MODELING SKIN BLOOD FLOW
A Neuro-physiological Approach

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Abstract: In humans skin blood flow (SBF) plays a major role in body heat loss. Therefore the accuracy of models of human thermoregulation depends for a great deal on their ability to predict skin blood flow. Most SBF-models use body temperatures directly for calculation of skin perfusion. However, humans do not sense temperature directly, yet the information is coded into neuron fire rates. The aim of this study was to investigate whether SBF can be adequately modelled through simulation of temperature sensitive neurons and neuro-physiological pathways of excitation and inhibition. Methods: In this study a mathematical model for SBF was developed based on physiological knowledge on neural thermo-sensitivity and neural pathways. The model was fitted on human experimental data. Mean squared residuals (MSR) were estimated through k-fold cross-validation. Results: The model adequately explains the variance of the measurements (r^2=0.91). Furthermore the averaged MSR is close to the natural variation in the measurements (AMSR=0.087 vs. σ^2=0l.080) indicating a small bias. Conclusion: In this study we developed a model for skin perfusion based on physiological evidence on thermo-reception and neural pathways. Given the highly explained variance this study shows that a neuro-physiological approach is applicable for modelling skin blood flow in thermoregulation.

1 INTRODUCTION

In order to maintain the core temperature within narrow limits, the human body balances both heat gain and heat loss (Hardy and Dubois, 1937). Conservation of body heat during mild cold challenges is primarily achieved by vasoconstriction (i.e. constriction of blood vessels), which decreases skin blood flow (Kellogg, 2006). Thereby heat transport from the core to the skin is diminished and eventually heat loss to the environment is decreased. Hence, the accuracy of models of human thermoregulation depends for a great deal on their ability to predict skin blood flow. In the past various

models predicting skin perfusion responses have been developed (Parsons, 2003). What these models have in common is that they require an explicit set-point; i.e. a reference temperature which is compared with the actual body temperatures to generate error signals. The effector response (in this case vasoconstriction) is assumed to be proportional to the error signal (Mekjavic and Eiken, 2006).

Although from an engineering perspective the meaning of a set-point might be clear, application of the concept in human physiology is still under debate as it is not clear how this set-point could be contained (Romanovsky, 2007). Alternatively, it is hypothesized that thermoregulatory effectors could also be modelled by using bell-shaped neural

activation patterns of thermo-sensitive neurons, and reciprocal cross inhibition (RCI) (Bligh, 2006). An advantage of this approach is that the model structure remains true to current neurophysiologic knowledge on thermoregulation. For instance, the thermoregulatory system does not sense temperature directly, yet the information is coded into neuron fire rates (Nakamura and Morrison, 2008a). Hence skin blood flow is modelled from first principles instead of simple regression.

In this study a mathematical model for skin blood flow during cold exposure was developed based on physiological data on neural thermo-sensitivity and neural pathways. The aim of this study was to investigate whether skin blood flow can be adequately modelled through simulation of thermo-sensitive neurons and neuro-physiological pathways of excitation and inhibition.

2 METHODS

The model for the central control of skin blood flow was based on thermal reception and neural pathways that were mostly established by in vivo animal experiments. To underline the importance of modelling physiological responses from first principles we first address the physiological mechanisms, thereafter a mathematical translation is described.

2.1 Physiology of Vasoconstriction

Physiological experimental evidence indicates that skin flow is regulated by both reflex (neural) and local mechanisms (Kellogg, 2006). Neural control of vasoconstriction is mediated by the sympathetic nervous system. Under thermoneutral conditions blood vessels are under a baseline sympathetic vasoconstrictor tone. During a cold challenge an increase in sympathetic vasoconstrictor tone causes blood vessels to constrict (Savage and Brengelmann, 1996).

The ability of the body to react to a cold challenge is determined by thermal reception, neural integration of thermal information and vessel responsiveness to the increased vasoconstrictor tone.

2.1.1 Thermal Reception

Thermal reception is mediated through temperature sensitive neurons. The steady state fire rate vs. temperature has a characteristic bell-shaped form.

In addition to steady state fire rates, temperature

dynamics influence the neuron fire rate such that cold sensitive neurons will fire more often (also referred to as bursts) during cooling than during warming in the same temperature range (Zotterman, 1953, Mekjavic and Eiken, 2006). Likewise a warm-sensitive neuron will fire more often when heated rather than cooled. Although there is spatial variation in the actual fire rate of neurons, the general response of individual temperature sensitive neurons has been accepted widely.
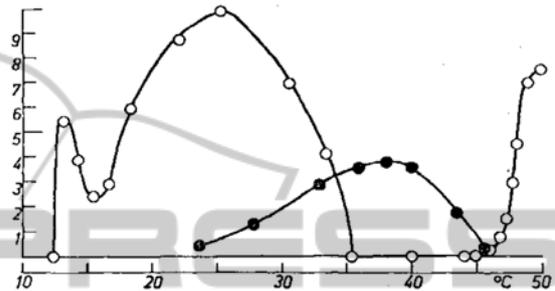
Figure 1: Figure after Zotterman (Zotterman, 1953), steady-state fire rate of cold sensitive neuron (open circle) and warm-sensitive neuron (closed circle).

2.1.2 Neural Integration

The specific integration of neural information through neural pathways is still enigmatic. However Nakamura and Morrison recently identified neural control of cold defensive responses to skin cooling in the rat (Nakamura and Morrison, 2008b, Nakamura and Morrison, 2008a). For the mathematical model we used their description of sensory pathways, effector pathways and related neuronal circuits (see Figure 1). Nakamura and Morrison showed that in a neutral situation, when there is virtually no cool input from the skin, cold defence pathways are inhibited by warm sensitive neurons in the hypothalamus. Hence, no vasoconstriction occurs. However, during environmental cooling, cold sensitive neurons at the skin are excited and increase their fire rate. Information of individual neurons is combined in neurons of the spinal cord where it is transmitted to the hypothalamus. There the warm sensitive neurons in the hypothalamus are inhibited, which leads to the increase of sympathetic adrenergic tone and ultimately vasoconstriction.

2.2 Modelling of Vasoconstriction

The description of thermal reception and neural integration was schematized in a diagram (See Figure 2).

In the left part of the figure local skin temperatures are transduced into neural coded information by cold and warm sensitive neurons. In the spinal cord section information from individual neurons is combined and transmitted to the hypothalamus. Warm sensitive neurons in the hypothalamus transduce core temperature and are inhibited by cold sensitive neurons from the periphery, whereas peripheral warm sensitive neurons perform an excitatory role. Control neurons responsible for cold defence pathways are inhibited by the warm sensitive neurons in the hypothalamus.
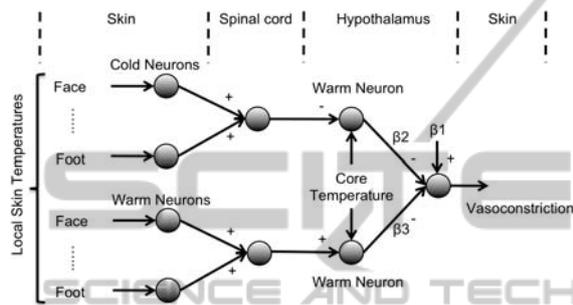
Figure 2: Schematic of neuronal model for control of skin blood flow. + and – denote excitatory or inhibitory pathways; $\beta1$ denotes the averaged combined effect of other inputs than thermoreception on skin blood flow; $\beta2$ and $\beta3$ denote weighing of the inhibition of the cold defense pathway by warm sensitive neurons in the hypothalamus.

2.2.1 Thermal Reception

The neural input for the model is based on activation patterns of thermo-sensitive neurons on the skin and in the core region of the body. Simulation of both the static and dynamic components of thermo-sensitive neurons is based on the approach of Mekjavic and Morrison (Mekjavic and Morrison, 1985). In their study they performed a polynomial fit of the static fire rate of temperature sensitive neurons. However, a typographical error seems to have slipped in their table of coefficients. Here we corrected the coefficients of the 2nd order of the polynomial for warm receptors as 0.7707699×10^3 and the coefficient of the 6th order of the polynomial for cold receptors as -0.26343323×10^0, see Table 1 for the used coefficients.

Equations 1 to 3 describe the simulation of the neuron fire rate (adjusted from Mekjavic, 1985):

$$C_{i,t} = \frac{1}{\Delta t} \sum_{j=0}^{j=\Delta t-1} F_1 + \left(A_0 \left(1 - e^{-j/K} \right) + P \times A \left(e^{-j/K_e} - e^{-j/K_i} \right) \right) \quad (1)$$

Here $C_{i,t}$ is the neural response at location i and time t (C for cold sensitive neurons, W for warm sensitive neurons); Δt is the time interval (60 sec); F_1 is the static neuron fire rate at $t=t-1$. A_0 and A are static gain factors that depend on the difference static fire rates between two moments in time.

$$A_0 = F_2 - F_1 \quad (2)$$
$$A = 5.0 \cdot F_1 \cdot |A_0| \quad (3)$$

Table 1: Coefficients for the 10th order polynomial function of static neuron fire rate as given in Mekjavic and Morrison (1985). Coefficients in bold are corrected values.

Polynomial order	Cold sensitive neuron	Warm sensitive neuron
0	-0.19005313e6	0.1526647e5
1	0.85318078e5	-0.5147704e4
2	-0.16974919e5	**0.7707699e3**
3	0.19724509e4	-0.67475955e2
4	-0.14833377e3	0.38244284e1
5	0.75486723e1	-0.14664175e0
6	**-0.26343323e0**	0.38526706e-2
7	0.62289589e-2	-0.68496075e-4
8	-0.95563808e-4	0.78889647e-6
9	0.85949930e-6	-0.53173142e-8
10	-0.34432887e-8	0.15936041e-10
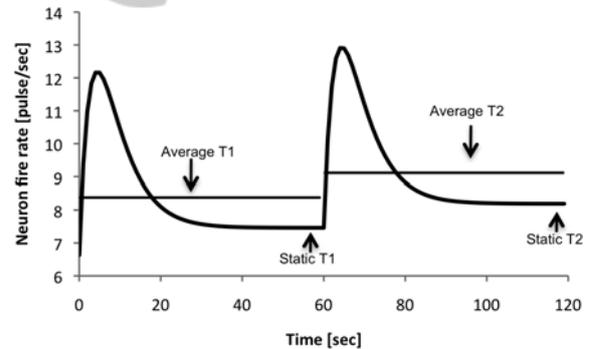
Figure 3: Example of simulated neuron response using Equation 1. The peak indicates an excitatory response, after which the fire rate returns to its static level. The dynamic component is larger for larger variations in temperature. The average fire rate during 1 minute was used as the input fire rate for the model.

$K=5.5$, $K_i=3.3$ and $K_e=5.5$ are static, inhibitory and excitatory gain factors respectively. P is a sign operator indicating an inhibitory or excitatory response. When cold sensitive neurons are heated P is negative, when the same neurons are cooled P is positive; vice versa for warm sensitive neurons. See Figure 3 for an example of neuron simulation.

2.2.2 Neural Integration

As can be seen in Figure 2, neural information from skin sites was integrated at the spinal neurons. From then on, neuron response was considered as a neural drive. The resulting neural drive (N) from cold (C) and warm (W) sensitive neurons was defined as the average fire rate over all locations.

$$N_{Skin,Cold} = \frac{\sum C_{i,t}}{n_{loc}} \qquad (4)$$

$$N_{Skin,Warm} = \frac{\sum W_{i,t}}{n_{loc}} \qquad (5)$$

It should be pointed out that due to the non-linear characteristics of neuron fire rates, as a function of temperature and temperature history, the mean skin temperature was not used to calculate the neural drive. For example, given two temperatures $T_1 = 25°C$ and $T_2 = 35°C$, due to the bell-shaped form of the static neuron fire rate, the neuron fire rate of the averaged temperature (30°C) is not equal to the averaged neuron fire rates at T_1 and T_2.

The hypothalamic neural drive was calculated as the neural response to core temperature. The response of neurons in the body core is shifted by 2°C (Mekjavic and Morrison, 1985). Inhibition of core neural drive by peripheral cold neurons was calculated by subtraction of cold peripheral neural drive from the core neural drive. Likewise, excitation of core neural drive by peripheral warm neurons was simulated by addition of warm peripheral neural drive on the core neural drive.

$$H_{cold} = N_{Core,Warm} - N_{Skin,Cold} \qquad (6)$$

$$H_{warm} = N_{Core,Warm} + N_{Skin,Warm} \qquad (7)$$

Here H denotes the net hypothalamic neural drive of either warm or cold pathway and N denotes the neural drive of neurons given their position and type.

Weighting factors for the neural drive on cold sensitive neurons ($\beta2$ and $\beta3$ in Figure 2) were estimated by least squares regression using the following model:

$$y = \beta_1 - \beta_2 H_{cold} - \beta_3 H_{warm} \qquad (8)$$

Here y denotes the perfusion response. The constant $\beta1$ can be interpreted as the averaged combined effect of other factors on skin blood flow.

2.3 Validation

The model is validated by k-fold cross validation. This method maximizes the available data by fitting the model on the average response of n-1 subjects and calculating the mean squared residuals (MSR) on the remaining subject.

$$MSR = \sum \frac{(y_t - f(x_t))^2}{n} \qquad (9)$$

Where y_t is the measured perfusion at time point t, $f(x_t)$ is the model prediction at t and n is the number of measurement points in one recording. The MSR provides a measure of the quality of the model prediction, irrespective of the length of measurement. This process is iterated k times ($k=n$) where each fold the model is fitted and tested on a unique subset. Hence k-fold cross validation provides a measure of the ability of the model to predict the vasoconstriction response over individuals whilst maintaining the experimental conditions constant. The average MSR over k iterations is used as general measure of the capability of the model to predict perfusion.

2.4 Experimental Protocol

Eight young adult males (18 to 28 yrs) were included (characteristics in Table 2). All subjects were healthy, non-obese and not taking medications. Subjects were in fastened state and refrained from caffeinated or alcoholic beverages in the morning prior to the test. The medical ethical committee of Maastricht University Medical Centre+ approved the study. Each subject gave verbal and written informed consent prior to participation in the study. All procedures conformed the standards of the Declaration of Helsinki.

Table 2: Subject characteristics.

Variable	Mean $\pm$ SE
Age, yr	23.63 ± 1.05
Height, m	1.81 ± 0.02
Mass, kg	69.05 ± 3.49
BMI, kg/m^2	21.07 ± 1.07
Mean BP, mmHg	85.00 ± 1.98
Whole body fat, %	15.93 ± 1.60
Leisure Activity Level	3.34± 0.19

2.4.1 Protocol

Subjects arrived at the laboratory at 9:00 a.m. Skin temperature was measured in 1-minute intervals by

i-buttons (type DS1921H; Maxim/Dallas Semiconductor Corp., USA) at the 14 positions of the ISO standard for mean skin temperature (Parsons, 2003, van Marken Lichtenbelt et al., 2006). Core temperature was measured in 1-minute intervals using a telemetric pill (Coretemp,USA). Whole body skin temperature was controlled by a water perfused suit (DTI, TUBEsuit) in combination with a water temperature control unit (Blanketrol II, Cincinnati Sub-Zero). Skin perfusion was sampled at 8Hz using laser-Doppler flowmetry (Perimed, PF 5000, Sweden) at the ventral side of the hand between the base and metacarpal of the thumb. Custom made Peltier elements in the casing of the probe allowed for local temperature control. Whole body fat percentage was measured using Dual X-ray absorptiometry. Leisure activity level was indexed by a Baecke questionnaire. Subjects were in supine position and were able to watch TV. Room air temperature was kept at 24°C. A small draft in the room was allowed to assure sufficient ventilation. Before starting the measurements subjects maintained in supine position for 1 hr to become accustomed to the environment. During this period the temperature of the water suit was maintained at 33.5°C. Measurements were divided in a 15-minute baseline period where the water temperature of the suit was kept at 33.5°C followed by 15-minutes of whole body cooling where the temperature control unit was set to 10°C. Short term cooling was preferred to minimalize the influence of other factors than acute sympathetic activation of the nervous system on vasoconstriction (Johnson, 2007). To avoid interference from local skin perfusion regulation, local skin was clamped at 33°C throughout the entire experiment (Kingma et al., 2010).

2.5 Data Handling

Data handling and model development was performed using Matlab R2007a, figures were created with Microsoft Excel 2008 for Mac; statistical tests on subject characteristics were performed with SPSS16.0 for Mac. Perfusion data was resampled to 1-minute intervals using a (lowpass) FIR filter and normalized over the baseline period. Temperature data were sampled on a minute base. Peripheral warm and cold neuron fire rates were simulated in 1-minute intervals for each measured location and sequentially averaged over subjects.

3 RESULTS

Estimated coefficients, regression statistics and k-fold cross validation results of the neural model are presented in Table 3.

Table 3: Estimated model coefficients, $\beta1$: model constant; $\beta2$: integrated pathway of peripheral cold neurons and hypothalamic warm neurons; $\beta3$: integrated pathway of peripheral warm neurons and hypothalamic warm neurons. Regression statistics: p-value, r^2 and averaged mean squared residuals (MSR).

$\beta1$	25.48
$\beta2$	-1.44
$\beta3$	3.26
R^2-value	0.91
p-value	p<0.001
Averaged MSR	0.087
Averaged variance	0.080

Neural model regression analysis yielded significant fits on the measured data. Given the high r^2–values the majority of the measured variance could be explained by the model (Table 3). Furthermore the averaged MSR of the k-fold cross validation is close to the time-averaged variance in the measurements, indicating that there is a small bias in the model prediction.

Perfusion measurements and the model prediction are shown in Figure 4. After t=15 subjects were cooled and vasoconstriction is observed immediately. After 10 minutes of cooling perfusion reached a nadir. The fitted line through the data points represents the prediction of the neural model.
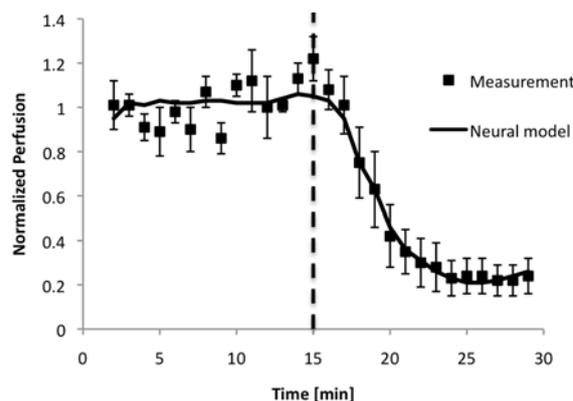
Figure 4: Measured and fitted perfusion response. After 15 minutes whole body cooling was performed. Error bars represent SEM.

4 DISCUSSION

In this study a model for skin blood flow during cold exposure was developed based on neuro-physiological concepts. Simulation of thermo-reception through warm and cold sensitive neurons was adapted from work by Mekjavic and Morrison (Mekjavic and Morrison, 1985). Pathways of neural integration were based on animal experiments by Nakamura and Morrison (Nakamura and Morrison, 2008a, Nakamura and Morrison, 2008b). Neural drives that were calculated by the model were fitted to human experimental data on hand skin perfusion. Given the high value of explained variance, the model predicts vascular responses to a mild thermal cold stimulus adequately. Furthermore, the averaged MSR values are close to the variance of the measurements. Therefore, this study shows that an explicit declaration of a set point is not necessary for modelling skin perfusion during short term cooling.

4.1 Limitations

The neuron response and neural afferent pathways are established in small mammals and projected on human response. Therefore, the modeled pathways might deviate from the actual pathways in humans. However, as long as no detailed human studies on neural pathways and integration are available we have to rely on these elaborate animal studies.

In general the thermoregulatory response is subject to both thermal factors and non-thermal factors like exercise or pathologies like motion-sickness and fever (Mekjavic and Eiken, 2006). The experimental set-up was developed to minimize the influence of other factors than central sympathetic regulation on vasomotor response. Also, other factors such as humoral effects, or local regulation (Q_{10}-effect) are now neglected, but are known to affect vasoconstriction. Therefore no conclusion can be made on the relative influence of factors that work either before or after the reciprocal cross-inhibition.

The authors acknowledge that the current model coefficients were not validated against data sets with different experimental conditions. Therefore it is not possible to conclude that the coefficients hold for other types of thermal challenges.

In this study we did not incorporate the effect of differences in spatial thermo-sensitivity. With a greater dataset it might be possible to assign weights to the individual branches of thermo-sensitive input (face, hand, chest, etc.). It is however not possible to use data of published studies, because usually mean skin temperatures are presented. Our model instead requires local skin temperature data.

5 CONCLUSIONS

In summary, this study presents a mathematical model for skin blood flow during cold exposure based on thermo-sensitive neurons and neuro-physiological pathways. The model was fitted to experimental data where young adult males were exposed to a short mild cold exposure. The model explained over 90% of the variance in the measurements (r^2=0.91). Hence, although further research is warranted, the results of this model based on first principles of neuro-physiological control of skin blood flow are promising.

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