(-\frac{FV_m}{RT}\right) \end{aligned} \quad (5)$$

Before solving equation (1) by Space State technique the equations were linearised. For our convenience we write 'u' in lieu of Ca^{2+} and 'v' in lieu of Na^+ . Further, the equations were transformed into matrix equations after using a number of transformations:

$$\begin{aligned} \frac{du}{dt} &= au - b - a'v \\ \frac{dv}{dt} &= cv - d + c'u \end{aligned} \quad (6)$$

where,

$$\begin{aligned} a &= \frac{2P_{Ca}FV_m \exp\left(\frac{2FV_m}{RT}\right)}{RT(1 - \exp\left(\frac{2FV_m}{RT}\right))}, b = \frac{2P_{Ca}FV_m u_{out}}{RT(1 - \exp\left(\frac{2FV_m}{RT}\right))}, a' = \frac{u_{out}}{v_{out}} \exp\left(\frac{FV_m}{RT}\right), \\ c &= \frac{P_{Na}FV_m \exp\left(\frac{FV_m}{RT}\right)}{(1 - \exp\left(\frac{FV_m}{RT}\right))}, d = \frac{P_{Na}FV_m v_{out}}{(1 - \exp\left(\frac{FV_m}{RT}\right))}, c' = \frac{v_{out}}{u_{out}} \exp\left(-\frac{FV_m}{RT}\right) \end{aligned}$$

Using another transformation of

$$\begin{aligned} \bar{u} &= u \exp\left(\frac{2FV_m}{RT}\right) - u_{out} \\ \bar{v} &= v \exp\left(\frac{FV_m}{RT}\right) - v_{out} \end{aligned} \quad (7)$$

Using equation (7) in equations (6) it is reduced to

$$\frac{d}{dt} \begin{bmatrix} \bar{u} \\ \bar{v} \end{bmatrix} = \begin{bmatrix} -\frac{u_{out}}{v_{out}} \exp(2\varepsilon) & \frac{2P_{Ca} \exp(2\varepsilon)}{1 - \exp(2\varepsilon)} \\ \frac{P_{Na} \varepsilon \exp(\varepsilon)}{1 - \exp(\varepsilon)} & -\frac{v_{out}}{u_{out}} \exp(-2\varepsilon) \end{bmatrix} \begin{bmatrix} \bar{u} \\ \bar{v} \end{bmatrix} - \begin{bmatrix} u_{out} \\ -v_{out} / \exp(2\varepsilon) \end{bmatrix} \quad (8)$$

here, ε is a dimensionless quantity equal to FV_m / RT . If we use matrix notations and use another transformation then equation (8) can be reduced to the form which is readily solvable by the method of Space State,

$$\frac{dY}{dt} = AY \quad (9)$$

where,

$$Y = AX + C, X = \begin{bmatrix} \bar{u} \\ \bar{v} \end{bmatrix}, C = \begin{bmatrix} u_{out} \\ -v_{out} / \exp(2\varepsilon) \end{bmatrix}, A = \begin{bmatrix} -\frac{u_{out}}{v_{out}} \exp(2\varepsilon) & \frac{2P_{Ca} \exp(2\varepsilon)}{1 - \exp(2\varepsilon)} \\ \frac{P_{Na} \varepsilon \exp(\varepsilon)}{1 - \exp(\varepsilon)} & -\frac{v_{out}}{u_{out}} \exp(-2\varepsilon) \end{bmatrix}$$

with initial conditions,

$$Y(0) = \begin{bmatrix} 0.002 \\ 74.361 \end{bmatrix} \quad (10)$$

Solving equation (9 – 10) with help of space state technique and using inverse transformations, we have,

$$\begin{aligned} u(t) &= 256.41(0.002 - 0.00005(-37.18 - 37.31(\sinh(kt)) + 74.36(\cosh(kt) \\ &\quad - 0.012(\sinh(kt)))) + 0.012(-0.002(-0.002 - 0.004(\sinh(kt)) + 0.002(\cosh(kt) \\ &\quad + 0.0002(\sinh(kt)))))) \\ v(t) &= 16(0.145 - 0.0002(-37.18 - 37.31(\sinh(kt))) + 74.36(\cosh(kt) \\ &\quad - 0.0118(\sinh(kt)))) - 18589.7(-0.002 - 0.004(\sinh(kt)) + 0.002(\cosh(kt) \\ &\quad + 0.0002(\sinh(kt)))) \end{aligned}$$

here, k is the eigen value of matrix A which has two values:

$$k_1 = -1.00579$$

$$k_2 = 0.99253$$

It is evident that $k_1 \approx -k_2$, the results are plotted using the same hypothesis in the coming section.

3 Results and Discussion

This section comprises of the results and conclusion obtained from our methodology and hypothesis. The parameters used for simulation are as stated in Table 1

Table 1 Values of the parameters used

Parameter	Symbol	Value
Faraday's Constant	F	96487 Coulombs / moles
Membrane Potential	V_m	-70 mV
Real Gas Constant	R	8.314 J per Kelvin mole
Temperature	T	293 K
External Calcium Concentration	u_{out}	2 mM
External Sodium Concentration	v_{out}	145 mM
Ca ²⁺ diffusion coefficient	D_{Ca}	250 μm^2 /second
Na ⁺ diffusion coefficient	D_{Na}	480 μm^2 /second
Membrane thickness	L	7 nm
Ca ²⁺ permeability	P_{Ca}	3.3×10^{-2} metre / second
Na ⁺ permeability	P_{Na}	6.4×10^{-2} metre / second

Fig. 1 shows the plot of Ca^{2+} against time

In figure 1, the impact of $\text{Na}^+ / \text{Ca}^{2+}$ exchange is shown on the temporal scale. Ca^{2+} is shown on the mM scale and time is shown on the second scale. It is evident from the figure when Ca^{2+} concentration rises above a certain level it triggers $\text{Na}^+ / \text{Ca}^{2+}$ exchange protein and initializes the extrusion of Ca^{2+} for intake of Na^+ ions. As soon as, $\text{Na}^+ / \text{Ca}^{2+}$ exchange is triggered the rising of Ca^{2+} stops and it starts decaying. Also, biologically, this mechanism of Ca^{2+} extrusion / Na^+ inflow is known to reverse as soon as the Ca^{2+} level goes below a certain level (which is different for different cell types). But, no such thing is evident from figure 1 because we have not modeled this process, since it would have lead to a more complex mathematical model. In this paper, we have shown the effect of $\text{Na}^+ / \text{Ca}^{2+}$ exchange protein over cytosolic Ca^{2+} and Na^+ profiles while keeping our mathematical model simple, so as to reduce computational power required for the simulation of the mathematical model.

Fig. 2 shows the plot of Na^+ against time

In figure 2, the increasing Na^+ is plotted against time. Intracellular Na^+ is in the units of mM and time is on the scale of seconds. Since, there is no parameter in equation 1 to regulate intracellular concentration, therefore, Na^+ concentration goes on increasing. But that is not the case in reality as there is a Na^+ / K^+ ATPase which extrudes excess Na^+ from inside the cytosol [10]. Further, the $\text{Na}^+ / \text{Ca}^{2+}$ exchange functions both ways when the Ca^{2+} is high it exchanges intracellular Ca^{2+} for extracellular Na^+ and when Na^+ is high it exchanges intracellular Na^+ for extracellular Ca^{2+} [11]. The numerical results and graphs are obtained using Mathematica 6.0.

Since, the model proposed needed to be a linear one we have to drop the non-linear terms and hence the Na^+ concentration is not decreasing. On the other hand, this paper helps us to observe the apparent effect of $\text{Na}^+ / \text{Ca}^{2+}$ exchange over intracellular Ca^{2+} concentration while keeping the model a simple one. Further, the use of space state technique simplifies the solution and gives an analytic solution. In a similar manner, we can incorporate more parameters in this model to have a more realistic model which can be used either for simulation of cytosolic diffusion or excitation contraction coupling problem. Also, the solution used obtained here can be used to study the relationship for normal and abnormal conditions which can again be beneficial to biomedical scientists for developing protocols that can be used for diagnosis and treatment of neurological disorders.

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