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A model for thermal exchange in axons during action potential propagation

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Abstract Several experiments have shown that during propagation of the action potential in axons, thermal energy is locally exchanged. In this paper, we use a simple model based on statistical physics to show that an important part of this exchange comes from the physics of the effusion. We evaluate, during the action potential propagation, the variation of internal energy and of the energy associated with the chemical potential of the effusion of water and ions to extract the thermal energy exchanged. The temperature exchanged is then evaluated on the area where the action potential is active. Results give a good correspondence between experimental work and this model, showing that an important part of the thermal energy exchange comes from the statistical cooling power of the effusion.

Keywords Statistical physics · Thermal analysis · Neurons

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Introduction

Over the past two decades, experiments (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975) have shown that propagation of an action potential is associated with mechanical and thermal changes in axons. In fields such as water diffusion MRI (Bihan 2007), quantifying these thermal changes has become a central issue, as the autodiffusion constant of water is known to change with temperature (Bihan 2007). Furthermore, there is a strong debate about the role of water during action potential propagation (Bihan 2007) (also active in the community working with water diffusion MRI), as the exchange of water may play an important role in thermal exchange and mechanical modifications of the excitable cells. Finally, local temperature changes may have consequences for the energetic states of the membrane proteins, modifying the local geometry and the activation energies of these proteins.

Experiments (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975) that have been performed to measure changes in temperature have yielded results that range over an order of magnitude for the thermal change, from a few micro Kelvin to a few tens of micro Kelvin. Most experiments have used the pyroelectric effect to detect thermal changes using large area detectors (e.g. a few squared millimetres). These detectors can only give an average value of thermal changes because of their large surfaces. The extreme local values of thermal changes are therefore truncated, thus preventing measurements of subtle local temperature variation. Our modelling is focused on finding a formula to give this average value, while keeping in mind that temperature changes may be much more important locally.

Understanding the source of these thermal exchanges would allow for better prediction of the scale at which these exchanges occur, and would allow a better evaluation of the state of water near neurons. The state of water near neurons is a very important matter because it acts on both the stability of transmembrane proteins and on the local constraints of the membrane itself. Several models describe possible sources for this thermal exchange (Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975; Wei 1972; Margineanu and Schoffeniels 1977; Coleman 1952; Ritchie 1973). Most of them link it to either electrical activity or thermodynamical energy transfer via free enthalpy. An important issue is the magnitude of the thermal exchange. It may originate from several physical phenomena, such as calcium rebinding (Tasaki et al. 1989), dipole flip-flop heating (Margineanu and Schoffeniels 1977), electrical heating (Ritchie 1973), or conformational changes in membrane proteins (Coleman 1952). To date, no model has been either completely debunked or confirmed. The main challenge for current models is that most of the action potential energy should be transferred into thermal energy to predict a temperature variation with the appropriate order of magnitude, but this is not physically possible because the action potential will have no more energy to propagate.

Yet, there are possible sources of thermal energy that may come from the metabolism of the cells. Indeed, ATP activity, glycolysis and mitochondrial activity may also play a role in thermal exchanges. It is probable that these effects would be stronger in small cells and axons because of the proximity of all the elements, in squids axons for example dilution effects may strongly reduce the extent of thermal exchanges due to the metabolism. Furthermore, in biologic systems exchanging massive quantities of ions, the sudden unbalanced quantity of ions may also generate strong metabolic reactions, linked for example to mitochondrial activity and cytosqueletton dynamics (because of osmotic pressure), and so if the system has a small size to generate changes in the local temperature. We may notice that axons do not exchange many ions during action potential propagation. A very interesting approach of thermal activity linked to metabolism can be found in the paper of Ritchie (1973). More extensive experimental work would be needed to evaluate the different components of the thermal exchange between metabolism and the effusion cooling that is described in the following text.

In this alternative model, we show, theoretically, that a non-negligible part of the thermal exchange may arise from the statistical filtering induced by transfer of ions and water through the nanochannels (ion gates, Tritsch et al. 1998; Fain 1999; Purves 2004) in the membrane of the axons. During the action potential, the statistical filtering induced by sodium gates, potassium gates, and the gates used to transfer water creates a molecular migration (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975; Tritsch et al. 1998; Fain 1999; Purves 2004). The ion and water gates operate a statistical selection in the velocity distributions resulting in a thermal exchange due to an effusion-like process. This simple model, mainly based on physical modelling, will be constructed with many simplifications to obtain the correct order of magnitude of the thermal exchange; therefore, all the characteristics of the ion gates and of the action potential propagation will not be taken into account.

Physical parameters of axons during an action potential propagation

There is a first condition necessary to assure that local thermal exchange will not be immediately thermally diffused by water. This condition applies to the surface of the membrane involved in the action potential propagation. Let λ be the thermal conductivity of the liquid, ρ the density of the liquid, and C_p the specific heat capacity of the liquid. Furthermore, let S be the surface of the thermal exchange and the surface where the action potential is active. The characteristic time of thermal exchange is

$$\tau_{\text{therm}} = \frac{\rho C_p S}{\lambda}, \tag{1}$$

obtained from the heat equation $\Delta T = \frac{\lambda}{\rho C_p}\frac{\partial T}{\partial t}$.

It has been experimentally observed that the time of thermal exchange (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975) is approximately equal to the action potential propagation time (Tritsch et al. 1998; Fain 1999; Purves 2004) τ_{axon}, i.e. $\tau_{\text{therm}} \approx \tau_{\text{axon}}$. The order of magnitude of τ_{axon} is 3 ms. Thus

$$S \geq 3 \times 10^{-10}\,\text{m}^2. \tag{2}$$

For most excitable cells, especially neurons, this surface is inferior to the surface where the gates are active during the action potential propagation (Tritsch et al. 1998; Fain 1999; Purves 2004). Therefore, thermal energy will not be immediately dissipated.

Let us evaluate a very rough order of magnitude for the number of ions exchanged during the action potential by assuming that the number of ions exchanged is equal to the net charge flow. In doing so we neglect the fact that there is a complex interplay of ion flows. However, this gives an acceptable order of magnitude for the number of ions exchanged.

For most axons, the order of magnitude of the electric capacity of the membrane (Tritsch et al. 1998; Fain 1999; Purves 2004) is $C_m = 10^{-2}$ F m^{-2} (Tritsch et al. 1998;

Fain 1999; Purves 2004). The charge exchanged during a variation of potential ΔV is

$$\Delta Q = C_m S \Delta V \tag{3}$$

and then the number of exchanged ions may be approximated as:

$$N = \frac{\Delta Q}{e} = \frac{C_m S \Delta V}{e}, \tag{4}$$

with e the charge of the electron.

The maximum potential during an action potential propagation (Tritsch et al. 1998; Fain 1999; Purves 2004) typically reaches 70–100 mV. The order of magnitude of the maximum number of ions exchanged per unit of axon membrane surface is then

$$N_{\max}^{\text{ion}} = 4.4 \times 10^{15}\,\text{ion m}^{-2} - 6.3 \times 10^{15}\,\text{ion m}^{-2}. \tag{5}$$

Furthermore, the exchange of water molecules needs to be taken into account (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975; Tritsch et al. 1998; Fain 1999; Purves 2004; Masson et al. 2006), because the size change during action potential propagation seems to indicate that there is a flow of water linked to this propagation. Knowing the approximate number of water molecules required to solubilize an ion (Debye 1929), a lower estimate of the average number of water molecules exchanged can be estimated as four molecules of water for one ion. Here, we do not affirm that water flows through the Na^+ or K^+ ion gates; most models (Hille 2001) describe the translocation of the ions as occurring without its surrounding water, and we just evaluate a characteristic number of water molecules that might pass through based on solubilization properties and on experimental data (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975). Therefore, the total number of elements exchanged per unit of membrane surface may be approximated by

$$N_{\max} \approx 5 \times N_{\max}^{\text{ion}} \approx 2.2 \times 10^{16}\,\text{m}^{-2} - 3.1 \times 10^{16}\,\text{m}^{-2}. \tag{6}$$

Using the autodiffusion constant, D, of liquid water, one may approximate the mean distance (Landau and Lifchitz 1967) travelled by a water molecule during the characteristic time of an action potential propagation by (Bihan 2007)

$$L_{\text{H}_2\text{O}} \approx \sqrt{D\tau_{\text{axon}}} \approx 2 \times 10^{-6}\,\text{m}. \tag{7}$$

Cooling power of an effusion

An effusion is, by definition (Landau and Lifchitz 1967), a process where individual molecules flow through a hole without collisions. This occurs, also by definition (Landau and Lifchitz 1967), if the diameter of the hole is considerably smaller than the mean free path of the molecules. In our case, the mean free path of the molecules is 2 µm, and an estimate of the ion gate opening diameter ranges from a few Angstrom to 1 nm. In this section, we evaluate the cooling power of effusion in a liquid, i.e. the variation of energy per unit of time, which is equal (Landau and Lifchitz 1967) to $P_c = C_v \frac{\mathrm{d}T}{\mathrm{d}t}$ (with C_v as the heat capacity of the liquid). From the thermodynamic point of view, the state of the liquid is defined by $\mathrm{d}U = C_v \mathrm{d}T + \left(\frac{\partial E}{\partial N}\right)_{T,V} \mathrm{d}N$ (first law of thermodynamics), with $\mathrm{d}U$ as the variation of internal energy, $C_v\,\mathrm{d}T$ the heat exchanged, and $\left(\frac{\partial E}{\partial N}\right)_{T,V} \mathrm{d}N$ the product of the chemical potential with the variation of the number of particles. During an effusion-like process (Epstein 1924; Bichowski and Wilson 1929; Wang and Wang 2006), this relation remains true (Landau and Lifchitz 1967) and its variation over time is given by

$$\frac{\mathrm{d}U}{\mathrm{d}t} = C_v \frac{\mathrm{d}T}{\mathrm{d}t} + \left(\frac{\partial E}{\partial N}\right)_{T,V} \frac{\mathrm{d}N}{\mathrm{d}t}. \tag{8}$$

The first term of Eq. 8 is the variation of internal energy, the second is the cooling power of the effusion, and the last term is the variation of energy linked to the variation of the number of elements (ions or water) of the system.

Let us consider a small opening of surface A where an effusion takes place. The first and the last terms of the Eq. 8 are equal to the product of A with the energy current, and the molecule current (Epstein 1924; Bichowski and Wilson 1929; Wang and Wang 2006) (multiplied by the chemical potential), respectively. If the state of the liquid is approximated by the lowest order of interaction development [lowest order of the Viriel (or cluster) expansion, Landau and Lifchitz 1967], the molecule ensemble can be described by an unperturbed Maxwellian distribution $f(v)$ (Landau and Lifchitz 1967). This approximation means that the statistic of particle velocity remains near equilibrium, and is also equal to an unperturbed Maxwellian distribution. Interactions in the liquid are neglected and will only be considered in the rest of the model with the effusion effect limited to a distance close to $L_{\text{H}_2\text{O}}$ (Eq. 7). The total number of molecules passing through the hole (molecule current) is

$$= \frac{1}{n} \int_0^{\infty} v^3 f(v)\,\mathrm{d}v \int_0^{2\pi} \int_0^{\pi/2} \sin\theta_v \cos\theta_v \mathrm{d}\theta_v \mathrm{d}\phi_v \tag{9}$$

where $f(v) = n\left(\frac{kT}{2\pi m}\right)^{3/2} \exp\left(-\frac{mv^2}{2kT}\right)$ is the Maxwellian statistic that is integrated in the three-dimensional space of velocities (v_x, v_y, v_z), $v^2 \sin\theta_v \mathrm{d}v \mathrm{d}\theta_v \mathrm{d}\phi_v$ is the element of integration in the three-dimensional space of velocities in spherical coordinates, $v\cos\theta_v$ is the distance in the direction of the hole per unit of time traveled by a particle, n is the density of particle, and kT is the thermal energy. The energy current is derived from Eq. 9 by adding the energy, 1/2 mv_z^2, of the passing particles, and is equal to

$$\frac{\pi}{n}\int\limits_{v_x=0}^{\infty}\int\limits_{v_y=0}^{\infty}\int\limits_{|v_z|=0}^{\infty} v_x^3 v_y^3 \frac{1}{2} m v_z^5 f(v)\mathrm{d}v. \tag{10}$$

Equation 8 shows that the cooling power, $C_v\frac{\mathrm{d}T}{\mathrm{d}t}$, is the difference between the rate of the energy current $(\frac{\mathrm{d}U}{\mathrm{d}t})$ and the rate of the particle current (Epstein 1924; Bichowski and Wilson 1929; Wang and Wang 2006) $(\frac{\mathrm{d}N}{\mathrm{d}t})$, and its value, positive or negative, depends on the relative strength of the two rates. The fluid velocity statistics depend only on the thermal energy and on the mass of the molecules. In a liquid such as water, which is strongly influenced by hydrogen bonding, the total energy is composed of translational and vibrational energy components (Schuster et al. 1929), but only the translational part plays a role in the cooling process. The vibrational part is shared between other molecules, increasing the effective mass of the surrounding solvation shell which consists of four to five water molecules (Schuster et al. 1929). So, by combining the two currents and replacing the mass of the molecules (in Eqs. 9, 10) by the effective mass in the Maxwellian distribution, the cooling power in the lowest order of interaction development may be written as

$$P_c = nA\frac{(kT)^{3/2}}{\sqrt{2\pi m_{\mathrm{eff}}}} \tag{11}$$

with $m_{\mathrm{eff}} \approx 5\ m$ the effective mass, A the surface of the hole, and kT the thermal energy.

The model

In order to finish the model, we need to explain the main hypothesis of this model. Ion gates are complex proteins, and the passing of ions through them is a complex event involving changes of conformation, changes in the energy state of the proteins, modification of the membrane, etc.; in this model, these gates are reduced to simple holes in the membrane of nerve cells. We focused our interest on effusion as the source of an important part of the thermal changes, and from the model point of view, gates are just the method used by ions and water to pass through the membrane. The effect of the gates may be modelled by adding in the exponential terms of the Eqs. 9 and 10 a potential term $\frac{V(\vec{r})}{kT}$, that would model the interaction between the ions or the water with the ion gate, and also by integrating the spatial coordinates. Yet, we stated that the model is at the lowest order of Viriel (or cluster) so $\exp\frac{V(\vec{r})}{kT} \approx 1$. Therefore, the gates may be approximated as holes in the membrane from the effusion point of view. Finally, the complex effects of the gates is not completely ignored, but it is introduced by adding experimental terms to the final equation.

Having described the main physical interactions and the main orders of magnitudes of this system, we may now evaluate the magnitude of the thermal exchange. In this model, we consider the axon (see Fig. 1) to be a cylinder of radius R, and we define the length d as the distance along the axis over which the action potential is active. The volume and the surface of the axon are $V_{\mathrm{axon}} = \pi R^2 d$ and $S_{AP} = 2\pi Rd$, respectively, and the volume where the thermal exchange takes place during the action potential propagation is $V_{\mathrm{therm}} = 2\pi RdL_{\mathrm{H_2O}}$. The total surface of holes on the membrane, where the action potential is active, is $A = N_c S \times s_c$, with N_c the number of active gates per unit of membrane surface, and s_c the surface of an ion gate. An estimation of N_c can be found by taking the average value of a number of active gates during the action potential propagation from experimental data (Tritsch et al. 1998; Fain 1999; Purves 2004). Furthermore, the density, n, in Eq. 11, can be approximated as $\frac{N_{\max}\times S_{AP}}{V_{\mathrm{axon}}}$. In order to evaluate the temperature exchange, the cooling power must be multiplied by the duration of the molecule exchange, and divided by the heat capacity of the volume of liquid involved in the thermal exchange. This thermal capacity is equal to $C_v\rho V_{\mathrm{therm}}$. Therefore, the variation of temperature is equal to

$$\Delta T = A\frac{N_{\max}S_{PA}}{V_{\mathrm{axon}}}\frac{(kT)^{3/2}}{\sqrt{2\pi m_{\mathrm{eff}}}}\frac{\tau_{\mathrm{axon}}}{C_p\rho V_{\mathrm{therm}}}. \tag{12}$$

If we expand this formula, we obtain:

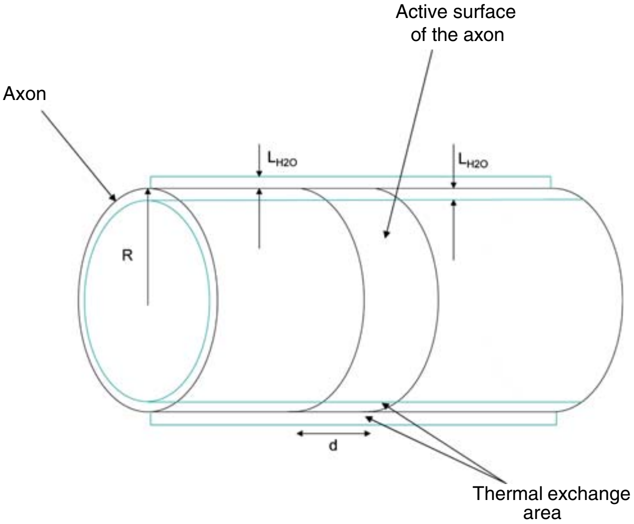

Fig. 1 Model of an axon. R is the radius of the axon, $L_{\mathrm{H_2O}}$ is the mean distance that a water molecule travels during the characteristic duration of an action potential propagation. The length d is defined as the distance along the axis over which the action potential is active

$$\Delta T = \frac{2N_{\max} N_c s_c (kT)^{3/2} \tau_{\text{axon}}}{R\sqrt{2\pi m_{\text{eff}}} C_p \rho L_{\text{H}_2\text{O}}} \qquad (13)$$

with the radius of the axon being the only explicit parameter.

Results and discussion

Using the expression of ΔT, we may evaluate the thermal variation of an axon of radius $R = 10$ μm with an action potential duration $\tau_{\text{axon}} = 3$ ms, knowing that:

- The total number of surface hole (ion gates) active during the full time of action potential propagation: $N_c \approx 50 \times 10^{12}$ m^{-2} (Tritsch et al. 1998; Fain 1999; Purves 2004)
- The surface $s_c \approx 10^{-18}$ m^2 (Tritsch et al. 1998; Fain 1999; Purves 2004)
- The thermal energy $kT = 4.29 \times 10^{-21}$ J (Landau and Lifchitz 1967)
- The effective mass $m_{\text{eff}} \approx 5\ m \approx 1.49 \times 10^{-25}$ kg (Debye 1929; Schuster et al. 1929)
- The specific heat capacity $C_p = 4{,}180$ J K kg^{-1} (Landau and Lifchitz 1967)
- The density of water $\rho = 1{,}000$ kg m^{-3} (Tritsch et al. 1998; Fain 1999; Purves 2004)

This leads to:

$$\Delta T \approx 22\ \mu\text{K}. \qquad (14)$$

The precision of the result based on experimental precision may be evaluated to 3–4 μK.

This result is close to the order of magnitude of the measured temperature variation of axons during action potential propagation. It must be noted that there is another parameter in this model, $N_{\max}$, the total number of molecules exchanged. Due to physiological reasons, some axons have a larger number of ions gates, or much more efficient ones, which allow them to exchange many more molecules and ions during one action potential. Giant axons (Tasaki et al. 1989; Bihan 2007; Tritsch et al. 1998; Fain 1999; Purves 2004) typically found in squids or in garfish olfactory nerves, have an $N_{\max}$ ten times larger than the value measured here, but their nerve radius lies between 50 and 400 μm, therefore leading to the same order of magnitude ΔT.

This simple model allows the evaluation of the temperature exchange during the axon activity τ_{axon}. At this point, the temperature will diffuse in all directions after the action potential has left the area. Furthermore, the source of thermal exchange is simply the consequence of the hot molecules being naturally filtered by the nanochannels. The evaluation of this thermal exchange gives an average of the true experimental value, because the model is based on a quasi-equilibrium approximation, and so does not model local extreme values that the temperature can take. Finally, this thermal exchange may play an important role in the state of the water surrounding the membrane of axons, thus modifying one of the autodiffusion constants of water (Bihan 2007).

Conclusion

In this paper, we showed that an important part of the thermal exchange in action potential propagation is the consequence of molecule filtering by effusion. The different gates in the membrane of the cells naturally filter molecules with high velocities, therefore changing velocity distributions on both sides of the membrane. The temperature difference, δT, found here, seems to be in good agreement with the experiments (Tasaki et al. 1989; Tasaki and Byrne 1990; Bihan 2007; Abbott et al. 1968; Howarth et al. 1968, 1975). Finally, the $\frac{1}{R}$ dependency of the δT expression may be tested experimentally, and may also help in evaluating the possible influence of metabolism on thermal exchange at different scales.

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