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Axonal Model for Temperature Stimulation

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Abstract

Recent studies indicate that a rapid increase in local temperature plays an important role in nerve stimulation by laser. To analyze the temperature effect, our study modified the classical HH axonal model by incorporating a membrane capacitance-temperature relationship. The modified model successfully simulated the generation and propagation of action potentials induced by a rapid increase in local temperature when the Curie temperature of membrane capacitance is below 40 °C, while the classical model failed to simulate the axonal excitation by temperature stimulation. The new model predicts that a rapid increase in local temperature produces a rapid increase in membrane capacitance, which causes an inward membrane current across the membrane capacitor strong enough to depolarize the membrane and generate an action potential. If the Curie temperature of membrane capacitance is 31 °C, a temperature increase of 6.6–11.2 °C within 0.1–2.6 ms is required for axonal excitation and the required increase is smaller for a faster increase. The model also predicts that: (1) the temperature increase could be smaller if the global axon temperature is higher; (2) axons of small diameter require a smaller temperature increase than axons of large diameter. Our study indicates that the axonal membrane capacitance-temperature relationship plays a critical role in inducing the transient membrane depolarization by a rapidly increasing temperature, while the effects of temperature on ion channel kinetics cannot induce depolarization. The axonal model developed in this study will be very useful for analyzing axonal response to local heating induced by pulsed infrared laser.

Keywords

axon; model; temperature; laser; stimulation

Introduction

Nerve stimulation by pulsed infrared laser has been studied extensively in recent years (Izzo et al., 2006; Wells et al., 2005a b, 2007b), because laser stimulation has many advantages over electrical stimulation including: 1. high spatial selectivity for stimulating different

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Conflict Interest

The authors declare that they have no conflict of interest.

nerve fibers; 2. no electrical artifacts to distort the recording of action potentials; 3. no direct contact with the nerve. Although the mechanism of action underlying laser stimulation is still not fully understood, local heating of the nerve by a laser pulse has been suggested to play a critical role (Wells et al., 2007a). A recent study of human embryonic kidney (HEK) cells (Shapiro et al., 2012) further shows that the transient increase in membrane temperature by a laser pulse can produce a rapid increase in membrane capacitance, causing a depolarizing membrane current. It is known that membrane capacitance is temperature dependent (Palti and Adelman, 1969) and a local increase in membrane capacitance can cause redistribution of electrical charges along the axon, thereby inducing a depolarizing membrane current (Wells et al., 2007a). Therefore, recent studies (Shapiro et al., 2012; Wells et al., 2007a) have indicated an important role of temperature in laser stimulation of nerve.

Axonal excitation by electrical stimulation is well understood and mathematically modeled (Hodgkin and Huxley, 1952; Rattay, 1989; Rattay and Aberham, 1993; Tai et al., 2005a, 2005b). However, the membrane capacitance in these axonal models does not change with temperature. In light of the potential mechanism of laser stimulation, an axonal model including a capacitance-temperature relationship is needed in order to mathematically analyze the role of the membrane capacitor in temperature stimulation. Therefore, in this study we modified the classical axonal model (Rattay and Aberham, 1993) by including a membrane capacitance that varies with temperature. The classical axonal model is based on the original Hodgkin-Huxley (HH) membrane model (Hodgkin and Huxley, 1952). The temperature stimulation was then analyzed and compared between the classical and the modified HH axonal models. In order to compare the temperature thresholds for axonal excitation between our model predictions and the animal experiments using laser stimulation (Wells et al., 2007a), we analyzed the influence of different model parameters including temperature rising time, length of heated axon, diameter of axon, global axon temperature, and the Curie temperature of membrane capacitance. The axonal model developed in this study should be useful for quantitatively analyzing and predicting the effects of laser stimulation once the spatial-temporal distribution of the laser heating effect is defined (Thompson et al., 2013).

Methods

A. The classical HH axonal model

The unmyelinated axon model (Fig. 1) consists of a 9-mm-long axon segmented into many small cylinders of length $\Delta x = 0.25$ mm, each of which is modeled by a resistance-capacitance circuitry. The ionic currents passing through the variable membrane resistance are described by HH equations (Hodgkin and Huxley, 1952). The change of the membrane potential V_n at the nth segment of the unmyelinated axon is described by:

$$c_m \frac{dV_n}{dt} = \frac{d}{4\rho_i}\left(\frac{V_{n-1}-2V_n+V_{n+1}}{\Delta x^2}+\frac{V_{e,n-1}-2V_{e,n}+V_{e,n+1}}{\Delta x^2}\right)-I_{i,n} \quad (1)$$

where $V_n = V_{a,n} - V_{e,n} - V_{rest}$; $V_{a,n}$ is the intracellular potential at the nth segment; $V_{e,n}$ is the extracellular potential at the nth segment; V_{rest} is the resting membrane potential (−70 mV);

d is the unmyelinated axon diameter; ρ_i is the resistivity of axoplasm (35.4 Ωcm); c_m is the capacitance of the membrane (1 $\mu F/cm^2$); $I_{i,n}$ is the ionic current at the nth segment described by HH equations as follows (Hodgkin and Huxley, 1952; Rattay, 1989; Rattay and Aberham, 1993; Tai et al., 2005a, 2005b):

$$I_{i,n}=g_{Na}m^3h\,(V_n-V_{Na})+g_K n^4\,(V_n-V_K)+g_L\,(V_n-V_L)$$

where g_{Na} (120 kΩ^{-1}cm^{-2}), g_K (36 kΩ^{-1}cm^{-2}) and g_L (0.3 kΩ^{-1}cm^{-2}) are the maximum conductances for sodium, potassium and leakage currents respectively. V_{Na} (115 mV), V_K (−12 mV) and V_L (10.589 mV) are reduced equilibrium membrane potentials for sodium, potassium and leakage ions after subtracting the resting membrane potential V_{rest} (−70 mV). m, h, and n are dimensionless variables, whose values always change between 0 and 1. m and h represent activation and inactivation of sodium channels, whereas n represents activation of potassium channels. The evolution equations for m, h, n are the following:

$$\begin{gathered} dm/dt=\alpha_m(1-m)-\beta_m m \\ dh/dt=\alpha_h(1-h)-\beta_h h \\ dn/dt=\alpha_n(1-n)-\beta_n n \end{gathered}$$

and

$$\begin{gathered} \alpha_m=\Phi\cdot\frac{2.5-0.1V_n}{\exp(2.5-0.1V_n)-1} \\ \beta_m=\Phi\cdot 4\exp\left(-\frac{V_n}{18}\right) \\ \alpha_h=\Phi\cdot 0.07\exp\left(-\frac{V_n}{20}\right) \\ \beta_h=\Phi\cdot\frac{1}{\exp(3-0.1V_n)+1} \\ \alpha_n=\Phi\cdot\frac{0.1(1-0.1V_n)}{\exp(1-0.1V_n)-1} \\ \beta_n=\Phi\cdot 0.125\exp\left(-\frac{V_n}{80}\right) \\ \Phi=3^{(T-6.3)/10} \end{gathered}$$

where T is temperature (°C). The initial values for m, h and n (when V_n = 0 mV) are 0.053, 0.596 and 0.318 respectively.

We assume that the unmyelinated axon is in an infinite homogeneous medium (resistivity ρ_e = 300Ωcm). After neglecting the small influence of the axon in the homogeneous medium, the extracellular potential $V_{e,n}$ at the nth segment along the axon can be described by:

$$V_{e,n}=\frac{\rho_e}{4\pi}\left[\frac{I(t)}{\sqrt{(n\Delta x-x_0)^2+z_0^2}}\right] \quad (2)$$

where $I(t)$ is an electrical current pulse delivered to a monopolar electrode (with the indifferent electrode at infinity) that is placed at a location (x_0, z_0) along the unmyelinated axon.

B. The modified HH axonal model for temperature stimulation

A previous study (Palti and Adelman, 1969) using the giant axons of squid (Loligo pealei) experimentally measured the relationship between axonal membrane capacitance (c_m) and the temperature (T). By assuming that the temperature-dependency of membrane capacitance obeys the ferroelectric Curie-Weiss law (Leuchtag, 1995), the experimentally measured capacitance-temperature relationship can be fitted very well by following equation:

$$c_m = c_0 + \frac{k}{T_c - T} \quad (3)$$

where k is a constant (2.2 $\mu F/cm^2 \cdot °C$); c_0 is a constant membrane capacitance (1.182 $\mu F/cm^2$); T_c is the Curie temperature of membrane capacitance (49.8 °C). Since the Curie temperature is a transition point from ferroelectric phase to paraelectric phase and the global heat block temperature can cause an axon to transit from an excitable state to an un-excitable state, it is assumed that the Curie temperature of membrane capacitance is identical to the global heat block temperature of an axon (Leuchtag, 1995). Therefore, the global heat block temperature for giant axons of Loligo pealei was predicted to be 49.8 °C.

Since the global heat block temperature could be different for different species of squid, i.e. 35–40 °C for Loligo forbesi (Hodgkin and Katz, 1949) but 49.8 °C for Loligo pealei (Leuchtag, 1995; Palti and Adelman, 1969), it is possible that the Curie temperature of membrane capacitance could also be different for different species of squid. The classical HH axonal model based on data obtained from Loligo forbesi (Hodgkin and Huxley, 1952) predicted a slightly lower global heat block temperature of 31 °C. In the HH model membrane capacitance is constant and heat block is caused by the accelerated kinetics of sodium and potassium channels (Rattay and Aberham, 1993). Because the Curie temperatures of membrane capacitance for different species of squid are not available, in this study we analyzed the effect of a range (31–50 °C) of Curie temperatures on temperature excitation of the axon.

In the classical HH axonal model (Rattay and Aberham, 1993), the membrane capacitance (c_m) is 1 $\mu F/cm^2$ at a temperature of 18.5 °C. If the Curie temperature of membrane capacitance (T_c) is 31 °C, we can calculate the constant membrane capacitance c_0 from equation (3) to be 0.824 $\mu F/cm^2$. Therefore equation (3) becomes:

$$c_m = 0.824 + \frac{2.2}{31 - T} \quad (4)$$

We also re-calculated the equation (4) with T_c at 35, 40, 45, or 50 °C and performed simulation studies to determine the effect of different Curie temperatures of membrane capacitance on temperature excitation of the axon.

The spatial-temporal distribution of the temperature along the axon induced by a laser pulse is approximately described by a Gaussian distribution of an exponential decay with time (Wells et al., 2007a):

$$T=T_0+\Delta T e^{-\frac{(x-x_1)^2}{2w^2}}\frac{t}{t_r}, \quad t \le t_r \tag{5}$$

$$T=T_0+\Delta T e^{-\frac{(x-x_1)^2}{2w^2}} e^{-\frac{t-t_r}{T_d}}, \quad t>t_r \tag{6}$$

where T_0 is the global axon temperature; ΔT is the maximal temperature increase at the location x_1 along the axon; t_r is the rise time of the temperature; T_d (100 ms) is the time constant for temperature decay with time (Wells et al., 2007a); 4w is defined as the length of the heated axon.

The axonal membrane capacitance c_m is now a variable of time because the axon temperature changes with time. Therefore, the membrane capacitor current I_c is now described by:

$$I_c=\frac{d[c_m \times (V_n+V_r)]}{dt} \tag{7}$$

$$I_c=c_m\left(\frac{dV_n}{dt}\right)+(V_n+V_r)\left(\frac{dc_m}{dt}\right) \tag{8}$$

Hence, the equation (1) can be modified as:

$$c_m\frac{dV_n}{dt}+(V_n+V_r)\frac{dc_m}{dt}=\frac{d}{4\rho_i}\left(\frac{V_{n-1}-2V_n+V_{n+1}}{\Delta x^2}+\frac{V_{e,n-1}-2V_{e,n}+V_{e,n+1}}{\Delta x^2}\right)-I_{i,n} \tag{9}$$

Since there is no electrical stimulation (i.e., $I(t)=0$), the extracellular potential $V_{e,n}$=0 based on equation (2). Therefore, we can further simplify equation (9) as:

$$c_m\frac{dV_n}{dt}+(V_n+V_r)\frac{dc_m}{dt}=\frac{d}{4\rho_i}\left(\frac{V_{n-1}-2V_n+V_{n+1}}{\Delta x^2}\right)-I_{i,n} \tag{10}$$

To simulate axonal excitation by a rapid increase in local temperature, the center of heating is placed in the middle of the 9-mm-long axon (see Fig. 1), i.e. at the location where x_1 = 4.5 mm in equations (5) and (6). The model equations were solved by the Runge-Kutta method (Boyce and Diprima, 1997) with a time step of 1 μsec. The simulation software was written

by the authors using Matlab computer language (MathWorks, Natick, MA), which is available at https://senselab.med.yale.edu/ModelDB/showModel.cshtml?model=189155. The simulation was always started at initial condition $V_n = 0$. The intracellular potentials at the two end segments of the modeled axon were always equal to the intracellular potentials of their closest neighbors, which implemented sealed boundary conditions (no longitudinal currents) at the two ends of the modeled axon.

Results

A. The classical HH axonal model

The rapid increase in local temperature as described by equations (5) and (6) was first applied to the classical HH axonal model [see equation (1)] in order to simulate axonal excitation by temperature stimulation. The increase in local temperature followed a Gaussian distribution along the axon (see Fig. 1). The classical HH axonal model failed to generate any action potential when the local temperature increased quickly (within 1–5 ms) by as much as 47 °C from a global axon temperature of 18.5 °C. The model became unstable when the temperature increase was greater than 47 °C. The high temperature (65.5 °C = 18.5+47 °C) is un-physiological, indicating the inability for classical HH axonal model to simulate temperature stimulation.

B. The modified HH axonal model

When the Curie temperature of membrane capacitance is 31 °C [see equation (4)], the modified HH axonal model [see equation (10)] successfully simulated the generation and propagation of an action potential induced by local temperature stimulation (Fig. 2). In the middle of the axon (4.5 mm location), a rapid (within 1 ms) increase in local temperature by 8 °C from a global axon temperature of 18.5 °C generated an action potential propagating in both directions (see Fig. 2). The temperature stimulation and axonal responses at the 4.5 mm location as shown in Fig. 2 were plotted in Fig. 3 for more detail illustration. The local temperature increase from 18.5 to 26.5 °C within 1 ms (Fig. 3A) caused the membrane capacitance to increase from 1 to 1.313 μF/cm^2 (Fig. 3B), which resulted in a peak inward current about 50 μA/cm^2 across the membrane capacitor (Fig. 3C) and produced a membrane depolarization strong enough to generate an action potential (see the 8 °C plot in Fig. 3D) that can propagate along the axon (see Fig. 2). A temperature increase less than 8 °C (see the 7.9 °C plot in Fig. 3D) failed to generate a propagating action potential, indicating that a minimal increase in local temperature (i.e. a threshold temperature) is required to excite the axon.

The threshold temperature increases linearly with the rise time (t_r) of the local temperature (Fig. 4A), while the rate of threshold temperature increase is inversely proportional to the rise time (Fig. 4B). The higher temperature required by a longer rise time also resulted in a larger increase in membrane capacitance (Fig. 4C).

Global axon temperature can also influence the threshold temperature. A higher global axon temperature requires a smaller increase in local temperature (Fig. 5A) to excite the axon. However, the total threshold temperature is still higher for a higher global temperature (Fig.

5B), which also results in a larger increase in membrane capacitance (Fig. 5C). For the same global axon temperature (18.5 °C), a small diameter axon requires a smaller temperature increase than large diameter axon for excitation (Fig. 6A), thereby a lower threshold temperature (Fig. 6.B) and a smaller increase in membrane capacitance (Fig. 6C).

The Curie temperature of membrane capacitance is critical for temperature stimulation of the axon. When the Curie temperature of membrane capacitance changes from 31 °C to 50 °C, the action potential generated by a rapid increase in local temperature can only be observed at Curie temperature of membrane capacitance below 40 °C (Fig. 7). A higher Curie temperature of membrane capacitance requires a higher temperature increase to generate an action potential. For a longer length of heated axon (2 mm), the temperature must increase quickly within a shorter time period (t_r = 0.5 ms) in order to generate an action potential when the Curie temperature of membrane capacitance is 40 °C.

The decay time of temperature (T_d) does not influence the temperature threshold for axon excitation (Fig. 8A). Reducing the length of the small axon segment from 0.25 mm to 0.1 mm only produces a negligible change of the temperature threshold (Fig. 8B).

Discussion

This study modified the classical HH axonal model by incorporating a relationship between membrane capacitance and temperature. This modified HH axonal model successfully simulated axonal depolarization and excitation induced by a rapid increase in local temperature, while the classical HH model failed to simulate this excitation. This result indicates that the capacitance-temperature relationship is critical for temperature stimulation of the nerve. It also provides theoretical evidence to support the hypothesis that pulsed infrared laser excites the nerve by a focused heating that rapidly increases local temperature of the nerve and producing membrane depolarization. The axonal model developed in this study will be useful for quantitatively analyzing the axonal response to laser stimulation with a defined spatial-temporal distribution of the laser heating effect (Thompson et al., 2013). The failure of the classical HH axonal model to simulate the generation of action potentials by temperature stimulation also indicates that the temperature effects on ion channel kinetics may influence the threshold for triggering action potentials as well as the frequency and pattern of firing (Shapiro et al., 2013), but are not responsible for the initial membrane depolarization that is essential for axonal excitation induced by temperature stimulation.

The modified HH axonal model reveals a possible mechanism for temperature stimulation of nerve. A rapid increase in local temperature can cause a rapid increase in local membrane capacitance, which can induce an inward capacitative current that depolarizes the axon membrane (see Fig. 3). The same mechanism has also been shown in HEK cells during infrared laser stimulation (Shapiro et al., 2012). A previous study using squid axon (Leuchtag, 1995; Palti and Adelman, 1969) also showed that an increase in axonal temperature can increase membrane capacitance from about 1 μF/cm^2 to 3 μF/cm^2. Therefore, in this study the membrane capacitance was limited to an increase less than 2 μF/cm^2 (see Fig. 4C). Within this capacitance range, the local temperature increase required

to excite the axon was 6.6–11.2 °C for a rapid temperature increase within 0.1–2.6 ms (Fig. 4A). A study using rat sciatic nerve showed that a 6–10 °C increase in temperature was required to elicit action potentials during laser stimulation with pulse durations of 0.005–5 ms (Wells et al., 2007a). Furthermore, our simulation results indicate that a smaller increase in local temperature can excite the axon if the temperature increase is faster (Fig. 4A–B), while previous studies in gerbil cochlea showed that a shorter duration laser pulse required less radiant exposure of laser energy to excite the auditory neurons (Izzo et al., 2007, 2008). The requirement for a rapid increase in local temperature for axonal excitation fits very well with laser stimulation because laser can rapidly increase the local temperature of a nerve within milliseconds.

Our results also predicted that higher global axon temperature will require a smaller increase in local temperature to excite the nerve (Fig. 5A). A previous study using rat sciatic nerve showed that laser stimulation at a frequency >5 Hz could gradually build up local temperature due to a slow dissipation of heat (Wells et al., 2007a). Therefore, our simulation result indicates that during high frequency laser stimulation, the laser pulse energy might be reduced after initial stimulation while still achieving the same stimulation effect. Although the increase in local temperature is smaller for a higher global axon temperature, the maximal local temperature required to excite the axon is higher for a higher global axon temperature (Fig. 5B). Since a local temperature build-up is inevitable with high frequency laser stimulation, reducing the laser pulse energy after the initial stimulation becomes critical to achieve prolonged high frequency stimulation. Otherwise, the excess heat could increase the local temperature to levels sufficient to cause heat block of action potential generation or nerve tissue damage.

The other prediction from this study is that a smaller increase in local temperature is required to excite axons of small diameter than axons of large diameter (Fig. 6A). This result indicates that laser stimulation might induce painful sensation when it is used to stimulate afferent nerves, because the small nociceptive afferent nerve fibers will always be excited before excitation of the large non-nociceptive afferent nerve fibers. However, this prediction would only be true when the small and the large nerve fibers are located in close proximity. This predication also indicates that laser stimulation might be able to produce a physiological recruitment of muscle fibers when stimulating the motor axons, i.e. activation of small motor axons first before activating large motor axons. Electrical stimulation does not have this advantage and always activates large motor axons first, producing an un-physiological recruitment of muscle fibers leading to quick muscle fatigue (Bickel et al., 2011).

The relationship between axonal membrane capacitance and temperature, i.e. equation (3), was derived based on ferroelectric Curie-Weiss law by fitting experimental data obtained from axons of Loligo pealei (Leuchtag, 1995; Palti and Adelman, 1969). It reveals that the Curie temperature of membrane capacitance for axons of Loligo pealei is 49.8 °C (Leuchtag, 1995). By assuming that the Curie temperature of membrane capacitance is identical to the global heat block temperature (Leuchtag, 1995), it is predicated that heat block of axons of Loligo pealei occurs at 49.8 °C. In this study we employed the equation (3) and tested a range of Curie temperatures (T_C = 31–50 °C) because different species of squid have

different global heat block temperatures and therefore may have different Curie temperatures of membrane capacitance. The axons of Loligo forbesi have a global heat block temperature between 35 and 40 °C (Hodgkin and Katz, 1949), but the classical HH axonal model (Rattay and Aberham, 1993) based on the data obtained from axons of Loligo forbesi predicts a global heat block temperature of 31 °C. Our simulation shows that temperature excitation of axons can only occur when Curie temperature of membrane capacitance is below 40 °C (Fig. 7), which is probably due to the fact that the ion channel kinetics in our model is derived from axons of Loligo forbesi (Hodgkin and Huxley, 1952). In order to successfully simulate temperature stimulation at 50 °C, ion channel kinetics derived from axons of Loligo pealei might have to be used in the model. However, currently the ion channel kinetic data are not available for axons of Loligo pealei. In addition, at the Curie temperature of 31 °C our model predicts that a 6.6–11.2 °C temperature increase is required for axonal excitation (Fig. 4A and Fig. 7), which agrees very well with the 6–10 °C increase required by laser stimulation of rat sciatic nerve (Wells et al., 2007a). This agreement indicates that the Curie temperature or global heat block temperature of 31 °C that is predicted by the HH model is also the best fit for the model to simulate the temperature stimulation. It is unfortunate that there is no animal data available describing the relationship between axonal membrane capacitance and the temperature for axons of Loligo forbesi. Therefore, the experimentally measured Curie temperature is not available for axonal membrane capacitance of Loligo forbesi. Additional experiments using Loligo forbesi to measure the axon membrane capacitance at different temperatures are warranted in light of our results and recent studies of laser stimulation of axons (Izzo et al., 2006; Shapiro et al., 2012; Wells et al., 2005a b, 2007b).

Although the modified HH axonal model could be further improved by optimizing the capacitance-temperature relationship, it has successfully simulated the axonal excitation by a rapid increase in local temperature and the temperature increase agrees well with animal studies (Wells et al., 2007a). Meanwhile, the predictions by this model will certainly need to be confirmed by future animal studies. The model developed in this study will be useful in analysis of axonal responses to laser stimulation because the spatial-temporal distribution of the heat generated by laser stimulation can be determined quantitatively (Thompson et al., 2013). The model analysis can help to optimize the parameters of laser stimulation, save laser energy, and avoid potential nerve tissue damage by excess heat. This new model will also be useful for analyzing the effects of local temperature change on axonal conduction or blockade.

Acknowledgments

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References

Bickel CS, Gregory CM, Jean JC. Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal. Eur J Appl Physiol. 2011; 111:2399–2407. [PubMed: 21870119]

Boyce, WE.; Diprima, RC. Elementary differential equations and boundary value problems. 6. John Wiley & Sons Inc; 1997. p. 436-457.

Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol (Lond). 1952; 117:500–544. [PubMed: 12991237]

Hodgkin, Al; Katz, B. The effect of temperature on the electrical activity of the giant axon of the squid. J Physiol. 1949; 109:240–249. [PubMed: 15394322]

Izzo AD, Richter CP, Jansen ED, Walsh JT Jr. Laser stimulation of the auditory nerve. Lasers Surg Med. 2006; 38:745–753. [PubMed: 16871623]

Izzo AD, Walsh JT Jr, Jansen ED, Bendett M, Webb J, Ralph H, Richter CP. Optical parameter variability in laser nerve stimulation: a study of pulse duration, repetition rate, and wavelength. IEEE Trans Biomed Eng. 2007; 54:1108–1114. [PubMed: 17554829]

Izzo AD, Walsh JT Jr, Ralph H, Webb J, Bendett M, Wells J, Richter CP. Laser stimulation of auditory neurons: effect of shorter pulse duration and penetration depth. Biophys J. 2008; 94:3159–3166. [PubMed: 18192375]

Leuchtag HR. Fit of the dielectric anomaly of squid axon membrane near heat-block temperature to the ferroelectric Curie-Weiss law. Biophys Chem. 1995; 53:197–205. [PubMed: 17020847]

Palti Y, Adelman WJ Jr. Measurement of axonal membrane conductances and capacity by means of a varying potential control voltage clamp. J Membr Biol. 1969; 1:431–458. [PubMed: 24174059]

Rattay F. Analysis of models for extracellular fiber stimulation. IEEE Trans Biomed Eng. 1989; 36:676–682. [PubMed: 2744791]

Rattay F, Aberham M. Modeling axon membranes for functional electrical stimulation. IEEE Trans Biomed Eng. 1993; 40:1201–1209. [PubMed: 8125496]

Shapiro MG, Homma K, Villarreal S, Richter CP, Bezanilla F. Infrared light excites cells by changing their electrical capacitance. Nat Commun. 2012; 3:736. [PubMed: 22415827]

Shapiro MG, Priest MF, Siegel PH, Bezanilla F. Thermal mechanisms of millimeter wave stimulation of excitable cells. Biophys J. 2013; 104:2622–2628. [PubMed: 23790370]

Tai C, de Groat WC, Roppolo JR. Simulation analysis of conduction block in unmyelinated axons induced by high-frequency biphasic electrical currents. IEEE Trans Biomed Eng. 2005a; 52:1323–1332. [PubMed: 16041996]

Tai C, de Groat WC, Roppolo JR. Simulation of nerve block by high-frequency sinusoidal electrical current based on the Hodgkin-Huxley model. IEEE Trans Neural Syst Rehab Eng. 2005b; 13:415–422.

Thompson AC, Wade SA, Cadusch PJ, Brown WG, Stoddart PR. Modeling of the temporal effects of heating during infrared neural stimulation. J Biomed Opt. 2013; 18:035004. [PubMed: 23471490]

Wells J, Kao C, Jansen ED, Konrad P, Mahadevan-Jansen A. Application of infrared light for in vivo neural stimulation. J Biomed Opt. 2005a; 10:064003. [PubMed: 16409069]

Wells J, Kao C, Konrad P, Milner T, Kim TJ, Mahadevan-Jansen A, Jansen ED. Biophysical mechanisms of transient optical stimulation of peripheral nerve. Biophys J. 2007a; 93:2567–2580. [PubMed: 17526565]

Wells J, Kao C, Mariappan K, Albea J, Jansen ED, Konrad P, Mahadevan-Jansen A. Optical stimulation of neural tissue in vivo. Opt Lett. 2005b; 30:504–506. [PubMed: 15789717]

Wells J, Konrad P, Kao C, Jansen ED, Mahadevan-Jasen A. Pulsed laser versus electrical energy for peripheral nerve stimulation. J Neurosci Methods. 2007b; 163:326–337. [PubMed: 17537515]

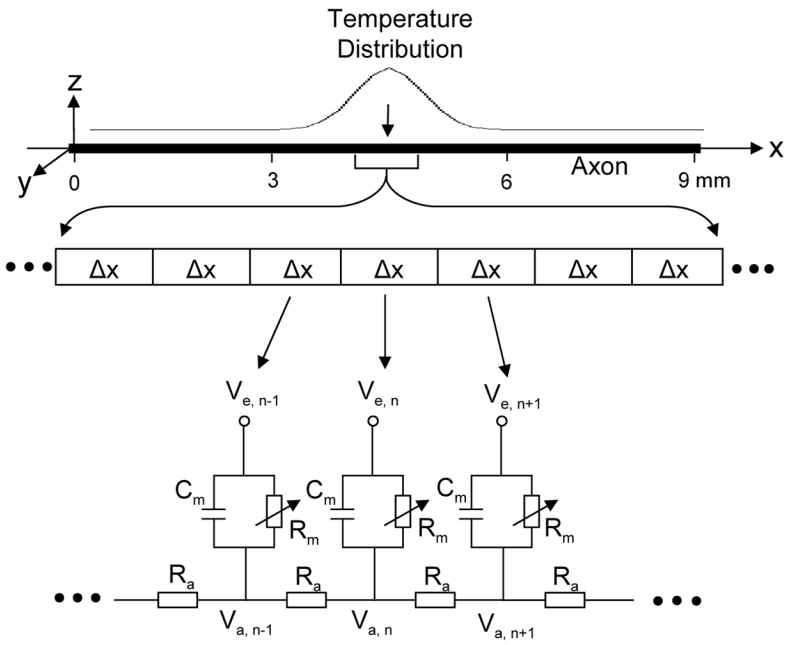

Fig. 1.

Unmyelinated axon model to simulate action potential generation by temperature stimulation. A: The unmyelinated axon is segmented into many small cylinders of length Δx, each of which is modeled by a resistance-capacitance circuit based on the Hodgkin Huxley model. R_a: Axoplasm resistance. R_m: Membrane resistance. C_m: Membrane capacitance. V_a: Intracellular potential. V_e: Extracellular potential.

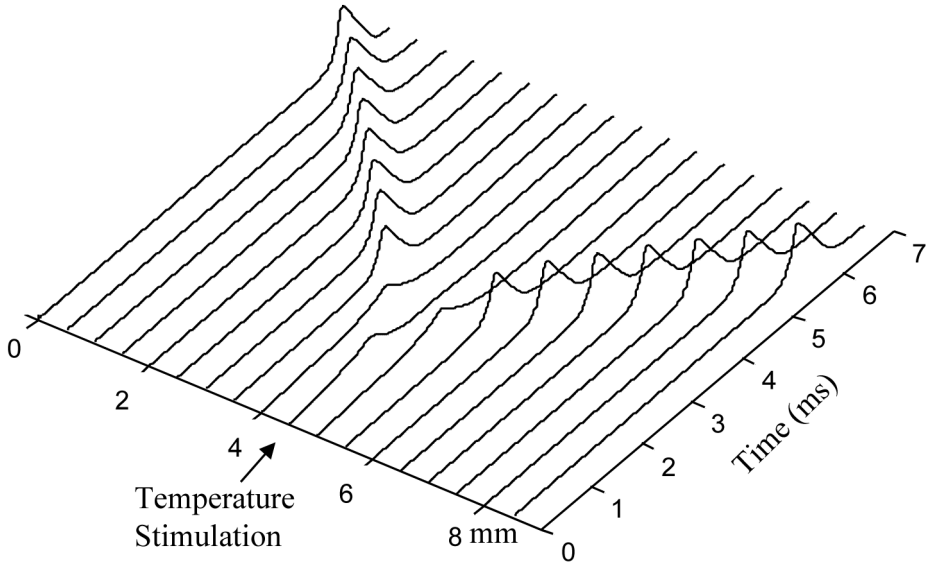

Fig. 2.

Action potential is induced by a rapid increase in local temperature at the 4.5 mm location along the axon and propagates in both directions. The local temperature rapidly increased by 8 °C from 18.5 °C within 1 ms. The length of heated axon is 2 mm with a Gaussian distribution of the temperature centered at 4.5 mm. Axon diameter: 2 μm.

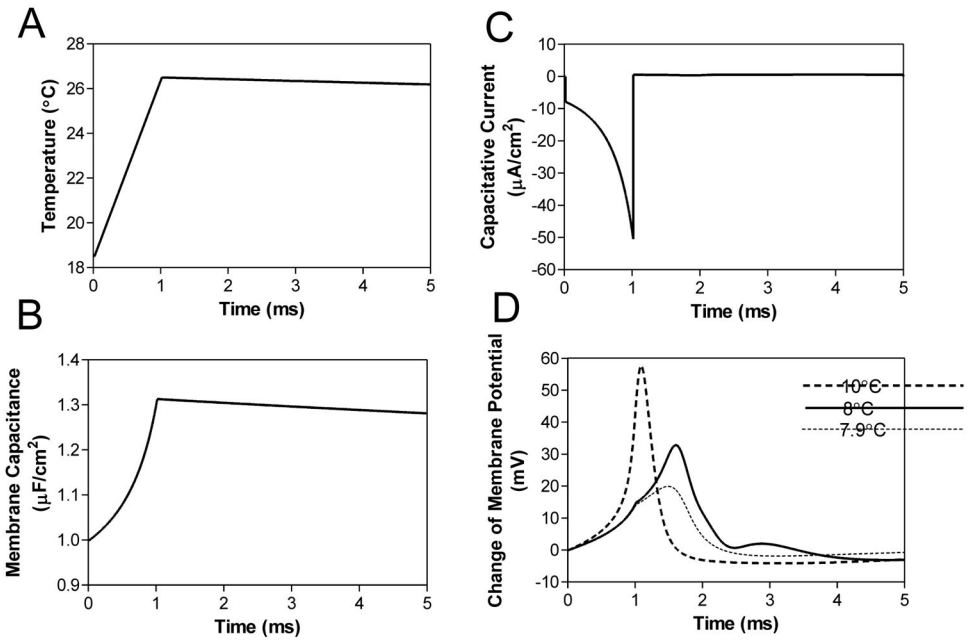

Fig. 3.

A rapid increase in local temperature (A) caused an increase in membrane capacitance (B) that generated inward current across the membrane capacitor (C) and produced membrane depolarization and a propagating action potential (D). The solid lines in A–D were taken from Fig. 2 at the center of temperature stimulation (4.5 mm location). Legends in D indicate that an 8 °C increase from 18.5 °C within 1 ms was the threshold temperature for generating a propagating action potential. Axon diameter: 2 μm.

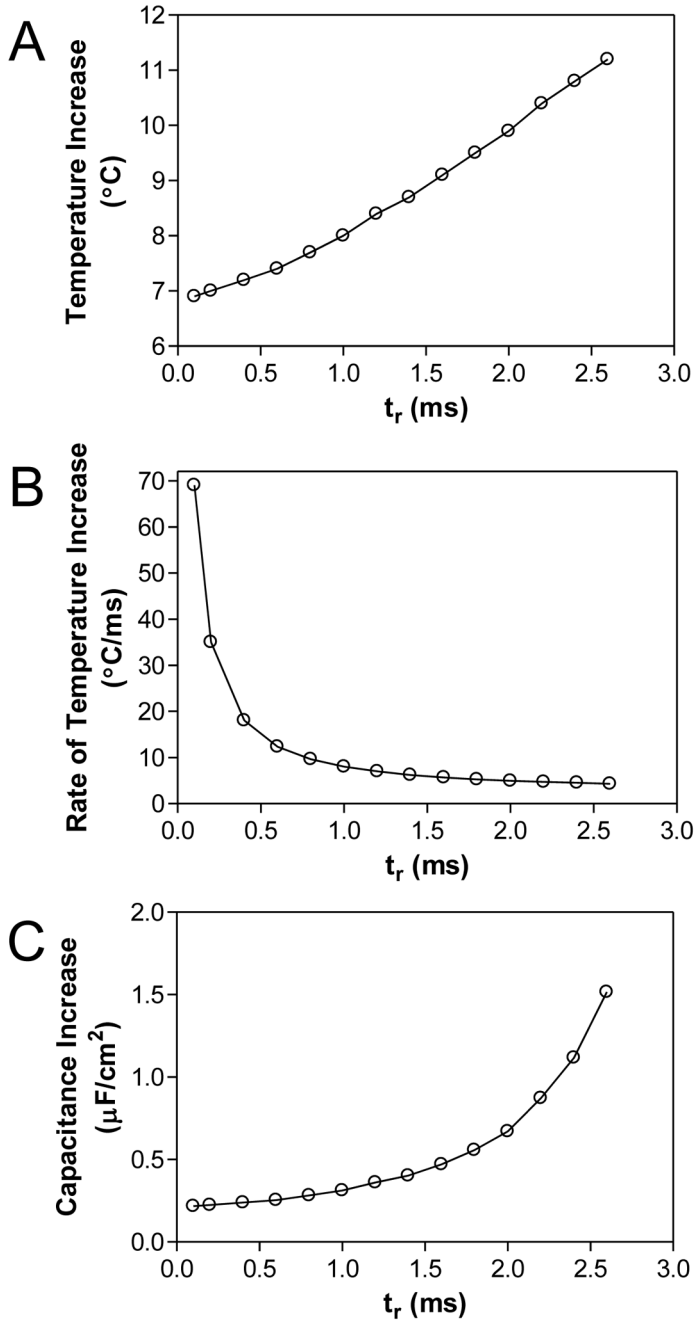

Fig. 4.

The rise time (t_r) of local temperature determines the minimal temperature and capacitance increases required for generating an action potential. A. Temperature increase. B. Rate of temperature increase. C. Capacitance increase. Axon diameter: 2 μm. Global axon temperature: 18.5 °C. Length of heated axon: 2 mm.

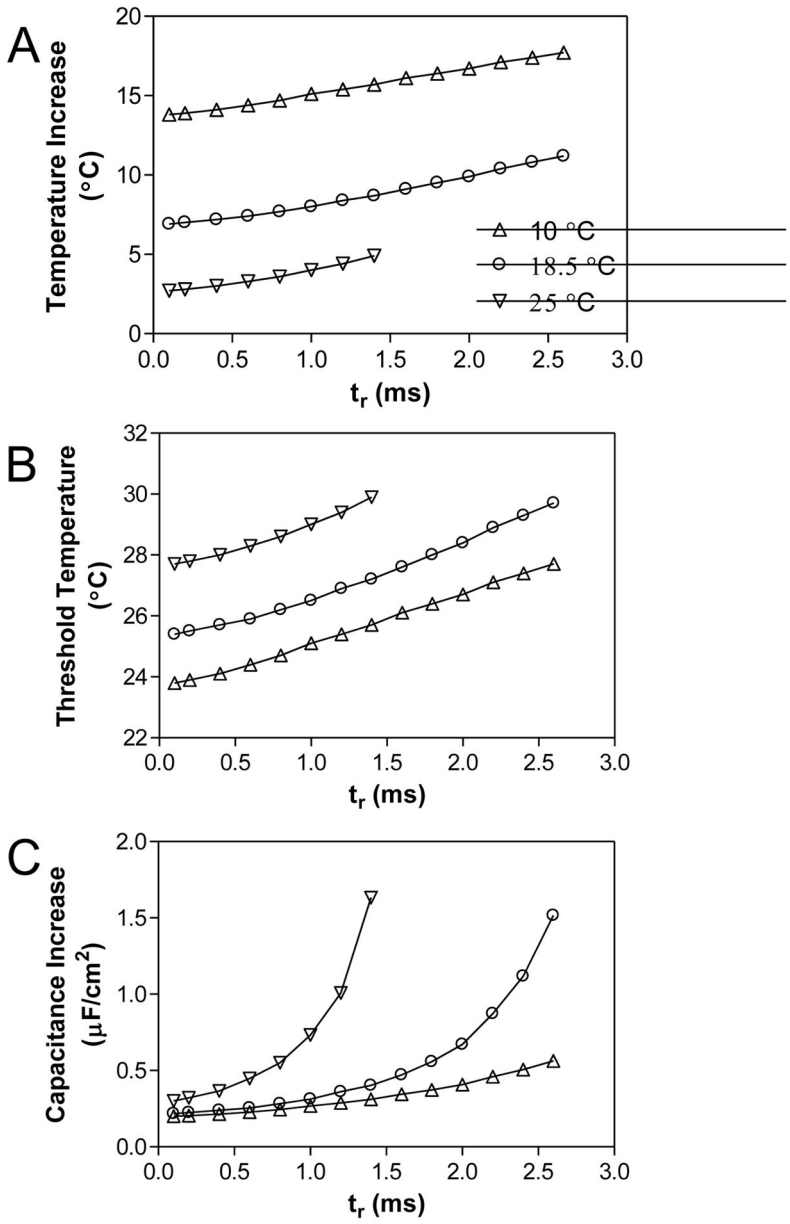

Fig. 5.

Influence of global axon temperature on the minimal temperature and capacitance increases required for generating an action potential. A. Temperature increase. B. Threshold temperature. C. Capacitance increase. Legends in A indicate the global axon temperature. Axon diameter: 2 μm. Length of heated axon: 2 mm.

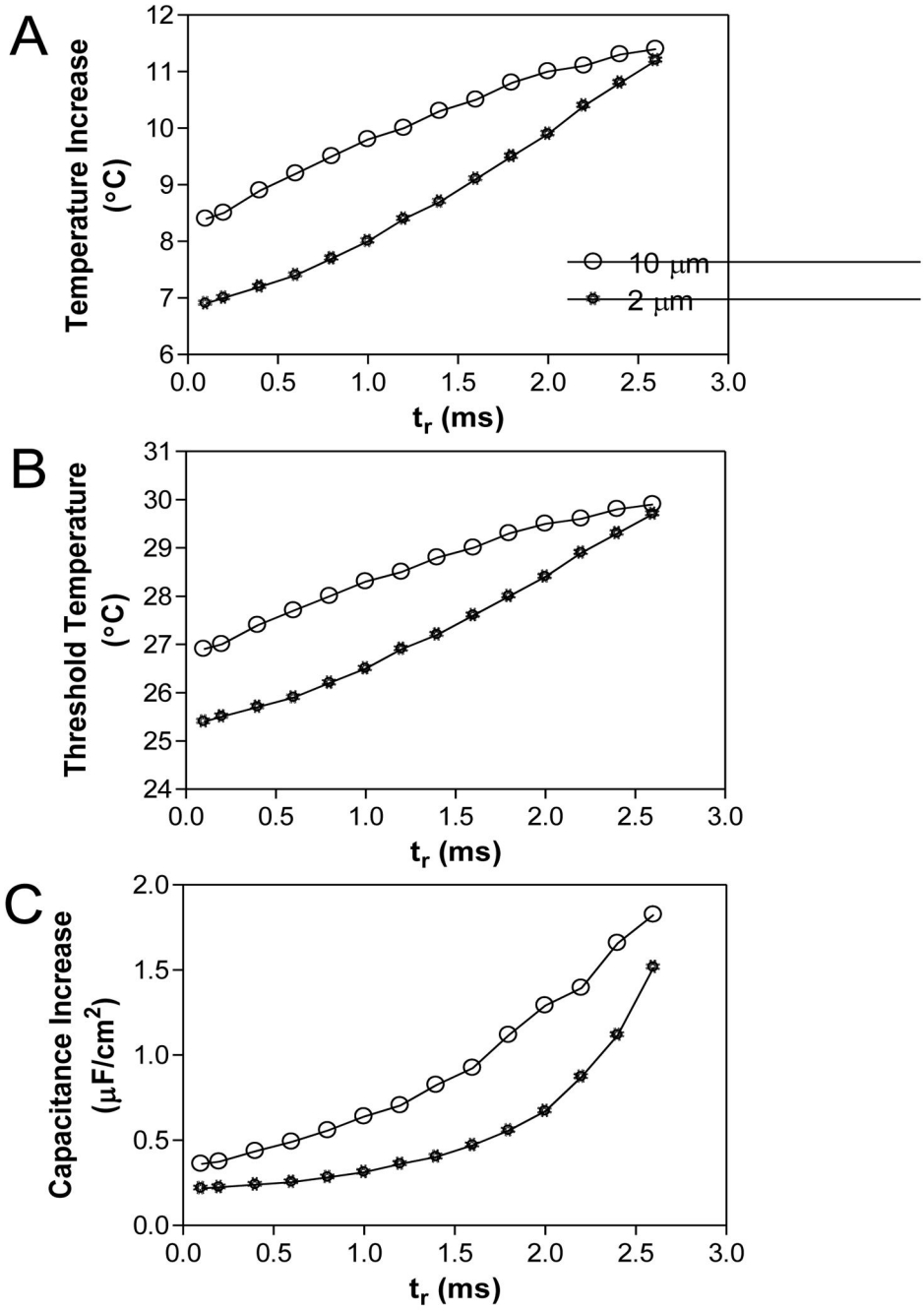

Fig. 6.

Influence of axon diameter on the minimal temperature and capacitance increases required for generating an action potential. A. Temperature increase. B. Threshold temperature. C. Capacitance increase. Legends in A indicate the axon diameter. Global axon temperature: 18.5 °C. Length of heated axon: 2 mm.

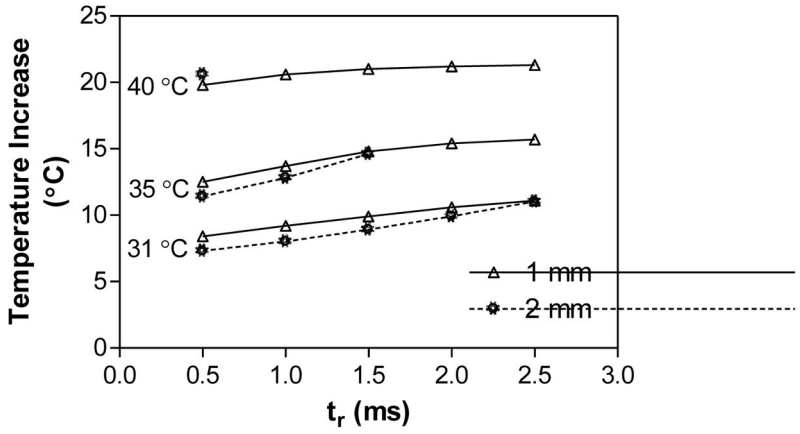

Fig. 7.

The minimal temperature increase required for generating an action potential is increased as the global heat block temperature (T_b) increases from 31 °C to 40 °C. For a longer length of heated axon (2 mm), the temperature must quickly increase within a short time period (t_r = 0.5 ms) in order to generate an action potential when the global heat block temperature is high (40 °C). Global axon temperature: 18.5 °C. Axon diameter: 2 μm.

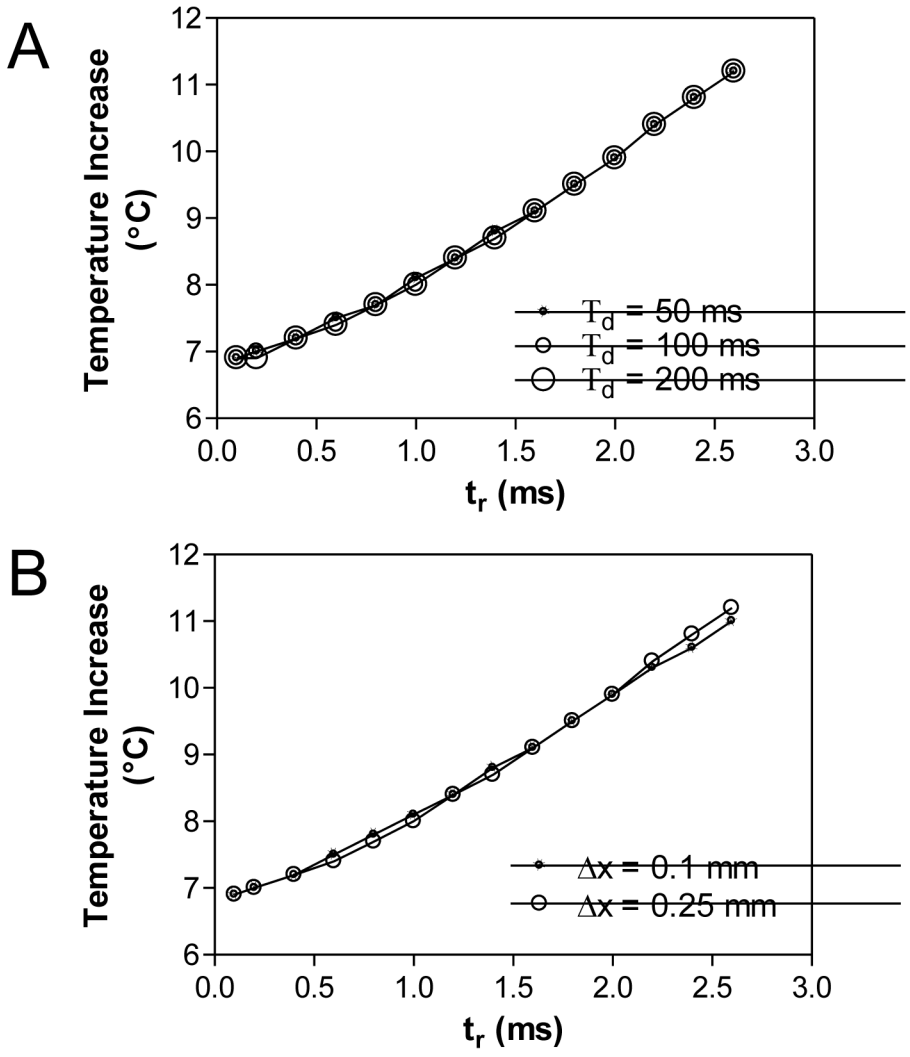

Fig. 8.

The minimal temperature increase required for generating an action potential is not changed significantly by different decay time of the temperature (A) or by reducing the length of axon segment (B). Global axon temperature: 18.5 °C. Axon diameter: 2 μm. Length of heated axon: 2 mm.