

Supplementary Material

Molecular biology of the W-Z model:

In the W-Z model, the authors derived the action potential of neurons in the cerebral cortex and its corresponding energy function using the Hamiltonian energy function and Lagrangian function. They also provided the curve of energy consumption during neuronal activity over time based on the exact solution of the energy function (Figure 1). It was found that the energy change of the action potential is inconsistent with the traditional neuroscience theory that action potentials consume energy.

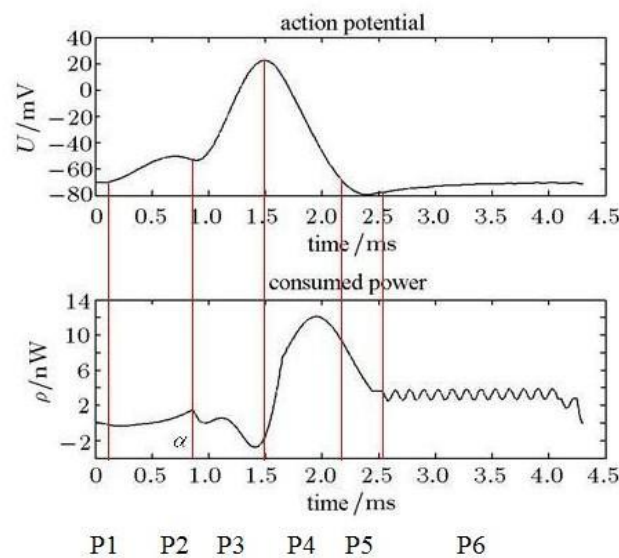


Figure 1. Segmental comparison of action potentials and changes in action potential energy of neurons

For the molecular biological interpretation of each segment in Figure 1, please refer to reference [1]. It can be observed that the change in the energy function corresponding to the neuronal action potential consists of two parts: one is oxyhemoglobin with a negative power component, and the other is deoxyhemoglobin, which is used for consuming oxygen and glucose. That is to say, during the rising phase of the action potential, neurons do not consume energy but absorb energy from the bloodstream. Here, we focus on the depolarization phase of the action potential in the W-Z model. During the depolarization phase, the action potential increases rapidly, while energy consumption does not increase correspondingly; instead, it decreases, and even energy with a negative power component appears (1.2ms ~ 1.5ms). We provide the following molecular biological explanation for this phenomenon [2]:

The phenomenon of reduced energy consumption and negative energy is mainly due to local hyperemia caused by neural activity. Vasodilation and increased blood flow

lead to an increase in arterial inflow, resulting in an increase in oxyhemoglobin flowing into the tissues [3], and neurons take up oxygen through oxyhemoglobin. However, at this time, the consumption of O_2 does not increase proportionally with the increase in blood flow and O_2 [4]. Fox et al. observed through PET that the oxygen extraction fraction (OEF) during event induction decreased from 40% at rest to 20%, which means that 80% of the delivered oxygen during the event is not metabolized physiologically. This indicates that the energy demand related to neural activation (compared with that required in the resting state) is small, and the hyperemic response of cerebral blood flow is affected by products of non-oxidative metabolism (such as lactic acid) [5]. Functional hyperemia has a direct effect on neuronal information processing. Due to the increase in blood flow and blood volume, local vascular pressure increases, causing dilation of local blood vessels. From the anatomical structure, neurons and glial cells are located near blood vessels, so the dilation of blood vessels will lead to the deformation of cell membranes. This mechanical signal can regulate mechanosensitive ion channels, thereby altering neural activity. In addition, blood flow plays a dominant role in the temperature of the brain. Local hyperemia can reduce brain temperature and mitigate the impact of heat generated by neural activity [6].

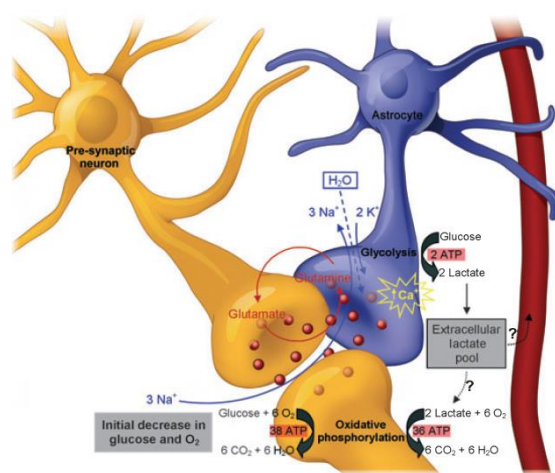


Figure 2. Cellular/molecular and hemodynamic changes induced by lactic acid products and calcium waves in astrocyte endfeet [3]

Due to the enhanced activity of Na^+ , K^+ , and Ca^{2+} channels, ATP consumption increases, which in turn stimulates ATP production. As shown in Figure 2-3, during the glycolysis of glucose in glial cells, 1 molecule of glucose generates 2 molecules of lactic acid and 2 ATP molecules, and this ATP is exactly used for the uptake and metabolism of glutamate. 1 molecule of glutamate, together with 3 Na^+ ions, is taken into astrocytes via a cotransporter, which then activates the Na^+/K^+ pump to restore the osmotic gradient. After entering astrocytes, glutamate is converted into substances such as glutamine and transported back to adjacent neurons. Moreover, the uptake of Na^+ is

a passive process, while the activation of the Na^+/K^+ pump and the conversion of glutamate into glutamine are both energy-consuming processes (each consuming 1 ATP) [7]. The lactic acid, a product of glycolysis, is transported out of the cell through lactate shuttle proteins on the cell membrane, then absorbed by neighboring neurons, and 36 ATP molecules are produced after oxidative metabolism [8]. It can be seen that although the increase in blood flow is mainly due to the increase in the concentration of lactic acid, a product of non-oxidative metabolism, most of the energy demand (98%) comes from the oxidative metabolic pathway [9]. Therefore, the phenomenon of negative energy is caused by cerebral hyperemia during neural activity. Cerebral hyperemia brings sufficient oxygen and glucose, but at this time, the oxygen uptake is only 20%, indicating that neurons only take up oxygen from a small part of oxyhemoglobin, which is converted into deoxyhemoglobin, and most of the remaining is still oxyhemoglobin. The mismatch between the increase in oxygen consumption and blood flow at this time leads to the phenomenon of negative energy in energy consumption. Subsequently, more and more Na^+ ions flow inward and K^+ ions flow outward, requiring more energy to reverse the ion flow direction. Therefore, the uptake of oxygen and glucose from the blood flow increases, more oxyhemoglobin is converted into deoxyhemoglobin, and the negative energy turns into positive energy.

Based on the above molecular biological explanation of the negative power component corresponding to the depolarization phase of the action potential, we further provide a brief qualitative description of the energy change process of neurons during the entire occurrence of the action potential according to molecular biological principles and existing experimental data.

During the action potential of neurons, neurons and glial cells regulate neurotransmitters, ion receptor channels, glucose, blood flow, and other mechanisms. It can be found that glial cells not only play an extremely important role in neural energy metabolism but also participate in neural information transmission.

Under resting conditions, the membrane potential is positive inside and negative outside. The concentration of K^+ inside the neuron is high, and the concentration of Na^+ outside the cell is high. Therefore, K^+ tends to flow outward and Na^+ tends to flow inward, increasing the potential outside the membrane. To maintain the resting potential, the Na^+ , K^+ -ATPase is activated, which needs to consume ATP to pump K^+ in and Na^+ out, thereby stimulating the oxidative phosphorylation of glucose to produce ATP. Eventually, a balanced state is achieved.

The generation of action potentials is due to the opening of Na^+ channels, which allows a large number of Na^+ ions to flow inward. To restore the ion concentration

gradient, a large amount of ATP is needed to reverse the ion flow direction. Therefore, the activity of Na^+ , K^+ -ATPase is enhanced, stimulating more glucose metabolism, resulting in a decrease in the glucose content in the blood flow in the region where the neuron is located, thereby inducing a hyperemic response. In addition, the influx of Ca^{2+} causes the release of NO, which also increases local cerebral blood flow.

During the propagation of action potentials (i.e., neural information transmission), neurons release neurotransmitters such as glutamate into the synaptic cleft. Glutamate, together with Na^+ ions, is taken up by postsynaptic neurons or glial cells and converted into glutamine within them, which is an energy-consuming process. Therefore, ATP is produced in glial cells through the glycolysis of glucose to support the sodium-potassium pump and glutamate metabolism, while lactic acid, the product of glycolysis, is released by them into the extracellular space, enters the blood, and then is absorbed by neurons as a substrate for oxidative phosphorylation.

(a) Energy consumption of neurons under different glucose supply conditions

Glucose, as the main energy source of the brain, its content level plays a crucial role in neural activities. In cases of low glucose/ischemia, the brain will suffer from insufficient energy supply, leading to a decline in brain function and even brain tissue damage. Therefore, it can be said that maintaining blood glucose homeostasis in the nervous system is a prerequisite for ensuring the normal and orderly progress of neural activities. Studying the activities of the nervous system using the method of neural energy is a novel research direction [10-15]. This paper attempts to study the neurodynamic problems from the molecular to the cellular level from the perspective of energy. The author referred to the FP model [16] and the pancreatic islet β -cell model proposed by scholars from Kyoto University [17, 18], and made some modifications based on experimental data [19-21] to obtain the glucose-sensing neuron model. This model was used to simulate the firing characteristics of neurons and the corresponding molecular mechanisms under different glucose supply conditions.

(b) Model and methods

This model is extended from the H-H type cell membrane model and incorporates more detailed cell membrane ion mechanisms (such as ion pumps, intracellular ion concentrations, Ca^{2+} dynamics of the endoplasmic reticulum, etc.), making it more consistent with real neurons. As shown in Figure 3, the glucose-sensing neuron model mainly includes three parts: the cell membrane, mitochondria, and endoplasmic reticulum. The cell membrane contains various ion channels such as Na^+ , K^+ , Ca^{2+} , and Cl^- , as well as ion pumps like the sodium-potassium pump; mitochondria are the main sites of glucose metabolism; the endoplasmic reticulum, as an intracellular calcium

store, not only participates in the regulation of Ca^{2+} homeostasis itself but also jointly regulates the activities of nerve cells through interactions with organelles such as mitochondria [22-24].

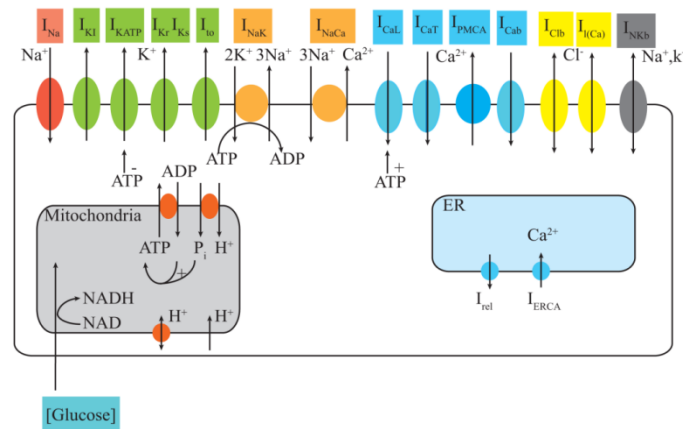


Figure 3. Schematic diagram of the glucose-sensing neuron model. It consists of three parts. (1) Ion currents on the membrane: I_{Na} , sodium current; I_{KI} , inward rectifier potassium current; I_{KATP} , ATP-sensitive potassium current; I_{Kr} , rapid delayed rectifier potassium current; I_{Ks} , slow delayed rectifier potassium current; I_{to} , transient inward current; I_{CaL} , L-type calcium current; I_{CaT} , T-type calcium current; I_{PMCA} , plasma membrane calcium pump current; I_{Cab} , background calcium current; I_{NaK} , sodium-potassium pump current; I_{NaCa} , $\text{Na}^+/\text{Ca}^{2+}$ ion exchange pump current; I_{NKb} , non-selective cation (mainly Na^+ and K^+) current; $I_{\text{l(Ca)}}$, calcium-activated cation current; I_{Clb} , background chloride current; (2) Mitochondria; (3) Ca^{2+} dynamics in the endoplasmic reticulum: I_{ERCA} , endoplasmic reticulum calcium pump current related to Ca^{2+} uptake; I_{rel} , Ca^{2+} release current.

(c) Mathematical description of the model

Figure 4 shows the equivalent circuit diagram of the cell membrane in the glucose-sensing neuron model. The mathematical description is given by the following equations:

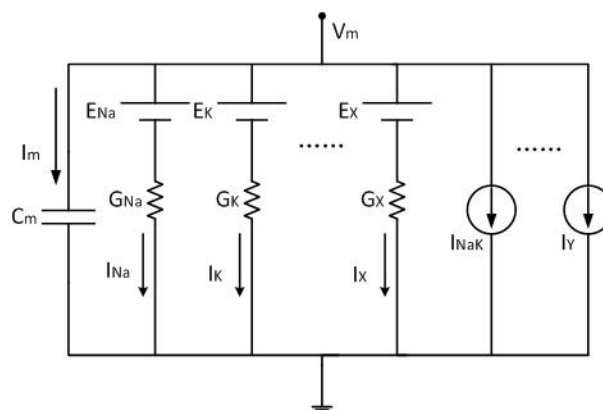


Figure 4. Equivalent circuit diagram of the cell membrane [17]. V_m is the membrane potential (mV); C_m is the membrane capacitance ($C_m = 1$ pF, the same below); E_x is the equilibrium potential of ion X; I_Y is the current flowing through transporter Y; I_m is the membrane current.

The membrane potential of a neuron is described by the following equation:

$$\frac{dV_m}{dt} = -\frac{I_m}{C_m} \quad (1)$$

where t is time, and the total current on the membrane is

$$I_m = I_{Na} + I_{Kl} + I_{Kr} + I_{Ks} + I_{to} + I_{CaL} + I_{CaT} + I_{NaK} + I_{NaCa} + I_{PMCA} + I_{NKb} + I_{KATP} + I_{Cab} + I_{Clb} + I_{l(Ca)} \quad (2)$$

For a certain ion X ($Na^+/K^+/Ca^{2+}/Cl^-$), the intracellular and extracellular ion concentrations are denoted as $[X]_i$ and $[X]_o$ respectively, and the ion valence is Z_x . Therefore, the relationship between intracellular and extracellular ion concentrations and membrane potential is described by the Goldman-Hodgkin-Katz equation as:

$$CF_x = \frac{z_x F V_m}{RT} \times \frac{\left([X]_i - [X]_o \times \exp\left(\frac{-z_x F V_m}{RT}\right) \right)}{\left(1 - \exp\left(\frac{-z_x F V_m}{RT}\right) \right)} \quad (3)$$

$$\frac{d[Na]}{dt} = -\frac{I_{net} Na}{F V_i} \quad (4)$$

$$\frac{d[K]}{dt} = -\frac{I_{net} K}{F V_i} \quad (5)$$

where V_i is the cell volume that allows ion diffusion (In cell biology, cell volume refers to the three-dimensional spatial size occupied by a single cell, with the cubic micrometer (μm^3) as its basic unit of measurement.); I_{netX} represents the sum of currents containing ion X, which are respectively:

$$I_{net} Na = I_{Na} Na + I_{Ks} Na + I_{to} Na + I_{CaL} Na + I_{l(Ca)} Na + I_{NKb} Na + 3I_{NaK} + 3I_{NaCa} \quad (6)$$

$$I_{net} K = I_{Kl} + I_{Kr} + I_{KATP} + I_{to} K + I_{Ks} K + I_{Na} K + I_{CaL} K + I_{l(Ca)} K + I_{NKb} K - 2I_{NaK} \quad (7)$$

E_x is the equilibrium potential of ion X is:

$$E_X = \frac{RT}{z_X F} \ln \frac{[X]_o}{[X]_i} \quad (8)$$

$$\text{Na Electrical conductivity } G_{Na} = (I_{net} Na - 3I_{NaK}) / (V_m - E_{Na}) \quad (9)$$

$$\text{K Electrical conductivity } G_K = (I_{net} K + 2I_{NaK}) / (V_m - E_K) \quad (10)$$

In this research, we assume that only aerobic metabolism occurs within neurons. Glucose is converted into pyruvate through glycolysis, and pyruvate is further oxidized to carbon dioxide and water, with the production of ATP accompanying this process. In this model, the glycolysis coefficient f_{glc} is expressed as:

$$f_{glc} = \frac{1}{1 + \frac{0.5}{[ATP]_i}} \frac{1}{1 + \left(\frac{13}{[Glucose]} \right)^{2.5}} \quad (21)$$

Among them, [ATP] represents the intracellular ATP concentration; [Glucose] represents the extracellular glucose concentration, which is the main variable to be controlled in the simulation below.

In this paper, we only list the main equations. For more details about this model, please refer to references [17,18].

(2) Results and discussion

First, the condition of constant blood glucose level over a period of time is assumed and simulated. Fig 1 shows the changes of several neuronal properties during the initial 0.3 seconds, respectively from 50s and 110s, and the corresponding glucose concentration, [Glucose], are 8mM/cm³ (Fig 5 left column) and 12mM/cm³ (Fig 5 right column). We can see from Fig 5A and Fig 5B, if the glucose level is higher, the firing rate of the neuron will be higher, but the maximum energy power for an AP will be lower. This result demonstrates that with increase in glucose supply, the energy consumption per AP decreases.

It's known that Na⁺ enters the neuron to produce APs and needs to be pumped out again by the Na⁺/K⁺-ATPase, consuming ATP. Na/K ion pump is believed to cost most energy on the membrane, so the Na⁺ influx largely determines the ATP cost or the energy consumption of the neuron. As shown in Fig 5C and Fig 5D, if the glucose level is higher, the maximum current and conductance of sodium will be relatively lower. Less Na⁺ influx implies that less energy is demanded to restore the sodium

concentration gradient for the neuron, leading to lower energy consumption for one AP, which is in good agreement with our previous result.

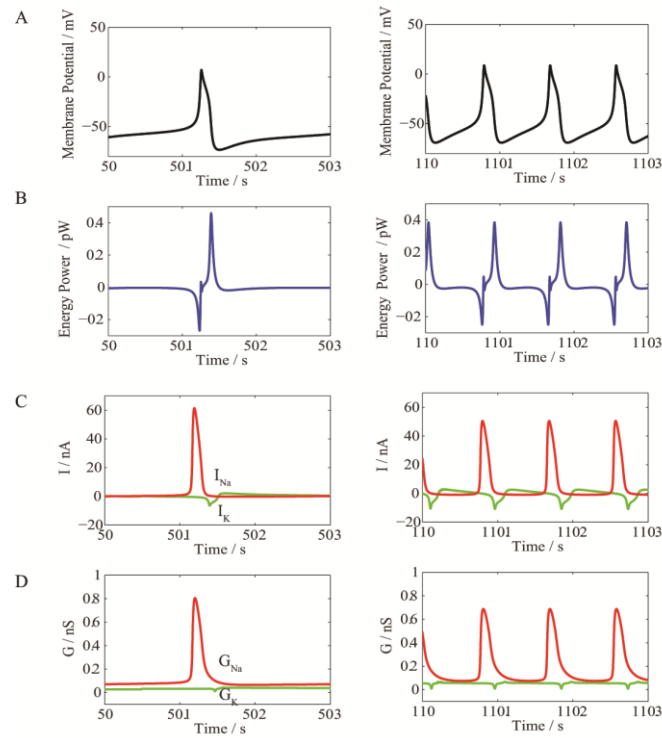


Fig 5. The changes in membrane potential(A), energy power(B), ionic currents(C) and ionic conductance(D).(Left)[Glucose]=8mM/cm³,(Right) [Glucose]=12mM/cm³. (Online version in colour.)

Then we simulated the condition of variable glucose level during neuronal activation. As seen in Fig 6, the membrane potential and extracellular glucose concentration are given, and the initial value of glucose concentration, [Glucose(0)], is set as constant (red dotted line)in each case.

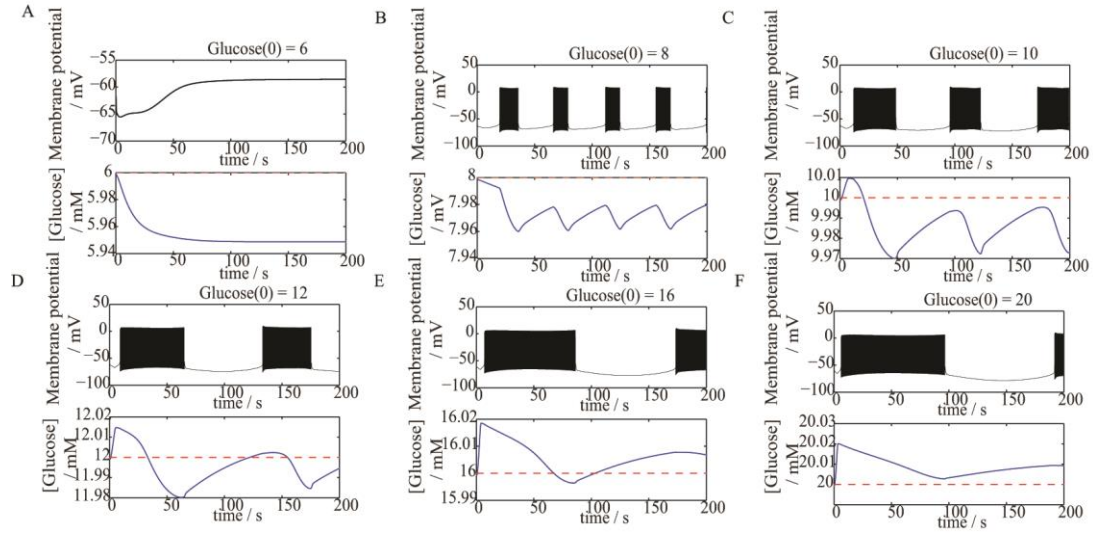


Fig 6. The changes in membrane potential (Up) and extracellular glucose concentration (Down). The initial value of glucose concentration is shown as a red dotted line in each case. (Online version in colour.)

Fig 6 shows that the concentration of extracellular glucose decreases with neuronal activation; and once the neuron returns to its resting state, the glucose level will return to its initial value to prepare for the next firing.

Notably, while the firing rate of the neuron is relatively high (Fig 6C, 6D, 6E and 6F), within a short period of time from the initiation, the concentration of extracellular glucose increases to a value larger than the initial value. It is considered as a simulation of local functional hyperemia evoked by neuronal activities because recent experiments [1,8,25] have demonstrated that neuronal activation requires large amounts of energy supply. And to meet this demand, more blood and glucose inflow will occur in the activated area.

This model can well simulate the release characteristics of glucose-sensing neurons and can also simulate the consumption of glucose by neurons under different initial value conditions. Based on this model, we analyzed the firing characteristics of neurons from the molecular to the cellular level from the perspective of energy, which laid the neural energy foundation for our research from the cellular to the network level.

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