Developing a Model to Simulate the Effect of Hypothermia on Cerebral Blood Flow and Metabolism

Joshua Russell-Buckland and Ilias Tachtsidis

Abstract Hypoxic ischemic encephalopathy (HIE) is a significant cause of death and neurological disability in newborns. Therapeutic hypothermia at 33.5 °C is one of the most common treatments in HIE and generally improves outcome; however 45–55% of injuries still result in death or severe neurodevelopmental disability. We have developed a systems biology model of cerebral oxygen transport and metabolism to model the impact of hypothermia on the piglet brain (the neonatal preclinical animal model) tissue physiology. This computational model is an extension of the BrainSignals model of the adult brain. The model predicts that during hypothermia there is a 5.1% decrease in cerebral metabolism, 1.1% decrease in blood flow and 2.3% increase in cerebral tissue oxygenation saturation. The model can be used to simulate effects of hypothermia on the brain and to help interpret bedside recordings.

Keywords Broadband NIRS · Hypothermia · Systems biology

1 Introduction

Hypoxic-ischaemic encephalopathy (HIE), often resulting from intrapartum hypoxic-ischemic (HI) injury, is a significant cause of death and morbidity. Somewhere between 700,000 deaths amongst neonates can be attributed to HIE alone [1]. Following neonatal HI injury or birth asphyxia, infants are treated with therapeutic hypothermia at a temperature of 33.5 °C, as well as a variety of medications such as morphine and atracurium [2]. However, 45–55% of cases treated with hypothermia end with death or moderate to severe neurodevelopmental disability [1, 3]. The brain of neonates undergoing hypothermia treatment is monitored through a variety of methods such as electro-encephalography (EEG) [4] and

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near-infrared spectroscopy (NIRS) [2, 5]. Additionally, in the few hospitals with appropriate facilities, when the infant is stable enough (usually a week after birth) and following treatment they image the brain with magnetic resonance spectroscopy (MRS) [6]. The collected multimodal data can provide not only diagnostic and prognostic information but also insights on the mechanisms of the injury.

Our approach to analyse this multimodal data has been multifaceted and includes the development and application of (1) a physiology-informed 'mathematical model' of the cerebral circulation under a systems biology approach, which is specially designed for the interpretation of NIRS signals [7–12]; and (2) 'signal processing' methods quantifying the interrelationships between signals both in time- and frequency-domain to quantify indices of cerebral blood flow, oxygenation and metabolic regulation [2, 5].

The development of systems biology-based models begin with the 'BRAINCIRC' model in 2005 [7]. This built on an earlier circulatory model by Ursino and Lodi [13] and combined models for the biophysics of the circulatory system, the brain metabolic biochemistry and the function of vascular smooth muscle. This model was succeeded by the 'BrainSignals' model [8], which simplified the previous BRAINCIRC model and added a submodel of mitochondrial metabolism. Additional versions were then developed from this, such as the 'BrainPiglet' model [9] which was developed to interpret data collected from a piglet model. It involved modifying the default values for 11 of the 107 parameters used and was extended to include simulated measurements for magnetic resonance spectroscopy values, which are available for the piglet model. In 2015, Caldwell et al. modified the BrainSignals model to produce the 'BrainSignals Revisited' model [10]. This made various simplifications to the BrainSignals model to reduce complexity and decrease the time taken to run a simulation, whilst being able to reproduce the same results and behaviour of the original model. This reduced model was later extended in 2016 to simulate scalp haemodynamics to produce the 'BSX' model [11]. This could be used to investigate the potential for systemic haemodynamics to confound fNIRS haemoglobin signals. The BrainPiglet model was also extended to model cell death following HIE producing the 'BrainPigletHI' model [12]. This history is shown schematically in Fig. 1.

However, the existing mathematical models have been developed to model brain physiology under 'typical' conditions, particularly at normal body temperature. In order to properly interpret data collected during therapeutic hypothermia, the models need to be able to reflect these biological conditions. It has been observed that both cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF) in piglets decrease with reduced body temperature [14]. For reliable inferences to be made through the use of systems biology models, they must be able to simulate this behaviour.

We present a new systems biology model of the piglet brain, a common animal model for the human neonatal brain, which incorporates temperature effects in the brain tissue physiology. This is an expansion of the BrainPigletHI model, as seen in [12]. The model is used to demonstrate how brain tissue temperature impacts brain physiology steady state behaviour for changing blood pressure, arterial oxygen saturation and partial pressure of CO_2. It is then shown how decreasing temperature impacts a variety of measurable signals.

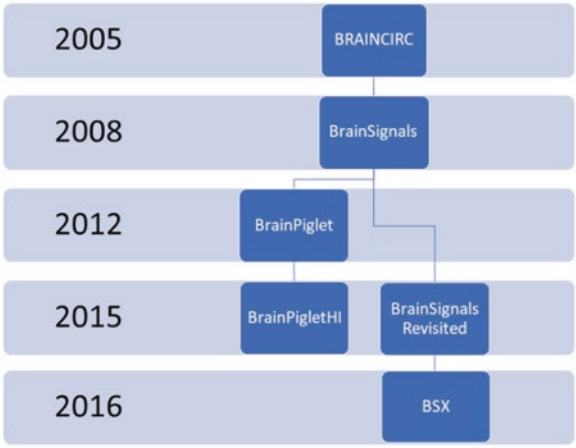

Fig. 1 History of the brainsignals family of models. A general overview of the brainsignals model history. The first model was the BRAINCIRC model in 2005, followed by the brainsignals model in 2008. This model was adapted for the physiology of piglets, a common neonatal preclinical animal model, in 2012 producing the brainpiglet model. The brainpiglet model was modified to include cell death in 2015, to produce the brainpigletHI model. Also in 2015, the brainsignal model was refactored for speed and clarity, producing the brainsignals revisited model. This was extended in 2016 to include scalp haemodynamics, producing the BSX model

2 Methods

Temperature is already incorporated into the BrainPiglet model as a constant value within the proportionality constant $Z = RT/F$, where R is the ideal gas constant, F is the Faraday constant and T is absolute body temperature. The constant Z is used within the model to determine the equilibrium constant for a variety of metabolic reactions, such as electron transfer within mitochondria. By making Z a function of temperature, temperature modulated electron transfer is incorporated into the metabolic submodel.

Temperature also impacts the rate of other reactions and processes, such as diffusion or Michaelis-Menten type behaviour. Orlowski et al. [15] expanded an existing model of cellular metabolism by incorporating temperature dependence into the rates of reaction and ion diffusion and a similar approach is taken here. Reaction rates, Michaelis-Menten rate constants and diffusion rates are modified by a quantity

$$k_{i,new} = k_{i,previous} \times Q_{10}^{\frac{T_{new} - T_{previous}}{10.}}$$

where $k_{i,\,new}$ is the new rate constant for reaction i at the new temperature T_{new}, $k_{i,\,previous}$ is the rate constant at temperature $T_{previous}$, and Q_{10} is the temperature

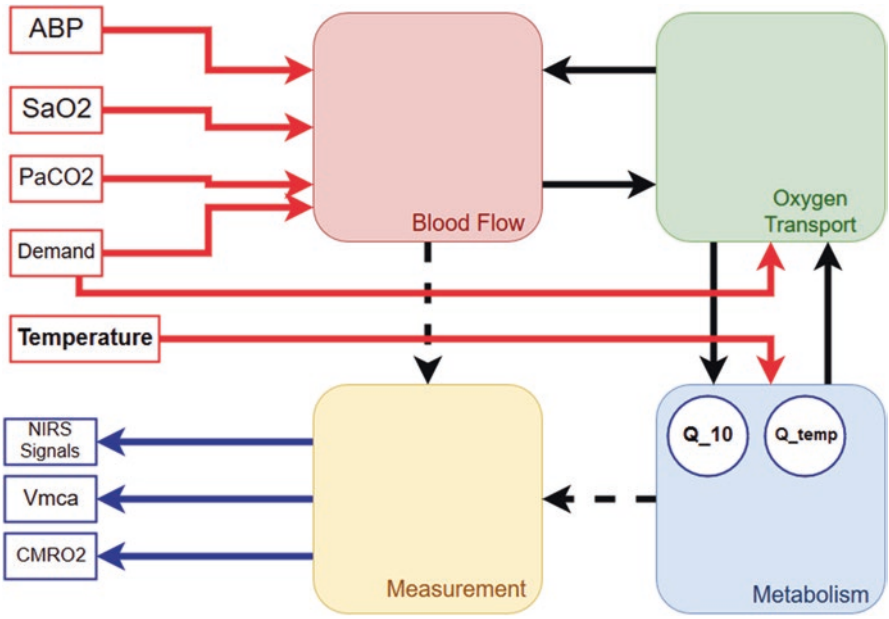

Fig. 2 General structure of the brainpiglet hypothermia model. Model inputs, arterial blood pressure (ABP, arterial oxygen saturation (SaO2), partial pressure of CO_2 (PaCO2) and demand, and outputs are shown, as well as each of the four sub-models and the general relations between each. New additions are shown in bold. Temperature is added as an input to the model. Q_10, a measure of the change in reaction rate when increasing temperature by 10 °C, is a new parameter. Q_temp, the factor by which a reaction rate is modified when changing temperature, is added as a new internal state variable local to the metabolism submodel

coefficient, defined as the ratio of reaction rates measured for the same reaction at two temperatures 10 °C apart, with an initial default value of 2.23, as per [15], but an expected final value within the range of approximately 2–3 as per most biological reactions [16]. Typically, $T_{previous}$ will be assumed to be normal body temperature of 37 °C, but this can be set as a model parameter. For simplification purposes, within the model

the temporary variable $Q_{temp} = Q_{10}^{\frac{T_{new} - T_{previous}}{10}}$ is defined. Figure 2 shows a simplified schematic of the model structure, with the new model additions of temperature, Q_{10} and Q_{temp} shown in bold.

Models were then tested and verified through steady state simulations, at 37 °C, 35 °C and 33.5 °C, varying arterial blood pressure, arterial oxygen saturation and partial pressure of CO_2. Following this, all model inputs except temperature were kept at their default values, whilst temperature was decreased between 37 °C and 33.5 °C for varying values of Q_{10}.

3 Results

Steady state simulations were carried out at three temperatures (33.5 °C, 35 °C and 37 °C) to investigate the effects of hypothermia on brain vascular autoregulation. The three main measured inputs of arterial blood pressure (P_a), arterial oxygen saturation (SaO_2) and partial pressure of CO_2 ($PaCO_2$) were both increased and decreased with CBF simulated at the end of 100 s at each step change. Figure 3 shows that cerebral autoregulation is preserved at all temperatures and for both increasing and decreasing changes in P_a, SaO_2 and $PaCO_2$.

Following this, the effect of decreasing temperature on physiology within the model was investigated through further use of steady state simulations. Temperature was decreased to 33.5 °C with all other inputs kept at baseline values for a range of Q_{10} values. Without a known value of Q_{10} it was important to investigate a range of values to ensure that the full range of model behaviour could be considered. As with the autoregulation simulations, output values were simulated after 100 s at each temperature step. Outputs considered are: (a) brain tissue oxygenation saturation (StO_2), (b) CBF, (c) brain tissue haemoglobin differences changes (ΔHbD = oxyhaemoglobin-deoxyhaemoglobin), (d) brain tissue changes in the concentration of the oxidation of cytochrome-*c*-oxidase (ΔoxCCO), and (e) cerebral metabolic rate of oxygen ($CMRO_2$). Figure 4 shows that, across all outputs except StO_2 and ΔHbD, the output decreases linearly, whilst for StO_2 and ΔHbD an increase in value is, instead, observed as temperature decreases. The rate of change increases with Q_{10}.

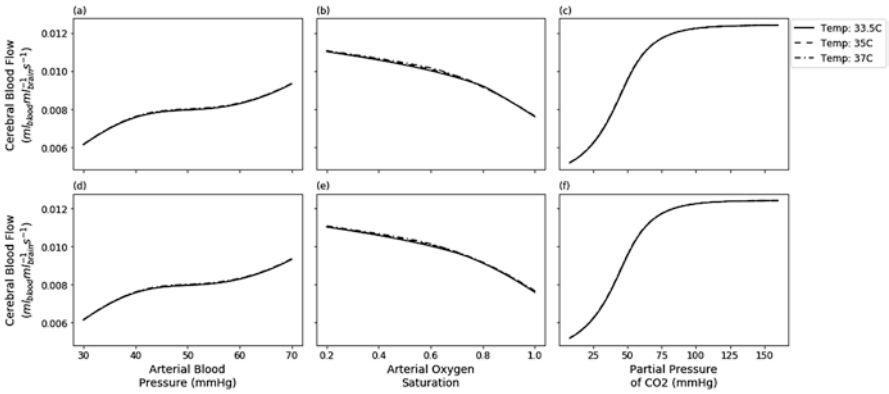

Fig. 3 Steady states curves showing cerebral blood flow against increasing (a) arterial blood pressure; (b) arterial oxygen saturation; (c) partial pressure of CO_2 and decreasing (d) arterial blood pressure; (e) arterial oxygen saturation; (f) partial pressure of CO_2 for temperatures of 33.5 °C, 35 °C and 37 °C. It can be seen in all figures that autoregulation is preserved across all three temperatures and there is little difference between increasing and decreasing values of input

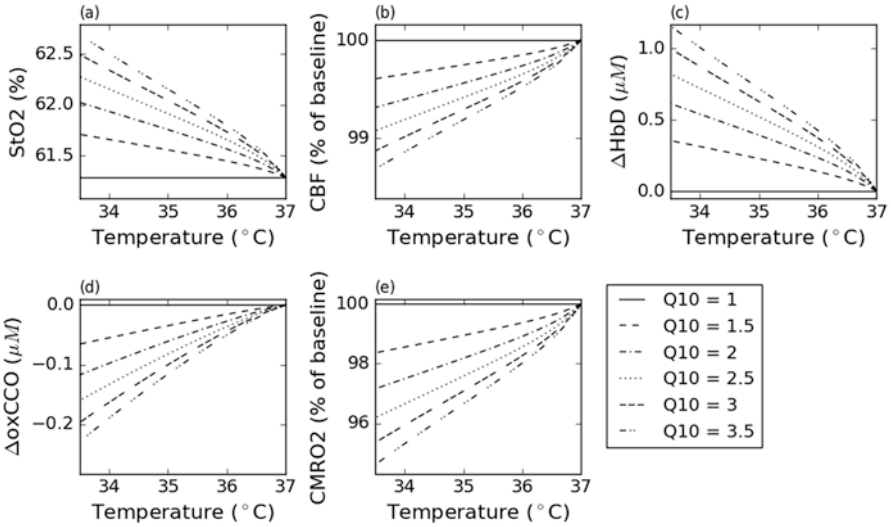

Fig. 4 Steady state curves showing the effect of decreasing temperature on (a) total oxygenation index; (b) cerebral blood flow; (c)velocity of the middle cerebral artery; (d) change in concentration of cytochrome-*c*-oxidase; (e) cerebral metabolic rate of oxygen for varying values of Q_{10}. Steady state simulations show expected behaviour across outputs, where information is available to confirm, such as the decrease cerebral blood flow and cerebral metabolic rate of oxygen with decreasing temperature down to 33.5 °C. The observed change is linear, with the rate of change increasing with the Q_{10} value

Considering Q_{10} values of 2.5, which is in the middle of the range given previously for most biological reactions, and 3.5, which is the largest value considered, CBF decreases by 1.1% and 1.6%, respectively whilst the $CMRO_2$ decrease by 5.1% and 7.1% respectively. StO_2 increases by 2.3% and 3.2% of normothermic values respectively.

4 Discussion

We have expanded an existing systems biology model of the piglet brain physiology to include the impact of hypothermia. This has been done by introducing a minimal number of new parameters and inputs and is able to produce qualitatively reasonable results. Simulations of cerebral autoregulation agree with the findings of Lee et al. who found that hypothermia did not change autoregulation within a piglet model for both hyper- and hypotensive changes [17] (Fig. 3).

When considering the effect of temperature on various measurable outcomes, we see that both CBF and $CMRO_2$ decrease with decreasing temperature, as found by Ehrlich et al. [9]. Whilst the model changes are smaller than those found by Ehrlich et al., the final cooled temperature is not as low and it is not the intention of the

model to simulate below a temperature of 33.5 °C. We expect changes in brain physiology at this temperature to be subtle but important. Below this temperature damage to the brain may occur causing a change in brain physiology not captured by this model.

Systems biology models were previously used by our group to investigate the effect of HI in the piglet model [12]; however, they were not able to incorporate the impact of therapeutic hypothermia alongside this injury. In particular, it was found that the pre- and post-injury brain is sufficiently different to require refitting of the model and a number of measurable differences could be explained through the incorporation of a parameter representing cell death within the brain. By combining this previously developed approach with the new hypothermia model, it may be possible to further explain other behaviour. We aim to apply the model to broadband NIRS data, including cytochrome-*c*-oxidase measurements, collected within the group that show differing responses to hypothermia in piglets who received the same injury. We will apply the model to data collected from human neonates, where we expect the same model structure to apply but with different model parameters to reflect the difference in human and pig physiology.

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