MODIFIED MULTI-LAYERED MODEL OF TEMPERATURE DEPENDENT MOTOR NERVE AXONS

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ABSTRACT

PURPOSE: Extensive sets of simulations are realized in this paper to gain insight into the problems of impulse propagation in temperature dependent motor nerve axons. The effect of temperature on the impulse threshold currents and action potential parameters (velocity, amplitude) is shown in simulated mammalian (rabbit) and human motor nerve fibres.

MATERIAL AND METHODS: Using our multi-layered model of human motor nerve fibre, temperature coefficients Q_{10}'s are involved for the conductivities of axoplasm, periaxonal space and for ionic currents (nodal and intermodal). The standard temperature for our model is 37°C. The temperature increases from 20 to 60°C.

RESULTS: The essential and very important result is that the simulated conduction block at 48 and 45°C in the rabbit and human motor nerve axons, respectively, is extremely sensitive to the rate constants of nodal sodium (P_{Na}), fast potassium (P_{Kf}) and slow (P_{Ks}) potassium maximum permeabilities. The temperature dependence of conduction velocity over a range of 20-42°C and 20-40°C for the rabbit and human motor nerve axons, respectively, is not linear or exponential. Due to this, a polynomial function of degree 2 (transfer standard parabola), which relates velocity to temperature, provides an accurate fit of the data.

CONCLUSION: Our modified multi-layered model used in this study is first ever in which the simulated temperature dependent velocities and conduction block in the rabbit and human motor axons are in good agreement with the experimental values.

Key words: *temperature, action potential parameters, motor axons, temperature dependent multi-layered model, computational neuroscience*

INTRODUCTION

Experimentally, it is clear that the axonal conduction velocity increases with temperature in the physiological range of 29-38°C (1,4,5,10,14,17), whereas the amplitude of nerve and muscle action potentials slightly decreases (2,3,16). The effect of temperature on the conduction block was also investigated and discussed (9,19).

Computations made for myelinated nerve fibres suffer from several defects. First, the temperature coefficients of the appropriate parameters for

mammalian nerve fibres either are unknown or at best are known only for a small range of temperature near room temperature (6,7,11-13,15,18,20,23,24). Second, there are conflicting results of simulations, on showing linear or exponential dependence of the velocity on temperature (12,13,18,27). Third, the models cited above except for the model of (23,24) do not simulate the conduction block of myelinated nerve axons. Moreover all models are one cable and are based on the equations of Hodgkin–Huxley (6,18) or Frankenhaeuser-Huxley (7,11-13,15,23,24). The standard temperature is 6.3°C for Hodgkin-Huxley models, whereas it is 20°C for Frankenhaeuser-Huxley models. Finally, some values of the conduction velocity agree with experimental values while others disagree by a factor as large as two.

The aim of this study is to modify the already existing our model of human motor nerve fiber (25) and to achieve values of the temperature dependent action potential parameters in reasonable agreement with the experimental data.

MATERIAL AND METHODS

The computations use our multi-layered model of human motor nerve fibre (25), in which the complex myelin sheath structure of 150 interconnected parallel lamellae is simulated by alternating 150 lipid and 150 aqueous layers. This model is also thoroughly described in (26). All calculations in the normal and modified model are carried out for fibres with: an axon diameter of 12.5µm; an external fibre diameter of 17.3µm; nodal diameter of 5µm; nodal area of 24µm²; myelin thickness of 2.4µm; periodicity of myelin lamellae of 16nm and periaxonal space thickness of 20nm. The standard temperature is 37°C.

Extensive sets of simulations are realized in this paper as the quantitative change in conduction velocity with temperature depends on which temperature–sensitive parameters are included. Temperature coefficients (Q_{10}'s) are involved in the used here model in order to determine the dependence of conduction parameters on the temperature. The equations in which the temperature coefficients enter explicitly are: Q_{10}'s=$Q_{10}^{(t_s-37.0)/10}$, where t_s are temperatures ($^{\circ}$C). $T_s = (273.16^{\circ}C+t_s)$, where T_s are temperatures (K). In the case when t equals 37°C, the

system of equations presented in the normal model (25,26) is realized. The action potential stimulation in the normal and modified model is simulated by adding a short (0.1 ms) rectangular depolarizing current pulse to the center of the first node. This case of point application of current intra-axonally at the node closely approximates the effects of point application of current extra-axonally at the node and realizes a point fibre polarization.

RESULTS

In the first set of simulations, the rate constants are modified using the following Q_{10} values: 2.2 for a_m, b_m (21,22); 2.9 for a_h, b_h (21,22); 3.0 for a_n, b_n (8,22); 3.0 for a_s, b_s (22). The maximum permeabilities of sodium (P_{Na}), fast potassium (P_{Kf}) and slow potassium (P_{Ks}) nodal channels are modified using the following Q_{10} values: 1.3 for P_{Na} (8,20,22,24); 1.2 for P_{Kf}, P_{Ks} (8,20,23,24). The Q_{10} is 1.25 (18) for the conductance of axoplasm ($1/R_{ax}$). The same Q_{10} value is included in the model for the conductance ($1/R_{pa}$) of periaxonal space. Electrolytes show a temperature increase in conductance with a Q_{10} of 1.25 to 1.3. The axoplasm and periaxonal conductivities are electrolytic and should be given similar temperature dependence. For this temperature dependent modified model, a conduction block of impulse propagation is not achieved when the temperature increases from 20°C to an extremely high value of 100°C.

In the second set of simulations, the temperature increases from 20 to 60°C. And the Q_{10}'s are changed in such a way, that conduction blocks to be achieved at 60, 48 and 45°C. Surprisingly, for temperatures higher than 37°C, the axonal conduction block was found to be quite sensitive to the maximum permeabilities of the nodal channels. And they are modified using the following Q_{10} values: (i) 2.4 for P_{Na} and 5.9 for P_{Kf}, P_{Ks} in the case of conduction block at 60°C; (ii) 3.5 for P_{Na} and 50.0 for P_{Kf}, P_{Ks} in the case of conduction block at 48°C; and (iii) 4.0 for P_{Na}, 220.0 for P_{Kf}, P_{Ks}, and 2.7 for a_m, b_m in the case of conduction block at 45°C. For the three (i-iii) cases at temperatures lower than 37°C, the Q_{10}'s values of the maximum permeabilities are equal and are the same as those involved in the (i) case, i.e. 2.4 for P_{Na} and 5.9 for P_{Kf}, P_{Ks}. The remaining Q_{10}'s values given above in the first investigated set of simulations are unchanged. The temperature dependence of action potential parameters [velocity
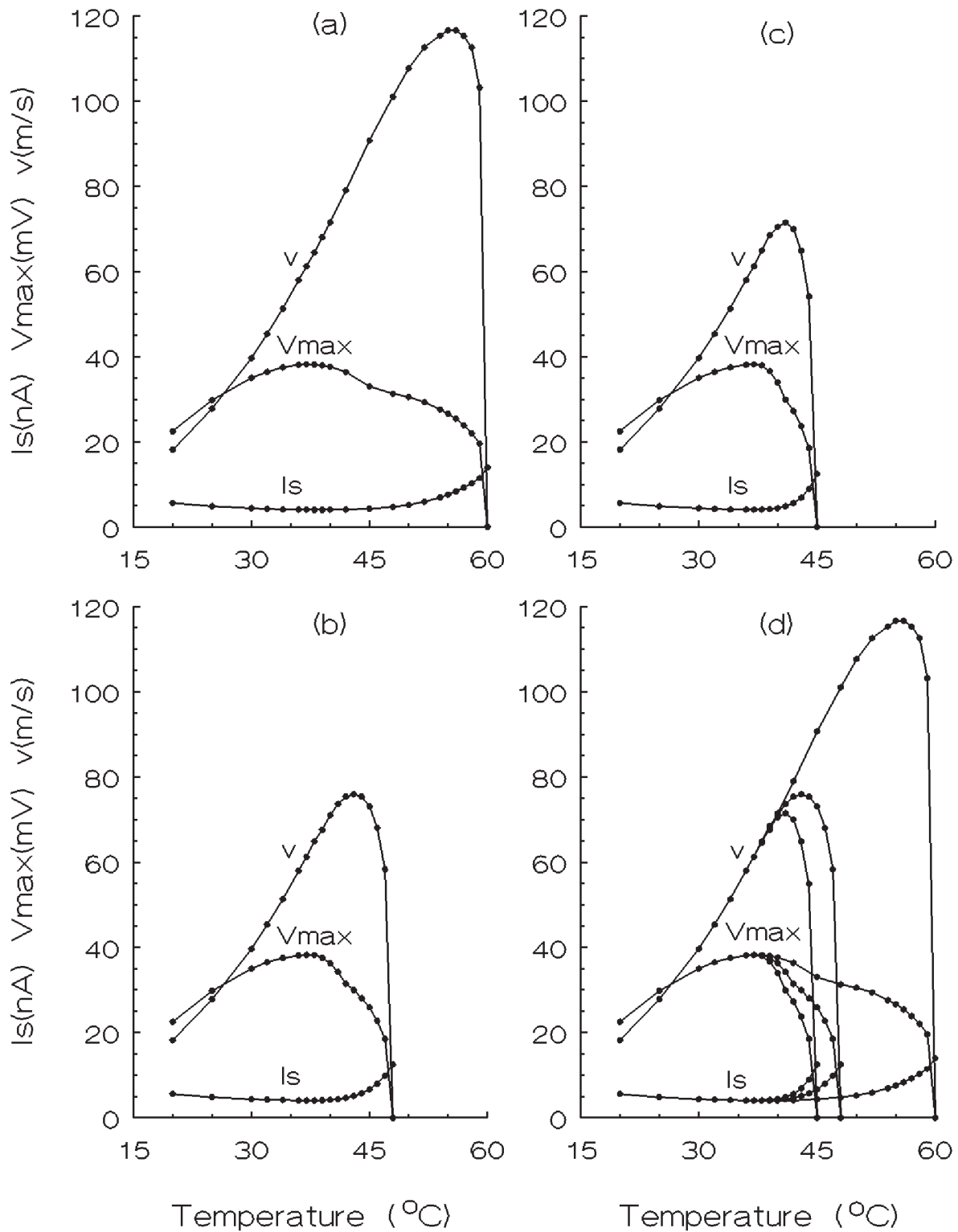
Fig. 1. Effect of temperature on the conduction velocity (v), action potential amplitude (Vmax) and impulse threshold current (Is) of motor nerve axons in the cases of conduction block at 60ºC (a); 48ºC (b); 45ºC (c). And the results from (a-c) are given together (d). Note that the y-scales of v, Vmax and Is are equal and overlapped, but they are with different dimensions in the a-d panel figures
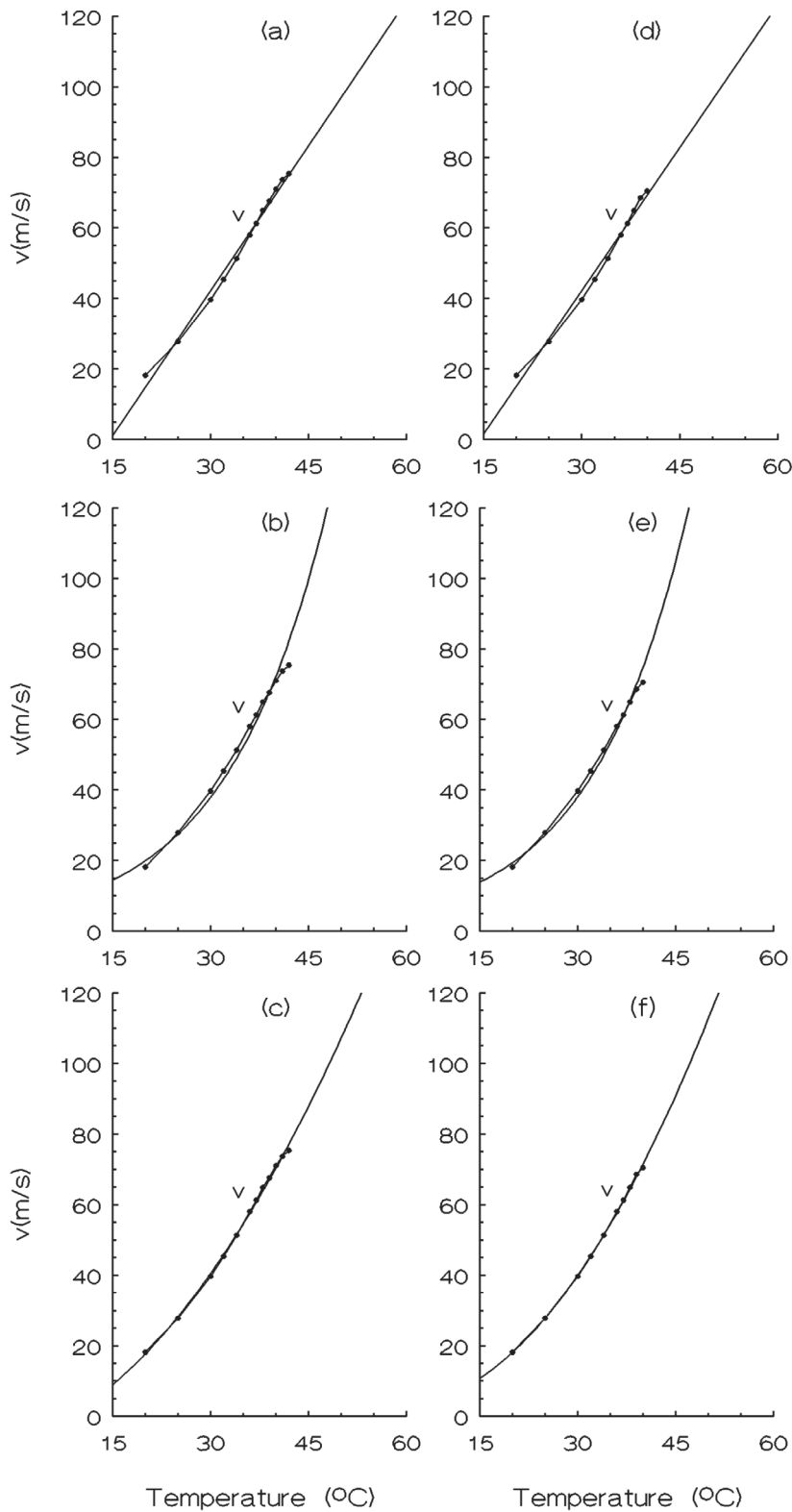
Fig. 2. *Temperature dependence of the conduction velocity over a range of 20-42°C (a-c) and 20-40°C (d-f) for the rabbit and human motor nerve axons, respectively. The curves are fitted by linear (a,d), exponential (b,e) functions and polynomial function of degree 2 (c,f)*

(v), amplitude (Vmax)] and impulse threshold current (Is) is investigated and shown in Fig. 1. To provide a better illustration these parameters are presented together in the panel figures where the parameter's y-scales are equal and overlapped, but they are with different dimensions. The conduction block that actually is observed in real myelinated nerve (at about 48°C in the rabbit and 45°C in the human) is in good agreement with our simulations (see v curves in Fig. 1b,c, respectively). An unrealistic case is given in Fig. 1a and all investigated cases are compared in Fig. 1d. The conduction velocities calculated from the times of the potential maxima at the nodes increase from 18.18 to 71.50 m/sec (in the human axon) and from 18.18 to 75.47 m/sec (in the rabbit axon) and then rapidly decrease achieving the blocking value. The potential amplitudes increase up to given temperature and then decrease with the increase of temperature. Conversely, the impulse threshold currents decrease up to given temperature and then increase with the increase of temperature. The results show that the temperature dependence of conduction velocity over a range of 20-42°C and 20-40°C for the rabbit (Fig. 2a-c) and human (Fig. 2d-f) motor axons, respectively, is not linear (Fig. 2a,d) or exponential (Fig. 2b,e). Due to this, a polynomial function of degree 2 (transfer standard parabola), which relates velocity to temperature, provides an accurate fit of the data for the rabbit and human axons (Fig. 2c,f).

DISCUSSION

A modified multi-layered model describing the behavior of motor nerve axons in the range of 10-60°C is suggested. The present study compares the effects of temperature on different conduction parameters of rabbit and human motor axons. For temperatures lower than 37°C, the conduction parameters (v, Vmax, Is) are equal in the rabbit and human motor axons. The conduction velocity of 18.18 m/sec at 20°C is the same as the calculated by (11,13,15). The conduction velocity increases by ~5% per degree C as the temperature increases from 28 to 38°C. The same values are characteristic for human nerve (4,14,17). The conduction block at about 48°C experimentally observed in the rabbit (19) is correctly reproduced in the model. The simulated conduction block at 45°C

in the human motor axon is in agreement with our previous investigation (23).

CONCLUSION

In summary, our modified multi-layered model used in this study is first ever in which the simulated temperature dependent velocities and conduction block in the rabbit and human motor axons are in good agreement with the experimental values. The results are important for the interpretation of excitability measurements from patients with peripheral nerve disorders and for deciding the best strategy to adopt when testing control groups and patients with different limb temperatures.

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