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# Simplified computational model of the BK channel–spermine interaction

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## Abstract

Spermine blocks large-conductance voltage- and calcium-activated potassium channels (BK channels). In recent years, interest in this interaction has increased because of its involvement in both physiological and pathological processes. This study aimed to develop a simplified mathematical model of the BK current and its blockade by spermine and to implement it in a computational simulator. To this end, a Hodgkin–Huxley-type mathematical model of the BK current was used, in which the steady-state channel activation follows a Boltzmann function that depends on membrane voltage and intracellular calcium concentration. Spermine block depended on the concentration of this polyamine and on the fraction of spermine molecules entering the channel as a result of the electrostatic attraction between the positive charges of spermine and the negative charges within the channel pore. This process was described, in a simplified manner, by a Boltzmann function with a behavior different from that of the activation function. The simulator reproduced the voltage and calcium dependence of the BK channel. Depending on the spermine concentration, channel block produced inward rectification of the BK current followed by a partial recovery of the current, indicating partial channel blockade. In conclusion, all variables of the mathematical model can be modified to evaluate their effects on the BK channel–spermine interaction. Careful selection of these variables, while maintaining values within electrophysiological ranges, allows the model to approximate several experimentally observed responses.

**Keywords:** BK channel; Spermine; Computational Simulation; Electrophysiology; Channel Blockade

## 1. Introduction

The large-conductance calcium- and voltage-activated potassium (BK) channel is blocked by polyamines under various normal and pathological conditions. Polyamines are small polycationic molecules carrying two, three, and four positive charges at physiological pH. The main polyamines are putrescine, spermidine, and spermine. They are essential for normal cell growth [1]. Polyamine concentrations are in the millimolar range; however, only a small fraction is present in the free form (in the micromolar range). Polyamines are bound to DNA (Deoxyribonucleic Acid), RNA (Ribonucleic Acid), and intracellular structures. Their synthesis depends on the enzymes ornithine decarboxylase, spermidine synthase, and spermine synthase [2]. Weiger and Hermann [3] reported that elevated spermine concentrations are associated with cancer. A low concentration has been found during aging [4]. Increased interest has emerged in polyamines as future research avenues for the prevention or treatment of several diseases, including certain types of cancer, ischemia, and pulmonary hypertension [5],[6].

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On the other hand, some ion channels are blocked by polyamines. In the BK channel, they produce inward rectification of the potassium current due to the positive charges on polyamine molecules, which are electrostatically attracted by a ring of negative charges located inside the channel vestibule. According to Li et al. [7] and Zhou et al. [8], they could be considered potential biomarkers for tumor diagnosis and therapeutic targets. Zamora-Cardenas et al. [9] reported in breast gland cancer cells an overexpression of BK channels within the cell as the tumor stage progresses, along with a decrease in their expression at the membrane. Polyamine blockade and reduced membrane expression result in a decrease in BK current and inward rectification [3]. Within the cell, BK channels are present in mitochondrial and nuclear membranes [10].

BK channels are activated synergistically by the intracellular calcium concentration ($[Ca^{2+}]_i$) and membrane depolarization [11]. The voltage-dependent steady-state activation is described by a Boltzmann function whose parameters depend on $[Ca^{2+}]_i$ [12] and membrane voltage [13].

The objective of this work is to develop and implement a simplified mathematical model of BK channel current incorporating intracellular spermine block. The model will be used to examine the effects of intracellular calcium and spermine concentrations on channel function under different channel densities and voltage sensitivities.

## 2. Material and methods

The simulator was based on a modified Hodgkin and Huxley-type BK current model [13], to which polyamine blockade was added (Equation 1).

$$I_{BK} = g_{BK} \cdot m \cdot (1 - \gamma B) \cdot (V - E_K) \quad (1)$$

$I_{BK}$ represents the BK current, $g_{BK}$ is the macroscopic BK conductance, γ is the blocking efficiency, B is the spermine blockade, V is the ramp stimulus voltage, and EK is the potassium equilibrium potential.

A Boltzmann function was used to describe the steady-state activation [14] (Equation 2). This function fits the normalized conductance relationship (G/Gmax) versus experimental voltage data [15]. This simplifies the mathematical model of the BK channel.

$$m_\infty(V, Ca) = \frac{1}{1+\exp\left(\frac{-V-V_{\frac{1}{2}}(Ca)}{k}\right)} \quad (2)$$

$V_{1/2}(Ca)$ is the half-activation voltage; it depends on the intracellular calcium concentration (Equation 3)

$$V_{1/2}(Ca) = V_0 - \alpha \ln(Ca) \quad (3)$$

Where $V_0$ is the half-activation voltage when $[Ca^{2+}]_i$ approaches 0, α is the $Ca^{2+}$ activation sensitivity, and k is the slope of the Boltzmann function.

The temporal dynamics of the activation gate (m) are determined by Equation 4.

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad (4)$$

Where $\tau_m$ is the activation time constant. $m_\infty$ is the equilibrium value. Under a ramp stimulus, it is continuously changing.

The spermine blockade is determined by Equation 5.

$$B = \frac{[Spm]}{[Spm] + Kd(V)} \quad (5)$$

Where [Spm] is the spermine concentration, and Kd(V) is the voltage-dependent spermine affinity.

The spermine blockade can be empirically approximated by a Boltzmann function that describes its movement through a fractional electrical distance (δ) across the channel electric field [16] (Equation 6).

$$kd(V) = kd(0)\exp\left(\frac{-z\delta FV}{RT}\right) \quad (6)$$

Where kd(0) is the spermine affinity at 0 mV, z is the valence, δ is the depth of the binding site within the BK channel, F is the Faraday constant, V is the voltage, R is the gas constant, and T is the temperature in Kelvin.

The BK current was evoked using a voltage ramp from -100 to 160 mV, with a slope of 130 mV/s and a duration of 2000 ms.

## 3. Results and Discussion

A Hodgkin-and-Huxley-type mathematical model was implemented, allowing its variables to be modified to reproduce the electrophysiological characteristics of BK channels and to simulate channel blockade by polyamines using a ramp voltage stimulation protocol. This experimental protocol generates a current-voltage relationship that allows visualization of polyamine blockade.

Simulations were conducted by changing one variable at a time while all other variables were kept fixed. The modified values are described in the text, whereas the values of the remaining variables are displayed in the corresponding fields within the user interface.

### 3.1. Simulator interface and BK channel activation by calcium and voltage

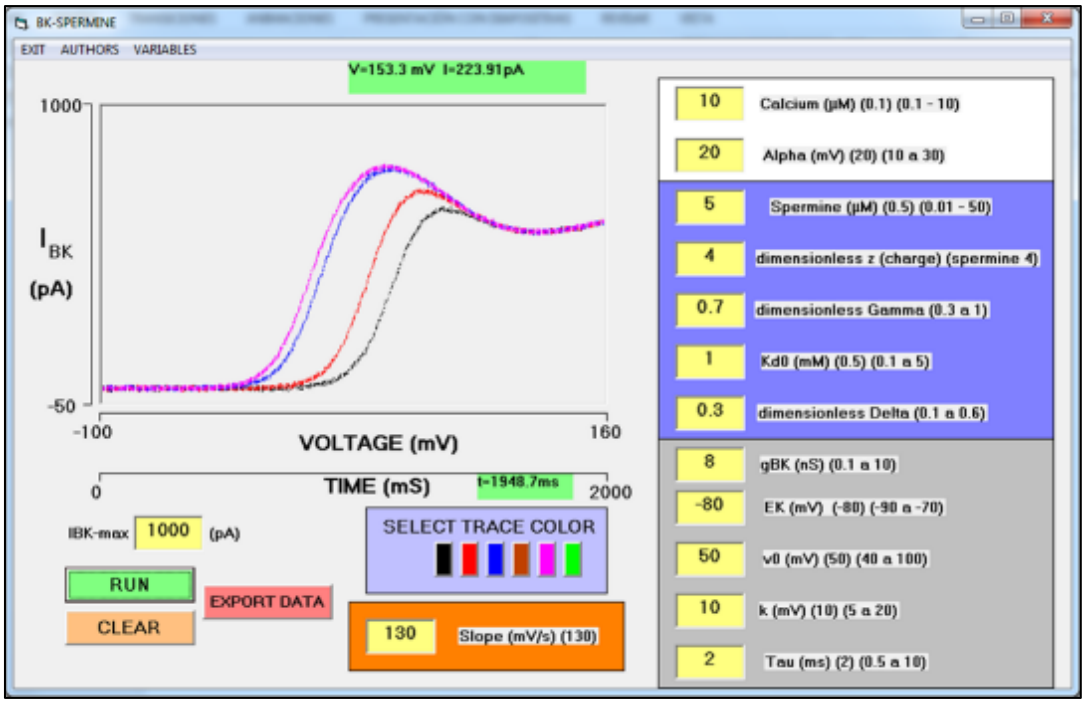


**Figure 1** Interface. On the left side, the traces generated by a ramp-voltage stimulus from -100 mV to 165 mV with a slope of 130 mV/s are shown. The variables used in the mathematical model are shown on the right side. The traces correspond to different intracellular calcium concentrations: 0.001 µM, 1 µM, 7 µM, and 10 µM, represented by the black, red, blue, and pink traces, respectively. Spermine = 5 µM. A partial block of the BK channel was observed in all cases

The simulator interface is shown in Figure 1. On the left side, an oscilloscope displays the macroscopic BK current traces generated by a ramp-voltage stimulus over a voltage range from -100 mV to 160 mV with a slope of 130 mV/s. On the right side, three blocks group the variables included in the mathematical model used. The upper block contains the fields for modifying intracellular calcium concentration and the affinity of calcium for the BK channel (Alpha). The immediately lower block groups the variables related to spermine: its concentration, valence (z), blocking efficiency (Gamma), spermine affinity at 0 mV (Kd0), and the depth of the blocking site (Delta). Finally, the lower block groups the variables related to the electrophysiological properties of the cell and the current trace: the macroscopic BK channel

conductance ($g_{BK}$), the potassium equilibrium potential (EK), the half-activation voltage in the absence of calcium (v0), the sigmoidal slope factor (k), and the time constant (Tau).

The mathematical model reproduces the leftward shift of the current–voltage curve resulting from an increase in $[Ca^{2+}]_i$. Similarly to the conductance–voltage (G–V) curve [13]. In the virtual experiment, the half-activation voltages were 47.8 mV, 37.8 mV, 11.7 mV, and 6.7 mV for the black (0.001 µM), red (1 µM), blue (7 µM), and pink (10 µM) traces, respectively, showing a progressive shift toward less positive values (Figure 1). Binding of calcium to specific structures within the BK channel [17] facilitates channel opening and enhances its voltage sensitivity [18]. The BK current reaches its maximum amplitude, and spermine blockade is observed at a concentration of 5 µM.

### 3.2. Spermine blockade of the BK current

Four simulations were performed at an intracellular calcium concentration of 7 µM and a conductance of 8 nS. In each simulation, the spermine concentration was varied: Spermine 0.5 µM (black trace): the current generated by the voltage ramp reached an amplitude of 1123 pA at 85 mV and then decreased due to blockade to 722 pA at 160 mV. Red trace, spermine 1 µM: blockade occurred more rapidly. The maximum current amplitude was 1022 pA at 72.8 mV and decreased to 642 pA at 160 mV. Blue trace, spermine 5 µM: the maximum amplitude was 765 pA at 49 mV and decreased due to blockade to 556 pA at 119 mV, after which channel reopening was initiated. Green trace, spermine 10 µM: the maximum amplitude was 668 pA at 43 mV and decreased to 508 pA at 106 mV, after which the channel became activated again.

It can be observed that BK channel blockade depends on spermine concentration. The blockade produced by low spermine concentrations is observed at more positive voltages. As spermine concentration increases, blockade occurs more rapidly. Once the channel opens, spermine initiates the blockade, resulting in a decrease in the slope of the current. Likewise, the maximum amplitude is reached at progressively less positive voltages, allowing channel reactivation to be observed. BK channel blockade by spermine was partial and concentration-dependent (Figure 2).

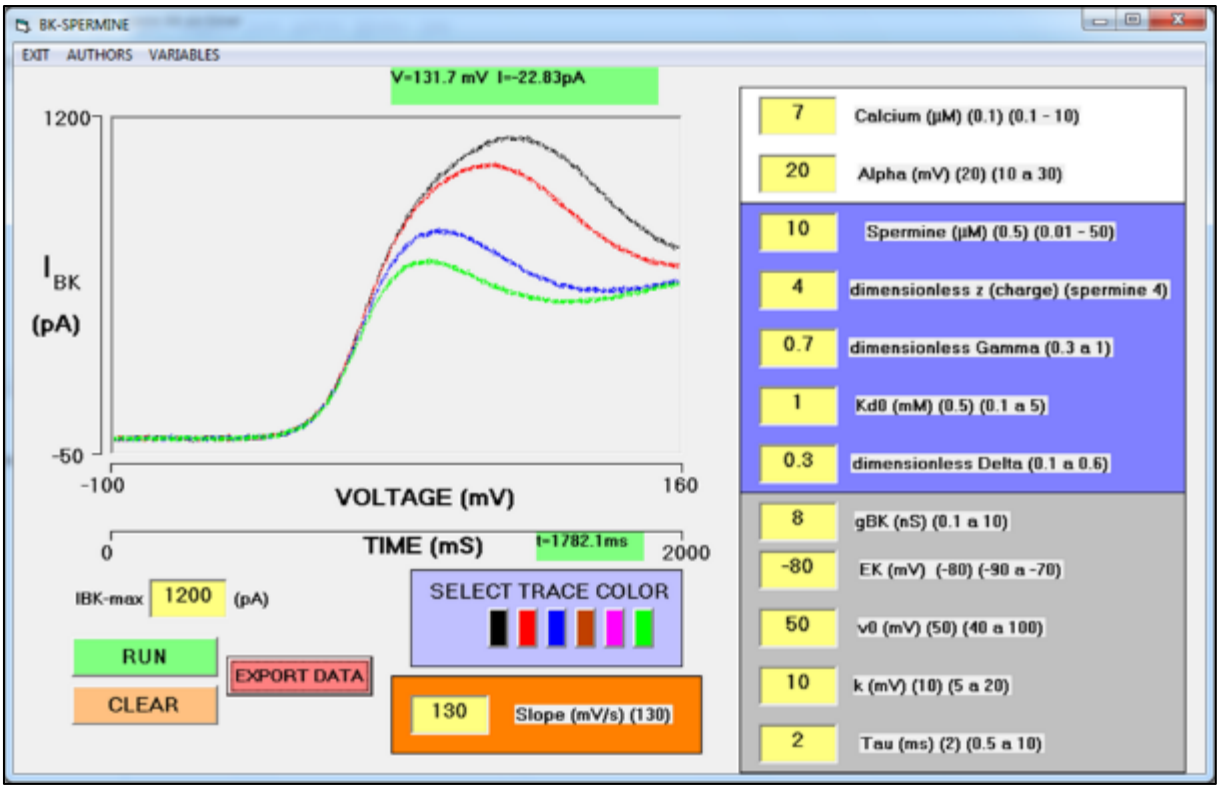


**Figure 2** Spermine blockade of the BK current. Spermine concentration was increased to 0.5 µM, 1 µM, 5 µM, and 10 µM, corresponding to the black, red, blue, and green traces, respectively. It can be observed that, as spermine concentration increases, the blockade becomes faster and of greater magnitude

Polyamines are present intracellularly at concentrations in the millimolar range; however, most are bound to DNA (deoxyribonucleic acid), RNA (ribonucleic acid), proteins, phospholipids, and cellular structures such as the

cytoskeleton [19]. Only a small fraction of polyamines exists in the free form. In the simulations, spermine concentrations ranging from 0.5 to 15 μM were used to observe partial channel blockade.

### 3.3. Blocking efficiency variable

In the BK current equation (Equation 1), the variable γ (Gamma, in the interface) represents the blocking efficiency. Four simulations were conducted to examine how increasing its value affects channel blockage. The spermine concentration was kept at 5 μM to produce a partial blockade. Figure 3 displays the BK currents. The black trace, Gamma = 0.6, shows a maximum amplitude of 815 pA at 55.6 mV, which decreased to 706 pA at 110.6 mV due to blockade. The red trace, Gamma = 0.7, shows that the maximum amplitude was 774 pA at 51.1 mV and decreased to 512 pA at 122.8 mV. Blue trace, Gamma = 0.8: the maximum amplitude was 738 pA at 47.2 mV and decreased to 398 pA at 133.9 mV. Brown trace, Gamma = 0.9: the maximum amplitude was 715 pA at 45.0 mV and decreased to 208 pA at 151.7 mV.

As the value of Gamma increases, the maximum amplitude of the BK current decreases due to an increase in blocking efficiency.

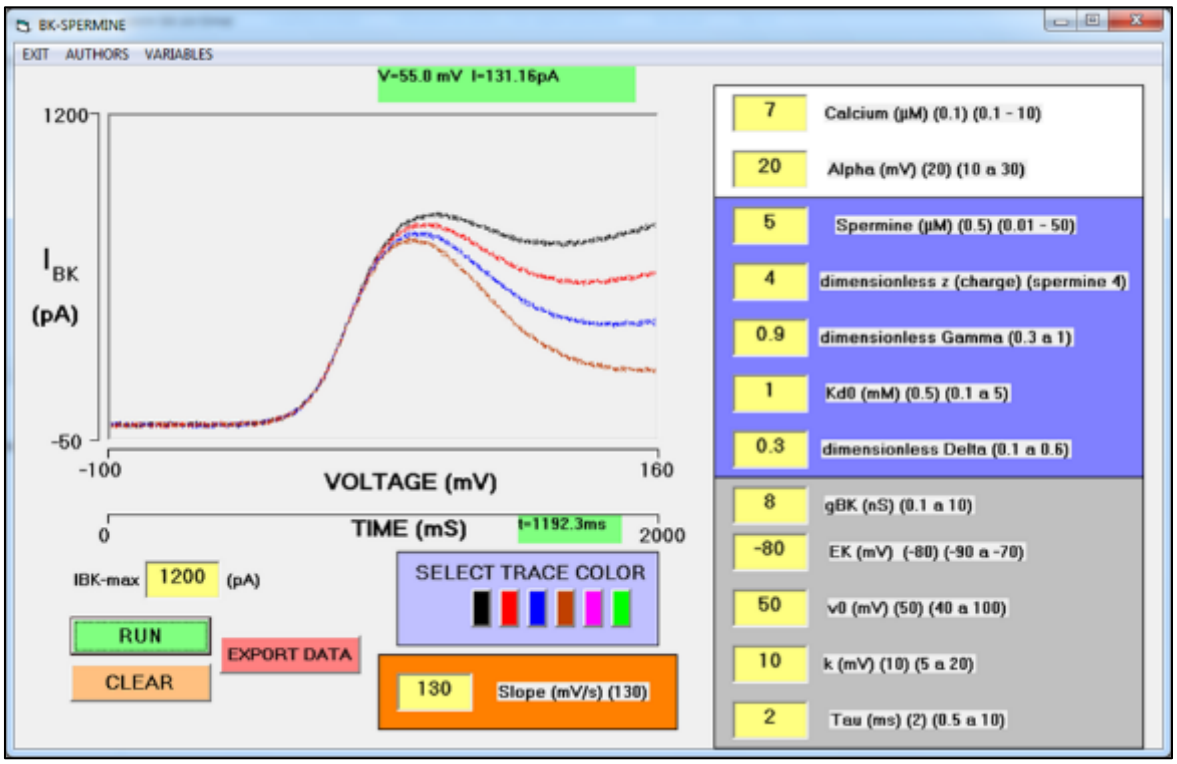


**Figure 3** Blocking efficiency. Four simulations were performed by varying the value of the blocking efficiency (Gamma) to 0.6, 0.7, 0.8, and 0.9, corresponding to the black, red, blue, and brown traces, respectively. BK channel blockade increased as the value of the Gamma variable increased. All simulations were performed at a spermine concentration of 5 μM

### 3.4. Effect of the v0 variable

When $[Ca^{2+}]i$ approaches zero, the voltage required for BK channel activation is represented by the variable v0. It represents channel opening determined almost exclusively by voltage. When the V1/2 value in a cell is shifted toward less positive values, the channel opens more readily. Steady-state activation was described by a Boltzmann function (Equation 2). Factors that can shift v0 toward more negative values include a high calcium concentration or the presence of auxiliary subunits (β1, β4, and δ1 (LRRC26) [20]). Elevated calcium concentration and the δ1 subunit are the factors that produce the most pronounced shifts in V1/2 [21].

Four simulations were performed with an intracellular calcium concentration of 7 μM and a spermine concentration of 5 μM. The v0 voltage was modified in each simulation to 50 mV, 40 mV, 30 mV, and 20 mV, corresponding to the black, red, blue, and brown traces, respectively (Figure 4). The resulting half-activation voltages (V1/2) were 14.4 mV, 3.9 mV, -3.3 mV, and -12.8 mV, respectively. By selecting appropriate values of $[Ca^{2+}]i$ and v0, it is possible to approximate the characteristic V1/2 value of a particular cell.

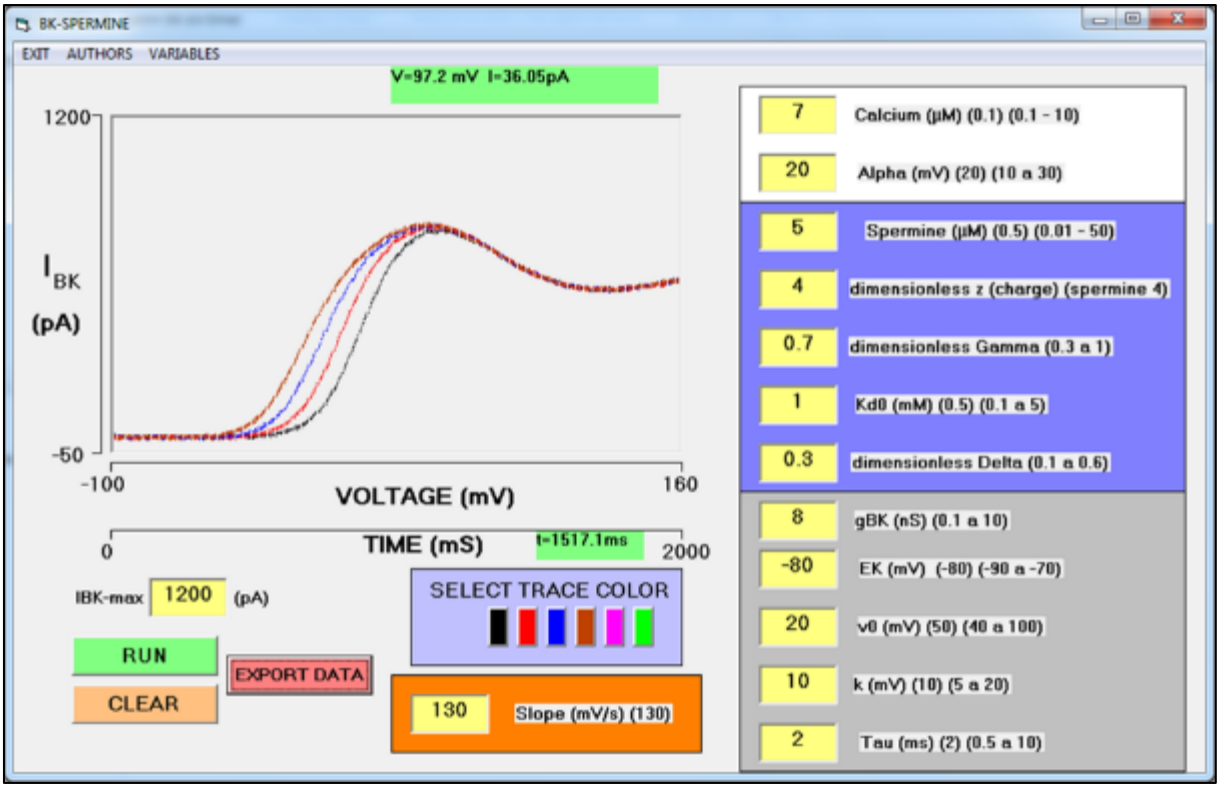


**Figure 4** Shift in V1/2 induced by (v0). Less positive values of (vo) produced a leftward shift in the V1/2 of the BK current. In the simulations, V1/2 values were 14.4 mV, 3.9 mV, −3.3 mV, and −12.8 mV for (vo) values of 50 mV, 40 mV, 30 mV, and 20 mV, respectively (black, red, blue, and brown traces)

### 3.5. Block depth

Spermine enters the BK channel from the intracellular side of the cell. Within the channel structure, rings of negative charges attract the small positively charged polyamine molecules, resulting in an electrostatic interaction. BK channels contain a ring of eight negative charges formed by residues E321 and E324 at the entrance of the intracellular vestibule. These negative charges electrostatically attract intracellular polyamines. Removal of these charges (E321N/E324N mutation) drastically reduces polyamine block [16]. This interaction is represented in Equation 5, where Kd(V) depends on voltage and charge. Equation 6 describes the thermodynamic component of the model. One of the variables used is the block depth, δ (Delta in the interface). Its values range from 0.1 (segment exposed to the cytoplasm) to 1 (segment located at the extracellular side of the membrane). Under conditions of spermine = 0.01 µM, vo = 5 mV, and gBK = 10 nS, four simulations were performed by varying δ (Delta in the simulator). With δ = 0.3, no block was observed (black trace). With δ = 0.4, the maximum current was 1890 pA at 127 mV and decreased to 1742 pA at 160 mV (red trace). With δ = 0.5, the maximum current was 1650 pA at 127 mV and declined to 1455 pA at 142 mV, where the rebound phase began (blue trace). In the brown trace (δ = 0.6), the peak current was 1511 pA at 83 mV, decreased to 1289 pA at 121 mV, and subsequently recovered. A partial block was observed in the last three traces, indicating a greater extent of channel blockade. The vestibule not only concentrates spermine, but may also act as a kinetic barrier that limits deep penetration when occupancy is high. However, with a low number of spermine molecules, some molecules appear to pass toward relatively deeper sites, where they produce a partial block.

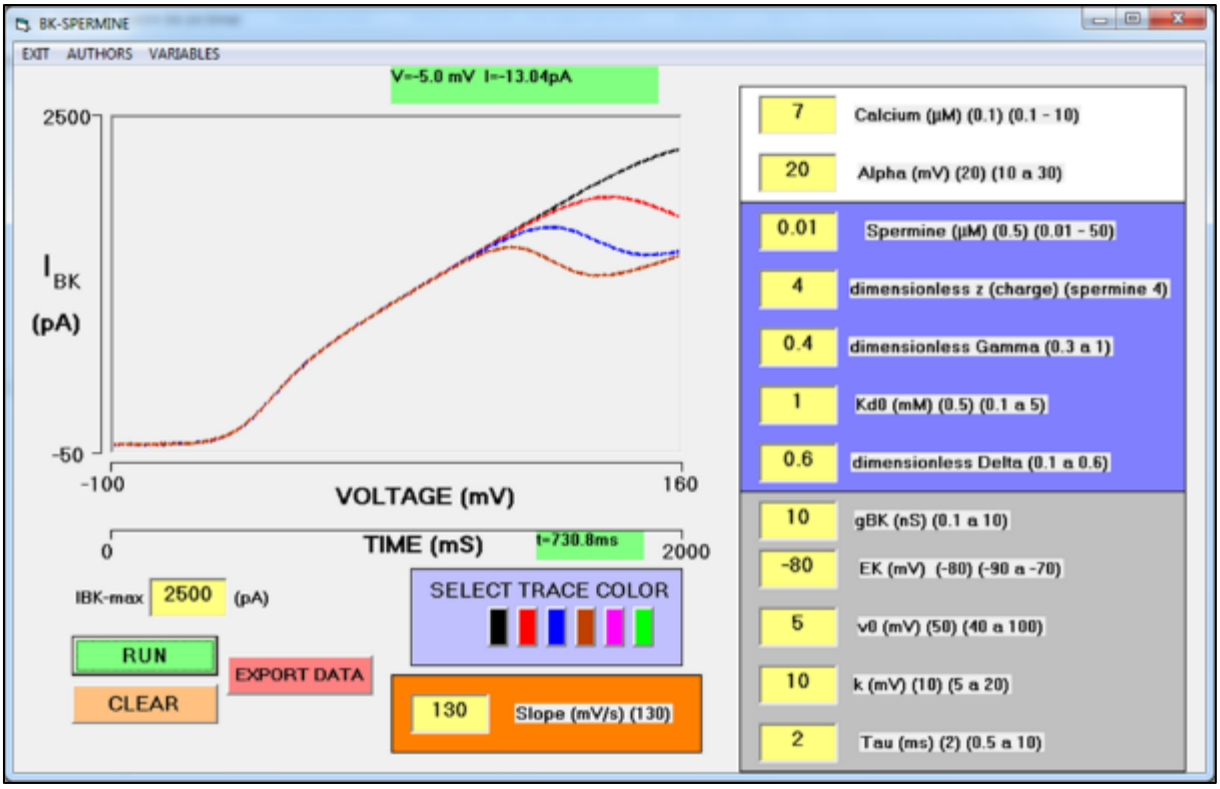


**Figure 5** Simulations exploring partial blockade at deeper sites within the BK channel. In each simulation, the Delta parameter was varied from 0.3 to 0.6, corresponding to the black, red, blue, and brown traces, respectively. A partial block was observed in the last three traces, indicating an increased degree of channel blockade. The values of the remaining variables are shown in the boxes on the right-hand side

### 3.6. Simulations in cells with high and low channel density

The right side of the interface displays all variables that can be modified and provides possible values. However, other values can also be used. For the simulation to provide meaningful results, variations in the variables should generate responses within a physiologically realistic range. In this section, a comparison was made between two cells with different characteristics. One cell had a high channel density (gBK = 10 nS), negative values of voltage sensitivity (vo = −10 mV, an extreme value), and a spermine sensitivity (Gamma) of 0.4. The remaining values are shown in the boxes on the left side (Figure 6). A spermine concentration of 1 µM was used. This simulation corresponds to the black trace.

The second cell had a low number of channels in the membrane (gBK = 4 nS), vo = 5 mV, Gamma = 0.5, and a spermine concentration of 10 µM. The values of the remaining variables are displayed in the boxes on the right side. This simulation corresponds to the red trace (Figure 6).

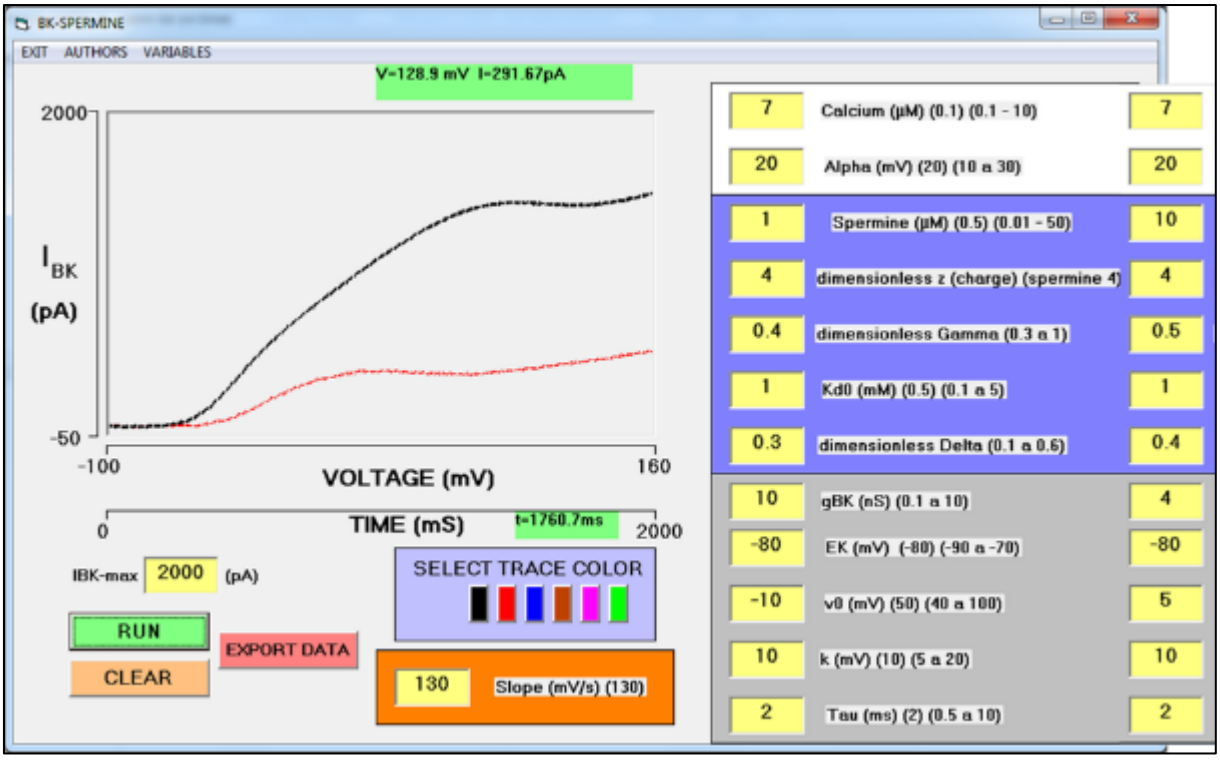


**Figure 6** Comparison of spermine block in two cells with different channel densities. High channel density: The conditions are shown in the variable row on the left. In the black trace, with a spermine concentration of 1 µM, the peak current was 1428 pA at 82.8 mV, with a slight block. Low channel density: Spermine concentration of 10 µM. The conditions are shown in the value row on the right. Block was observed from channel opening, producing a much lower peak current of 351 pA at 27.8 mV, in addition to a prolonged block with slight recovery

## 4. Conclusion

A mathematical model of BK channel block by spermine was implemented in a simulator. The model reproduces the macroscopic BK current generated by a ramp voltage stimulus and is based on a Hodgkin-Huxley-type model. The voltage- and calcium-dependent open probability proposed by Gupta and Manchanda [22], and used in the model of Reyes-Monreal et al. [13], was replaced by a voltage- and calcium-dependent Boltzmann function. The empirical adjustments of BK channel activation using this function support its use. However, the model does not reproduce experimental results corresponding to a specific cell type.

Applying the Boltzmann distribution in Equation 7 results in a sigmoidal relationship between block and voltage (Equations 5 and 6).

$$\Delta G(V) = \Delta G_0 - z\delta FV \qquad (7)$$

where ΔG is the change in Gibbs free energy, $\Delta G_0$ is the free energy at zero voltage, z is the effective valence of spermine, F is the Faraday constant, V is the voltage, and δ is the fraction of the electric field traversed by the molecule upon entering the pore.

The model is limited to reproducing the kinetics of the BK current in response to a ramp voltage stimulus. The BK current was dependent on voltage and calcium, as expected. The block was dependent on spermine concentration. Under the selected initial conditions, a partial block followed by current recovery was obtained. Careful selection of the variable values presented in the interface allows the approximation or reproduction of an experimental response.

The resulting simulator can be executed in Windows 10 and Windows 11 environments. It allows measurements to be performed with the pointer on the current traces and enables saving a run of four traces in a file for subsequent analysis. This tool may be useful for exploring the interaction between the BK channel and spermine.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Availability of data*

The simulator is available upon request by contacting the authors at arturoreyeslazalde@gmail.com. Permission to use the software is granted solely for academic, educational, and research purposes, provided that it is not used for any commercial or profit-making activities.

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