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Article

Can the Thermodynamic Hodgkin-Huxley Model of Voltage-Dependent Conductance Extrapolate for Temperature?

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Abstract: Hodgkin and Huxley (H-H) fitted their model of voltage-dependent conductances to experimental data using empirical functions of voltage. The thermodynamic H-H model of voltage dependent conductances is more physically plausible, as it constrains and parameterises its empirical fit by assuming that ion channel transition rates depend exponentially on a free energy barrier that in turn, linearly or non-linearly, depends on voltage. The original H-H model contains no explicit temperature terms and requires Q_{10} factors to describe data at different temperatures. The thermodynamic H-H model does have explicit terms for temperature. Do these endow the model with extrapolation for temperature? We utilised voltage clamp data for a voltage-gated K^+ current, recorded at three different temperatures. The thermodynamic H-H model's free parameters were fitted (Marquardt-Levenberg algorithm) to a data set recorded at one (or more) temperature(s). Then we assessed whether it could describe another data set, recorded at a different temperature, with these same free parameter values and its temperature terms set to the new temperature. We found that it could not.

Keywords: thermodynamic; Hodgkin-Huxley; model; voltage; temperature; computational neuroscience; action potential; *Q*10; transition state

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1. Introduction

Hodgkin and Huxley (H-H) quantitatively characterised the voltage-dependence of membrane currents in the giant squid axon, and showed how they can generate and propagate action potentials [1].

Their model can describe ion channels in the membrane, opening and closing in a voltage-dependent manner [2]. However, membrane currents are not just voltage-dependent, but temperature dependant also, and the H-H description is without any explicit temperature term. To describe data over a range of temperatures, the H-H model requires an empirical multiplicative constant, Q_{10}, to be applied to a number of its parameters [1].

Hodgkin and Huxley fitted their model of voltage-dependent conductances to experimental data using empirical functions of voltage. Thermodynamic Hodgkin-Huxley models describe voltage-dependence empirically as well, but can be construed to be more physically plausible, as they constrain and parameterise their fit with thermodynamic principles of transition state theory [3–7]. They consider that the rate of transition between channel states depends exponentially on the free energy barrier that separates them. The free energy barrier, in turn, is voltage dependent. It can vary linearly or non-linearly with voltage: linear and non-linear thermodynamic H-H models respectively [6,7].

In contrast to the original H-H model, thermodynamic H-H models do have explicit terms for temperature, on account of their incorporation of thermodynamic theory. We hypothesise that these temperature terms permit these models to describe voltage-gated currents at different temperatures *i.e.*, describe how currents change with voltage *and* temperature.

Voltage clamp data for a K^+ current was taken from [8]. The data was grouped at three temperatures: T15 (15 °C), T25 (25 °C) and T35 (35 °C). The thermodynamic H-H model (linear and non-linear) was fitted to each temperature set separately; the Marquardt-Levenberg algorithm [9] optimised the model's free parameters to find a best fit in each case. This was a success, with close fits being produced. We then investigated if the model, with its free parameters fitted to one temperature data set, could replicate the data of a different temperature set, when the temperature terms of the model were changed to the new temperature. We found that it could not.

We repeated this process but, in the fitting phase, we fitted the thermodynamic H-H model (linear and non-linear) to the combined data sets of two different temperatures: (T15 + T25) or (T15 + T35) or (T25 + T35). We then investigated if the model, with its free parameters fitted to two temperature data sets, could replicate the data of a third temperature set, when the temperature terms of the model were changed to the new temperature. We found that it could not.

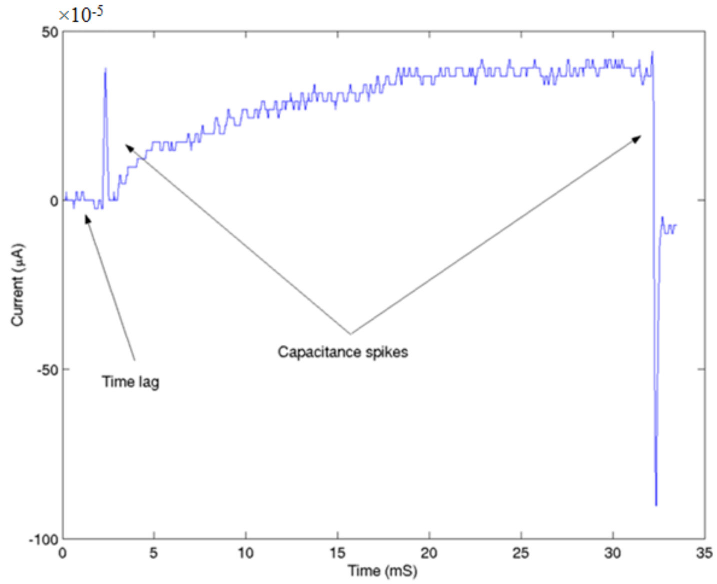
We find that the thermodynamic H-H model (linear or non-linear) cannot accurately predict data at temperatures that it is not specifically fitted to *i.e.*, it cannot extrapolate for temperature.

2. Experimental Section

2.1. K^+ Current Data

Tiwari and Sikdar studied non-inactivating K^+ currents, in a gonadotroph cell line, across a temperature range [8]. They assembled whole cell, voltage clamp data at a number of depolarising potentials, grouped at three temperatures: T15 (15 °C, 288 K), T25 (25 °C, 298 K), T35 (35 °C, 308 K). We obtained this data via personal communication and modified it, as shown in Figure 1.

Figure 1. K^+ current in a gonadotroph cell, when the holding voltage is stepped from −10 mV to +116 mV using a voltage clamp. We modified this data before we used it ourselves, removing the labelled capacitance spikes and time lag. We repeated this action for all other current data used. The *x*-axis presents time (mS); the *y*-axis presents K^+ current.



2.2. Thermodynamic H-H Models

α and β are forward and backward rate constants between the Closed (*C*) and Open (*O*) channel states.

$$C \underset{\beta}{\overset{\alpha}{\rightleftarrows}} O \tag{1}$$

When the channel switches between these states, it must pass through a high energy intermediate: the transition state (not shown). α and β are voltage (*V*) and temperature (*T*) dependent:

2.2.1. Linear Variant

$$\alpha(V) = \alpha_0 e^{-(a_1 + b_1 V)/RT} \tag{2}$$

$$\beta(V) = \beta_0 e^{-(a_2 + b_2 V)/RT} \tag{3}$$

R is the gas constant, *V* is the membrane voltage. α_0, a_1, b_1 are parameters describing the free energy barrier between the Closed and Transition state. β_0, a_2, b_2 are parameters describing the free energy barrier between the Open and Transition state. *T* is temperature; so this model has terms for temperature, unlike the original Hodgkin-Huxley formulation [1].

2.2.2. Non-Linear Variant (Quadratic)

$$\alpha(V) = \alpha_0 e^{-(a_1 + b_1 V + c_1 V^2)/RT} \tag{4}$$

$$\beta(V) = \beta_0 e^{-(a_2 + b_2 V + c_2 V^2)/RT} \tag{5}$$

R is the gas constant, V is the membrane voltage. α_0, a_1, b_1, c_1 are parameters describing the free energy barrier between the Closed and Transition state. β_0, a_2, b_2, c_2 are parameters describing the free energy barrier between the Open and Transition state. T is temperature; so this model has terms for temperature, unlike the original Hodgkin-Huxley formulation [1].

2.3. Thermodynamic H-H Model of a Non-Inactivating K^+ Current (I_K), Recorded in a Gonadotroph Cell Line

$$I_K = g_K(V - E_K) \tag{6}$$

$$g_K = \bar{g}_K \cdot n \tag{7}$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \tag{8}$$

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{9}$$

$$\tau_n = \frac{1}{\alpha_n + \beta_n} \tag{10}$$

I_K is the K^+ current, g_K is the K^+ conductance, $\bar{g}_K$ is the maximal K^+ conductance, V is the membrane potential, t is time and E_K is the reversal/Nernst potential for K^+ (set to −9.8 mV; [8]). To produce a linear thermodynamic H-H model, α_n and β_n are set by Equations (2) and (3) (respectively). To produce a non-linear thermodynamic H-H model, α_n and β_n are instead set by Equations (4) and (5) (respectively).

The maximal conductance ($\bar{g}_K$) for the T15, T25 and T35 membrane patches was calculated by deriving a maximal current ($\bar{I}_K$) value for the largest depolarising potential explored at each temperature (Figure 1D; [8]). Then:

$$\bar{g}_K = \frac{\bar{I}_K}{(V - E_K)} \tag{11}$$

2.4. Fitting the Thermodynamic H-H Model to the K^+ Current (I_K) Data

The free parameters in the thermodynamic H-H model, adjusted in order to fit the model to the data, are α_0, β_0, a_1, b_1, a_2, b_2 for the linear variant (refer to Equations (2) and (3)); with the addition of c_1 and c_2 for the non-linear variant (quadratic) (refer to Equations (4) and (5)). The fitting was performed using the criterion of least squares minimisation, implemented by the Marquardt-Levenberg algorithm [9] in Matlab (MathWorks Inc., Natick, MA, USA). Initial free parameter values were chosen arbitrarily. Repeated runs with different initial free parameter values checked that our fits were globally, and not just locally, optimal. No constraints were set for free parameter values.

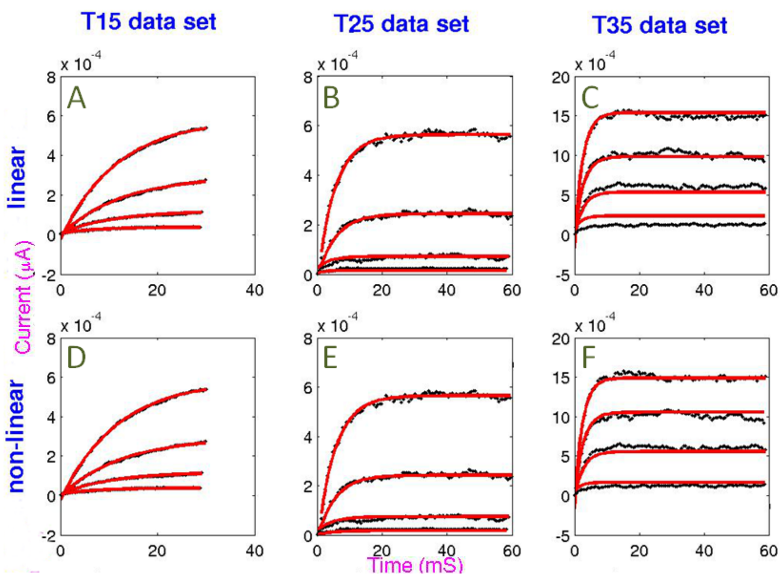
2.5. Temperature Extrapolation

The thermodynamic H-H model (linear and non-linear) was fitted to each temperature set separately: T15, T25 and T35. We then investigated if the model, with its free parameters fitted to one temperature data set, could replicate the data of a different temperature set, when the temperature terms of the model (in Equations (2)–(5)) were changed to the new temperature.

We repeated this process but, in the fitting phase, we fitted the thermodynamic H-H model (linear and non-linear) to the combined data sets of two different temperatures: (T15 + T25), (T25 + T35), (T15 + T35). At each temperature, the temperature setting in the thermodynamic model equations was set appropriately and the model's free parameters were optimised with experimental data spanning more than one temperature. We then investigated if the model, with its free parameters fitted to two temperature data sets, could replicate the data of a third temperature set, when the temperature terms of the model were changed to the new temperature.

So, to elaborate further on what was done for both the linear and non-linear models: where *p* denotes parameters and *d* is data: (T15p on T25d), (T15p on T35d), (T25p on T15d), (T25p on T35d), (T35p on T15d) and (T35p on T25d). Combined data sets were also used to "train" the free parameter values: (T15+T25p on T35d), (T15+T35p on T25d), (T25+T35p on T15d).

Figure 2. Thermodynamic Hodgkin-Huxley models, linear and non-linear, (red lines) fitted to K^+ current data (black circles). (**A**) Linear thermodynamic H-H model fitted to the T15 data set; (**B**) Linear thermodynamic H-H model fitted to the T25 data set; (**C**) Linear thermodynamic H-H model fitted to the T35 data set; (**D**) Non-linear thermodynamic H-H model fitted to the T15 data set; (**E**) Non-linear thermodynamic H-H model fitted to the T25 data set; (**F**) Non-linear thermodynamic H-H model fitted to the T35 data set. For all panels: the *x*-axis presents time (ms), the *y*-axis presents K^+ current (μA).



3. Results and Discussion

3.1. Curve Fitting

The thermodynamic H-H model (linear and non-linear) was fitted to each temperature data set separately. Figure 2 presents the linear and non-linear models fitted separately to the T15, T25 and T35 data sets. Each panel shows K^+ current in a gonadotroph cell (black circles; every tenth data point plotted) when the holding voltage is stepped from −10 mV to +57 mV, from −10 mV to +77 mV, from

−10 mV to +96 mV and from −10 mV to +116 mV [8]. So, there are 4 data plots at each temperature. Greater depolarisation produces greater K^+ current. Red lines show the thermodynamic Hodgkin-Huxley (H-H) model—linear or non-linear—fitted to the data; its free parameters optimised to the data by the Marquardt-Levenberg algorithm [9]. This was a success, with close fits being produced. For example, the non-linear model fit to the T15 data set has a logged reduced chi-square metric: $\log_{10}(x^2_{red}) = -0.05$. The worst fit was still good in absolute terms: the linear model fit to the T35 data set has a logged reduced chi-square metric: $\log_{10}(x^2_{red}) = 1.69$. Temperature and goodness of fit were inversely related, possibly due to data variance being a function of temperature. The non-linear model provided a slightly better fit than the linear model.

The thermodynamic H-H model (linear and non-linear) was then fitted to the combined data sets of two different temperatures: (T15 + T25), (T15 + T35), (T25 + T35). At each temperature, the temperature setting in the thermodynamic model equations was set appropriately and the model's free parameters were optimised with experimental data spanning more than one temperature. Figure 3 presents the linear and non-linear models fitted separately to the (T15 + T25), (T15 + T35) and (T25 + T35) data sets. This was a reasonable success, with reasonably close fits being produced. But, the fit to an amalgamation data set (recorded at 2 temperatures) is inferior to the fit of any of its individual component data sets (recorded at 1 temperature). Again, temperature and goodness of fit were inversely related. The non-linear model provided a slightly better fit than the linear model.

To conclude, the thermodynamic H-H formalisms can describe K^+ current data recorded at a certain temperature(s) well, if their free parameters are specifically tuned to describe that data.

Figure 3. Thermodynamic Hodgkin-Huxley models, linear and non-linear, (red lines) fitted to K^+ current data (black circles). (**A**) Linear thermodynamic H-H model fitted to the T15 and T25 data set combined (T15, T25); (**B**) Linear thermodynamic H-H model fitted to the T15 and T35 data set combined (T15, T35); (**C**) Linear thermodynamic H-H model fitted to the T25 and T35 data set combined (T25, T35); (**D**) Non-linear thermodynamic H-H model fitted to the T15 and T25 data set combined (T15, T25); (**E**) Non-linear thermodynamic H-H model fitted to the T15 and T35 data set combined (T15, T35); (**F**) Non-linear thermodynamic H-H model fitted to the T25 and T35 data set combined (T25, T35). For all panels: the *x*-axis presents time (ms), the *y*-axis presents K^+ current (μA).

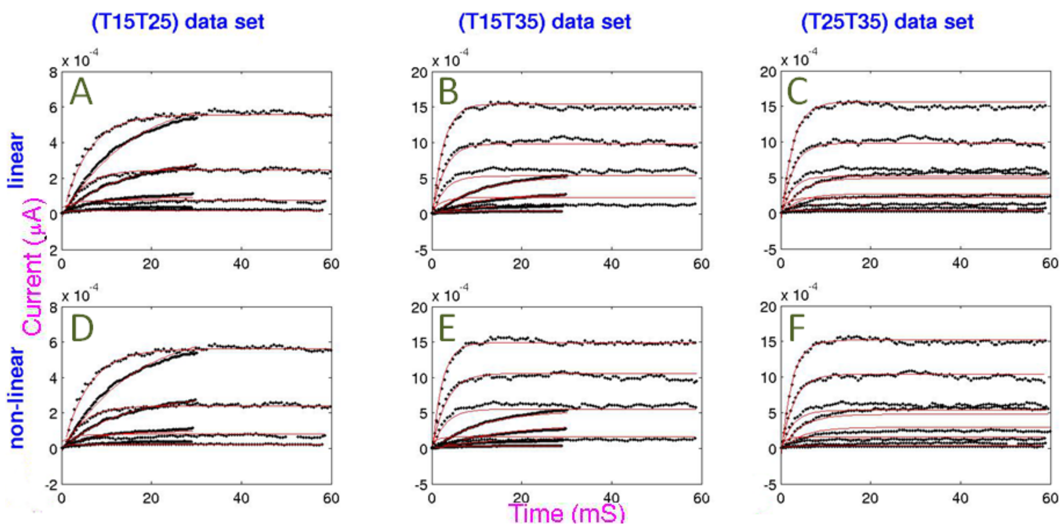
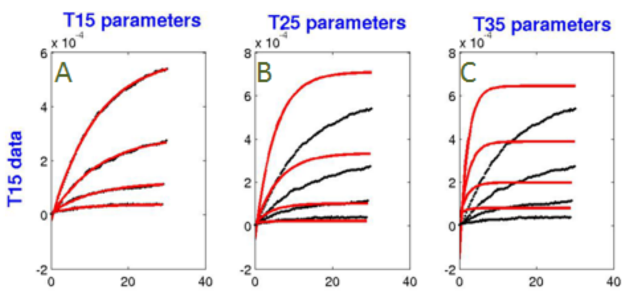


Figure 4. The LINEAR thermodynamic Hodgkin-Huxley (H-H) model, with its free parameters fitted to one temperature data set, cannot replicate the data of a different temperature set, when its temperature terms are changed to the new temperature. So, the model's temperature terms do not permit it to replicate data at temperatures that it has not been fitted to. (**A**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 15 °C. The model describes the data well; (**B**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**C**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**D**) Experimental K^+ current data recorded at 25 °C (black). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**E**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 25 °C. The model describes the data well; (**F**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**G**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 35 °C. The model does not describe the data well; (**H**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 35 °C. The model does not describe the data well; (**I**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 35 °C. The model describes the data well. For all panels: the *x*-axis presents time (mS), the *y*-axis presents K^+ current (μA).



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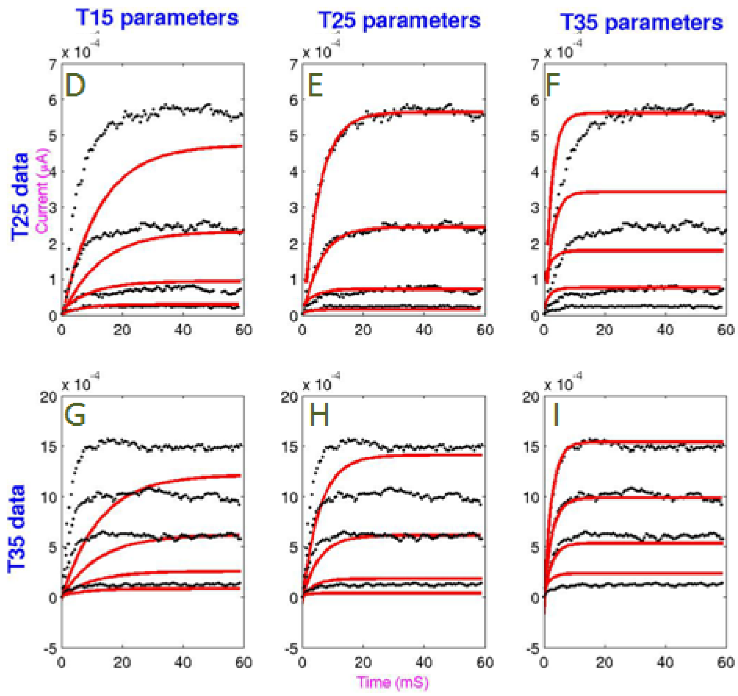


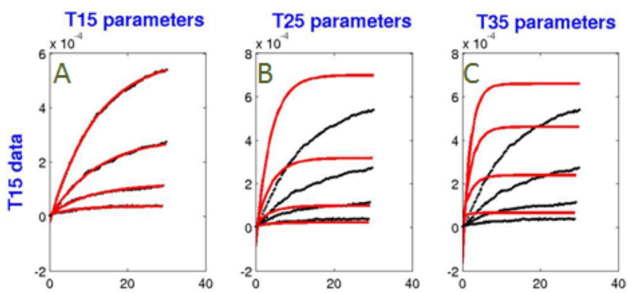
3.2. Temperature Extrapolation of the Model

The ability of a model to describe data not used in determining its parameters is an independent test of how well that model approximates reality. Can the thermodynamic H-H model, with its free parameters fitted to data at one temperature, replicate data at a different temperature upon the temperature terms of the model (in Equations (2)–(5)) being changed to the new temperature? We found that it could not.

Figure 4 shows linear model functions against experimental data. Figure 5 shows non- linear model functions against experimental data. In each panel, the plotted function (red line) utilises best-fit free parameter values derived at one temperature to predict the data set recorded at a second temperature (black circles). Figure 6 shows plotted thermodynamic functions (red lines), utilising best-fit free parameter values derived at *two* temperatures, to predict a data set at a third temperature (black circles). Figure 7 consolidates all the findings; it presents reduced chi-square values, which indicate the agreement between model and data [9]. The thermodynamic H-H model (linear and non-linear) can describe the data that it has been fitted to well; much better than other data, recorded at other temperatures. Indeed, relatively speaking, it cannot describe data at other temperatures very well at all. *Ceteris paribus*, the models describe data at higher temperatures worse, possibly due to data variance scaling with temperature. All other things being equal, the model's performance can be improved by fitting it to data recorded at two temperatures, rather than just one; but this effect is slight. The non-linear model can describe the data that it has been fitted to better than the linear model; but it offers little superiority in describing other data sets, recorded at other temperatures.

The data suggests that the thermodynamic H-H model (linear or non-linear) cannot accurately predict data at temperatures that it is not specifically fitted to *i.e.*, it cannot extrapolate for temperature.

Figure 5. The NON-LINEAR thermodynamic Hodgkin-Huxley (H-H) model, with its free parameters fitted to one temperature data set, cannot replicate the data of a different temperature set, when its temperature terms are changed to the new temperature. So, the model's temperature terms do not permit it to replicate data at temperatures that it has not been fitted to. (**A**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 15 °C. The model describes the data well; (**B**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**C**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**D**) Experimental K^+ current data recorded at 25 °C (black). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**E**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 25 °C. The model describes the data well; (**F**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**G**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C, and its temperature terms set to 35 °C. The model does not describe the data well; (**H**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C, and its temperature terms set to 35 °C. The model does not describe the data well; (**I**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 35 °C, and its temperature terms set to 35 °C. The model describes the data well. For all panels: the *x*-axis presents time (mS), the *y*-axis presents K^+ current (μA).



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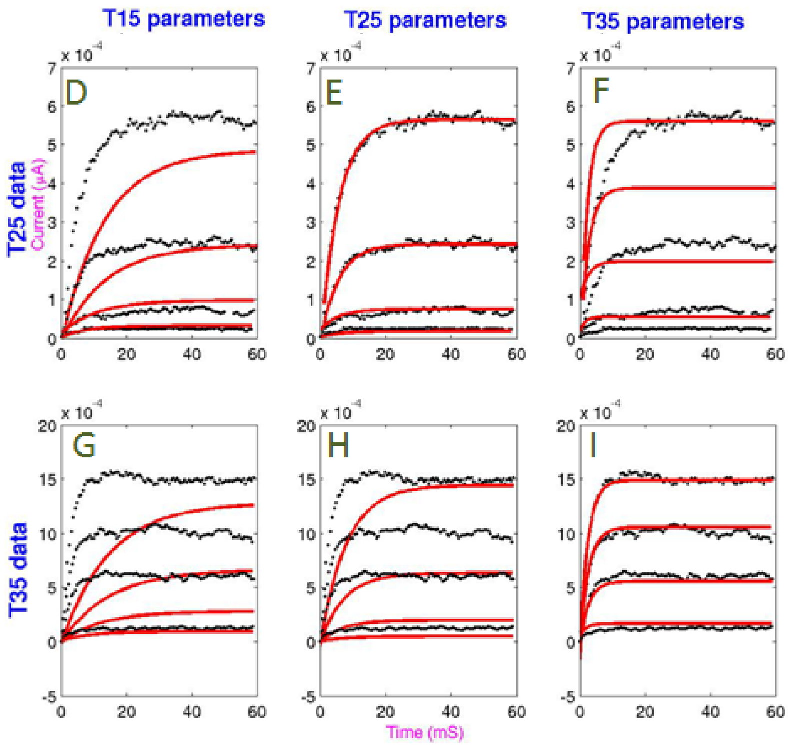


Figure 6. The thermodynamic Hodgkin-Huxley (H-H) model (linear and non-linear), with its free parameters fitted to data recorded at two different temperatures, does not replicate data recorded at a third temperature, when its temperature terms are changed to this third temperature. So, the model's temperature terms do not permit it to replicate data at temperatures that it has not been fitted to. (**A**) Experimental K^+ current data recorded at 15 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C and 25 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**B**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C and 35 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**C**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C and 25 °C, and its temperature terms set to 35 °C. The model does not describe the data well; (**D**) Experimental K^+ current data recorded at 15 °C (black). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 25 °C and 35 °C, and its temperature terms set to 15 °C. The model does not describe the data well; (**E**) Experimental K^+ current data recorded at 25 °C (black circles). Plots of the non-linear thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C and 25 °C, and its temperature terms set to 25 °C. The model does not describe the data well; (**F**) Experimental K^+ current data recorded at 35 °C (black circles). Plots of the non-linear

thermodynamic H-H model (red lines), with its free parameters having been previously fitted to data recorded at 15 °C and 25 °C, and its temperature terms set to 35 °C. The model does not describe the data well. For all panels: the *x*-axis presents time (mS), the *y*-axis presents K^+ current (μA).

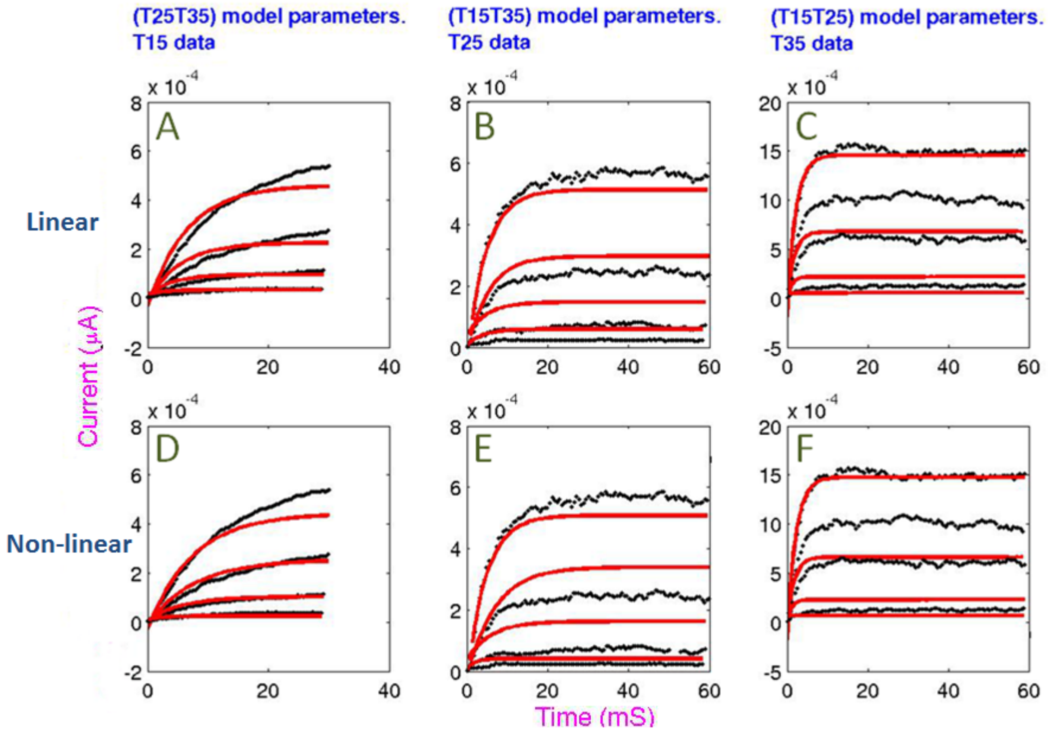
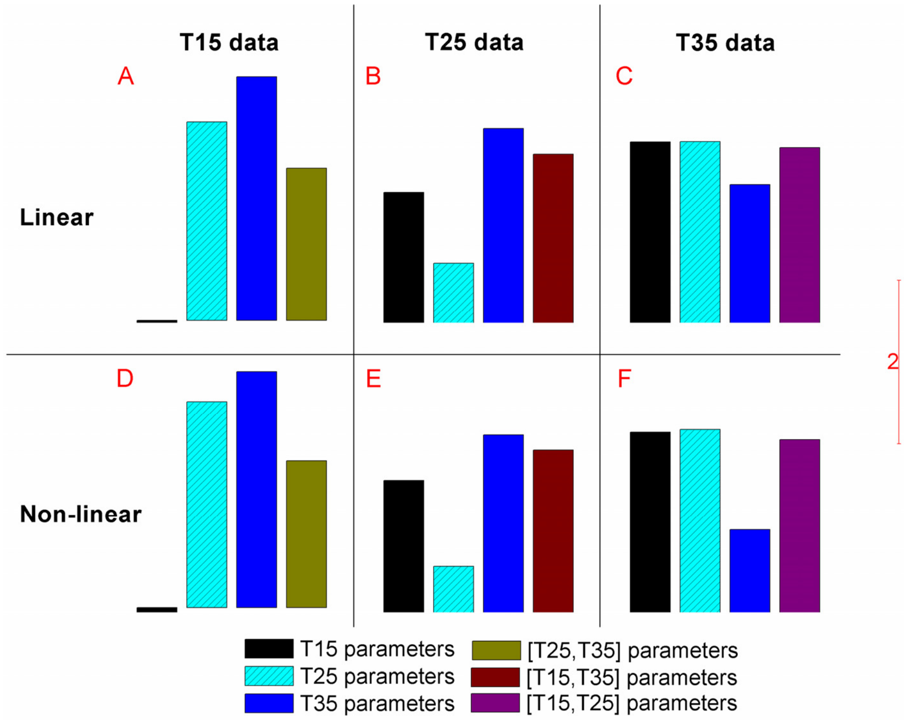


Figure 7. Logged ($\log_{10}$), reduced chi-square values indicating if the linear and non-linear thermodynamic H-H models—with their parameters optimised to data recorded at one (or more) temperature(s)—can describe different data recorded at a different temperature, if their temperature terms are set to this new temperature. (**A**) Bars show how well the linear variant describes K^+ current data recorded at 15 °C, if its free parameters have been fitted to this data (black bar) or if they have been fitted to different data recorded at 25 °C (turquoise bar), or 35 °C (blue bar) or (25 °C and 35 °C) (olive bar); (**B**) Bars show how well the linear variant describes K^+ current data recorded at 25 °C, if its free parameters have been fitted to this data (turquoise bar) or if they have been fitted to different data recorded at 15 °C (black bar), or 35 °C (blue bar) or (15 °C and 35 °C) (wine bar); (**C**) Bars show how well the linear variant describes K^+ current data recorded at 35 °C, if its free parameters have been fitted to this data (blue bar) or if they have been fitted to different data recorded at 15 °C (black bar), or 25 °C (turquoise bar) or (15 °C and 25 °C) (purple bar); (**D**) Bars show how well the non-linear variant describes K^+ current data recorded at 15 °C, if its free parameters have been fitted to this data (black bar) or if they have been fitted to different data recorded at 25 °C (turquoise bar), or 35 °C (blue bar) or (25 °C and 35 °C) (olive bar); (**E**) Bars show how well the non-linear variant describes K^+ current data recorded at 25 °C, if its free parameters have been fitted to this data (turquoise bar) or if they have been fitted to different data recorded at 15 °C (black bar), or 35 °C (blue bar) or (15 °C and 35 °C) (wine bar); (**F**) Bars show how well the non-linear variant

describes K^+ current data recorded at 35 °C, if its free parameters have been fitted to this data (blue bar) or if they have been fitted to different data recorded at 15 °C (black bar), or 25 °C (turquoise bar) or (15 °C and 25 °C) (purple bar). All bars are scaled by the presented *y*-scale bar.



4. Conclusions

The Hodgkin-Huxley (H-H) model of voltage-dependent conductances, for which Hogkin and Huxley were awarded the Nobel Prize in 1963, was and is a triumph. However, their model cannot intrinsically account for temperature. A modified variant of their model has been proposed, the thermodynamic H-H model, which suggests that channel transition rates depend on a free energy barrier by analogy with reaction rates. In this study, we investigate if this variant *can* intrinsically account for temperature unlike the original H-H description, which can't. We hypothesise that it might because this variant—unlike the original H-H form—has temperature terms in its equations.

We conclude that the temperature terms of the thermodynamic H-H model (linear or non-linear) do not permit it to describe voltage-gated K^+ current data, over a range of temperatures, with a single set of free parameter values. The model cannot extrapolate for temperature. Why this failure?

Eyring rate theory, which underpins the thermodynamic H-H formalisms, assumes that temperature has little or no effect on the relative energies of the states (Closed, Transition, Open). Its tenet is that temperature changes the probability of moving between states, it does not significantly change the states themselves [4]. However, an ion channel is likely to breach this assumption. Protein structure is temperature dependent [10–12] and membrane lipid structure is temperature dependent. The latter is relevant because it can change ion channel structure [13,14] and also because voltage-gated channels are gated by "voltage sensor paddles", which float and move in the lipid medium [15].

Our study only investigates one K^+ current data set and so the conclusions we draw are somewhat provisional. We hope that others will build on this work and follow our methodology with other, further data sets; because our hypothesis is an important issue to address.

The Hodgkin-Huxley model, in all its forms, is an abstraction. The reality is better approximated by a Markov model [2]. It can represent different voltage-gated channel states, and how these states change with voltage and time. They can be accurate and powerful but are computationally expensive to simulate (e.g., [16,17]). So, neuron modelling studies typically use the H-H model as opposed to Markov descriptions (e.g., [18,19]). Hence the H-H model is still relevant and important [20]. Presently, thermodynamic H-H variants are not typically to be found in neuron modelling studies. However, if they can be found to provide intrinsic temperature tenability, then their incorporation will increase the predictive power of neuron models immensely.

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Conflicts of Interest

The authors declare no conflict of interest.

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