In silico model of critical cerebral oxygenation after traumatic brain injury: Implications for rescuing hypoxic tissue

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Abstract:

Cerebral oxygen delivery is central to the modern intensive care of patients with severe traumatic brain injury. Low brain tissue oxygen tension ($P_{bt}O_2$) results from microvascular collapse and diffusion limitation and is associated with adverse outcome. A number of therapies to improve oxygen delivery are known to be effective in improving $P_{bt}O_2$. However their relative effectiveness and microscopic regions of hypoxia may exist/persist even in the presence of normal $P_{bt}O_2$. Unfortunately there are currently no methods for assessing this quantitatively.

We used an *in silico* (computational) simulation approach to understand the effect of common interventions on the microscopic distribution of brain tissue oxygen tension. We constructed a non-linear mathematical model of cerebral oxygen supply, diffusion and consumption for a simplified geometry. Model parameters were chosen to agree with clinical parameters. We found that it was possible to create a plausible diffusion-limited scenario with a significant hypoxic fraction by increasing the mean diffusion distance. *In silico* simulations can be useful in understanding the likely physiological effect of complex treatments for which measurement techniques do not exist. We found that increasing cerebral blood flow / blood oxygen content or suppressing cerebral metabolic rate were most effective at improving $P_{bt}O_2$ and reduced the hypoxic fraction. Within the limitations of our modelling assumptions, increasing the arterial oxygen partial pressure was less effective and only improved $P_{bt}O_2$ by creating a region of hyperoxic tissue with no improvement in hypoxic fraction.

Key words: Adult brain injury, traumatic brain injury, head trauma, blood flow

Introduction:

Traumatic Brain Injury (TBI) is a major cause of death and serious disability with global importance.[1] The critical care of patients with severe TBI is predicated on the assessment and optimization of cerebral oxygen delivery. The relatively high metabolic rate and limited reserve of brain tissue alongside the pathological evolution of TBI make the brain both prone and sensitive to dysoxia. This may occur as a result of a number of processes[2] which may vary from patient to patient or over time so care must be individualized. Multimodality monitoring, including the invasive measurement of $P_{bt}O_2$ with implantable oxygen-sensitive probes is widely used in neuroscience intensive care to diagnose the dominant pathology so that the most appropriate therapy can be instituted in a timely manner.[3]

Invasive $P_{bt}O_2$ measurement allows real-time assessment of the adequacy of oxygenation and has largely replaced jugular bulb oximetry as it is safe, accurate, easy to use and has a fast response time. A clear relationship between low $P_{bt}O_2$ and adverse outcome[4] has been established in numerous observational studies. Recently a Phase II study[5] has prospectively demonstrated the safety and feasibility of using brain tissue oxygenation measurements to guide therapy and even suggested a trend towards improvements in outcome-- a Phase III study is being planned. The study showed that a wide variety of interventions targeting cerebral oxygen supply or demand can be effective in improving low $P_{bt}O_2$ including improving cerebral blood flow, transfusion, cerebral metabolic suppression or increasing arterial oxygen tension PaO2 (for example by manipulating inspired oxygen concentration, F_IO_2, or manipulating ventilator positive end expiratory pressure, PEEP). However it is not clear *a priori* that all these interventions are equally effective or equivalent at the cellular level.

Indeed the interpretation of such cerebral oximetry measurements is not completely straightforward as $P_{bt}O_2$ is not only determined by the balance between oxygen supply and metabolic rate/mitochondrial utilization, but it is also greatly influenced by disturbances of diffusion.[6, 7] Perivascular oedema and capillary collapse has been demonstrated to be an important pathophysiological process[8] and therefore the mean oxygen diffusion path length may be greatly increased in these patients. Thus diffusion hypoxia appears to be critical to the pathology of TBI.[2]

In addition to macroscopic variations in oxygen tension due to lesions, at microscopic scales local oxygen tension may also vary significantly spatially and islands of hypoxic tissue distant from arteriolar capillaries have been seen in intravital microscopy measurements in animal models in pathology.[9, 10] $P_{bt}O_2$ is not directly sensitive to the microscopic distribution of oxygen tension but is instead a spatial average over larger scales. It therefore follows that it is possible to observe a

relatively normal $P_{bt}O_2$ even in the presence of a substantial hypoxic fraction if there is simultaneously balanced by a large volume of tissue with substantially higher oxygen tension. Unfortunately there are no clinical techniques available for detecting the presence of such microscopic regions of hypoxia.

"Halos" of flavoprotein fluorescence indicating a more oxidized redox state have been demonstrated around arterioles using intravital microscopy.[10] Interventions that increase $P_{bt}O_2$ by increasing the oxygen tension in already hyperoxic regions rather than improving the hypoxic fraction will not only fail to be beneficial but may actually be harmful as hyperoxia may lead to damage through oxidative stress and has been associated with higher in-hospital mortality.[11]

Unfortunately, there are to date no clinically available methods for quantitative oxygenation assessment with a spatial resolution capable of resolving the microscopic distribution of oxygen tension in the tissues. In this work, we use a novel modelling approach to quantitatively address this problem in the absence of techniques for clinical measurements. We construct a mathematical description of oxygen delivery, diffusion and consumption in a simplified microcirculatory geometry and solve it numerically. The model geometry was chosen as a balance between numerical complexity and physiological accuracy. A more realistic model would include the varied shapes and connection of the capillary network but this would be significantly more difficult to interpret and computationally intractable. Similarly, we model the global behaviour of oxygen diffusion rather than creating a realistic model of a heterogeneous brain. We therefore present a simplified model that illuminates physiological principles not apparent without a numerical approach. In this way we are able to conduct *in silico* experiments to compare and understand the effects of different therapies on the distribution of oxygen tension in brain tissues.

Materials and methods:

Mathematical model specification

The simulation geometry and parameters are depicted in Fig 1. We begin by assuming a homogeneous tissue with isotropic diffusivity for oxygen given by D and oxygen consumption per unit volume

$$\Omega = \Omega\left(\mathrm{P}_{O_2}(\mathbf{r})\right)$$

which is a non-linear function of P_{O_2} to allow for the fact that $CMRO_2$ is suppressed under conditions of hypoxia. Assuming that the concentration of oxygen is equal to the product of the partial pressure of oxygen and solubility, σ, then Fick's law of diffusion can be written as;

$$\frac{\partial P_{O_2}(\boldsymbol{r})}{\partial t} = D\nabla^2 P_{O_2}(\boldsymbol{r}) - \frac{\Omega\left(\mathrm{P}_{O_2}(\mathbf{r})\right)}{\sigma}$$

For the capillary geometry, it is convenient to assume a simple cylindrically symmetrical arrangement of capillaries first described by Krogh[12] where capillaries of radius a are spaced a distance $d \gg a$ apart and oriented along the z-axis (see Fig 1). For simplicity, we assume symmetrical boundary conditions. We can re-cast the above equation in cylindrical polar coordinates, viz.

$$\frac{\partial y}{\partial x} = D\left\{\frac{\partial^2 \mathrm{P}_{O_2}(\mathbf{r})}{\partial r^2} + \frac{1}{r}\frac{\partial \mathrm{P}_{O_2}(\mathbf{r})}{\partial r}\right\} + D\,\frac{\partial^2 \mathrm{P}_{O_2}(\mathbf{r})}{\partial z^2} - \frac{\Omega\left(\mathrm{P}_{O_2}(\mathbf{r})\right)}{\sigma}$$

Under equilibrium conditions, $\partial P_{O_2}(\boldsymbol{r})/\partial t = 0$ and if we neglect axial oxygen diffusion, the above reduces to:

$$\frac{\partial^2 \mathrm{P}_{O_2}(\mathbf{r})}{\partial r^2} = \frac{\Omega\left(\mathrm{P}_{O_2}(\mathbf{r})\right)}{\sigma D} - \frac{\partial \mathrm{P}_{O_2}(\mathbf{r})}{\partial r}$$

This second order, non-linear partial differential equation is conveniently solved numerically as a boundary value problem set up so that there is no net diffusion out of the cylinder and setting PO_2 adjacent to the capillary equal to the corresponding P_aO_2.

$\Omega\left(\mathrm{P}_{O_2}(\mathbf{r})\right)$ was implemented as a sigmoid function to avoid a step-function that would destabilize the differential equation solver. The cut-off for cerebral intra-cellular metabolism was taken as 0.4mmHg.[13]

$P_{bt}O_2$ as measured by invasive tissue oximetry could then be calculated by symmetry as a spatial average of local PO_2 over the whole Krogh cylinder by:

$$P_{bt}O_2 = \frac{1}{\pi {r_K}^2 z} \iiint_{cylinder} dP_{O_2}(\boldsymbol{r})\, d\boldsymbol{r}$$

We were able to model the behaviour of $P_{bt}O_2$ as a function of a variety of parameters such as capillary length and diameter, oxygen diffusivity, flow velocity and cerebral metabolic rate.

Arterial blood is assumed to enter the capillary with an oxygen partial pressure of P_aO_2 and velocity v (related to the cerebral blood flow, CBF). Oxygen is extracted progressively as the blood passes to the venous end and the effluent blood has oxygen tension P_JO_2 from which the jugular bulb oxygen saturation ($S_{Jv}O_2$) can be calculated. Our model aims to investigate a fundamental process – the diffusion of oxygen into brain tissues – and therefore does not directly account for intra-cranial pressure (ICP), however changes in ICP will affect the cerebral perfusion pressure and cerebral blood flow and indirectly change the velocity of flow.

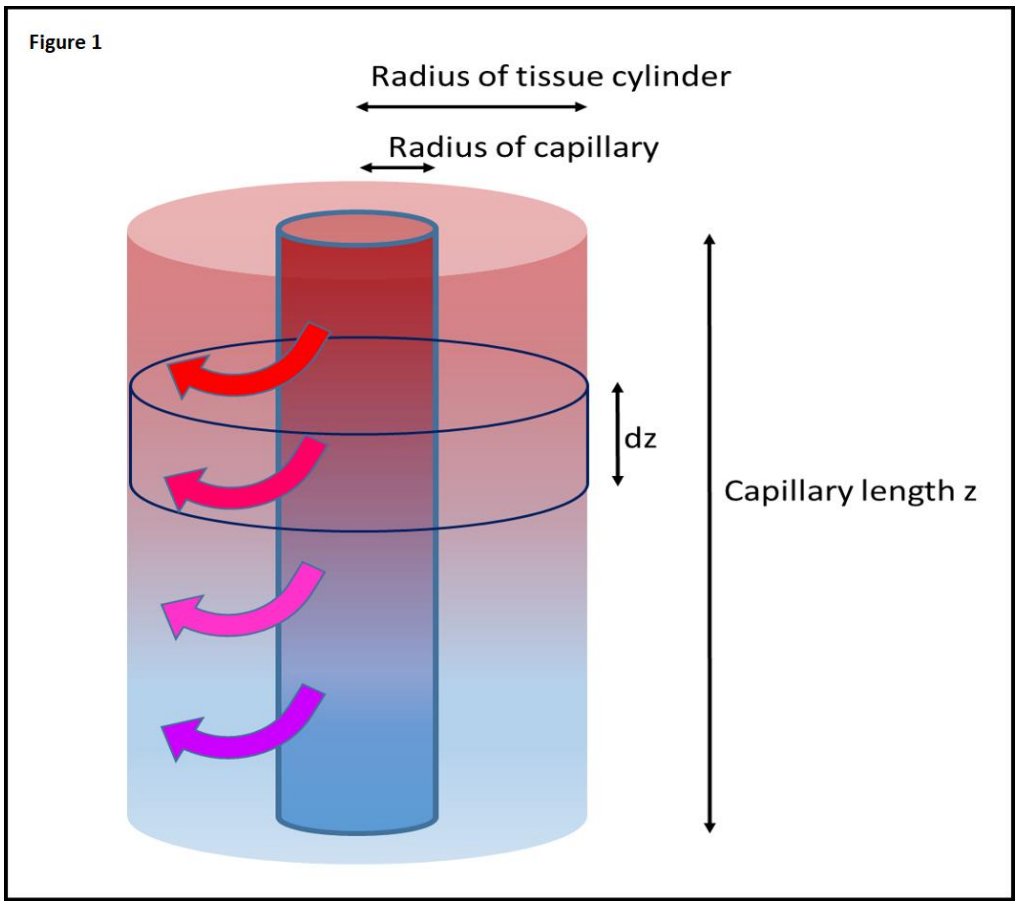

Figure 1:

Model geometry: The narrow cylindrical capillary is surrounded by a cylindrical section of tissue of length z and radius r_K. Arterial oxygenated blood enters the capillary and at each step along diffusion occurs into the surrounding tissue.

The blood oxygen content was modelled using a parameterised form of the oxygen-haemoglobin dissociation curve. Then the oxygen saturation was calculated via a look-up table from a polynomial representation of the dissociation curve, which was then used to calculate both the remaining oxygen content and the local $P_{bt}O_2$.

Perivascular oedema and capillary collapse observed after TBI[8, 14] leads to tissue hypoxia due to the increased mean inter-capillary distance (~$2r_K$). In our spatially-averaged model, we simulate diffusion hypoxia by increasing r_K; choosing this parameter to give a particular $P_{bt}O_2$ of interest. This model is therefore motivated by severe TBI processes, however, as it is based on simplified geometry and the

results are averaged over the whole brain, it is not a complete representation of severe TBI with its complex processes and regional variations.

Computational technique

Calculations were implemented in Python 3. The boundary condition differential equations were converted to a system of ordinary differential equations and solved using the solve_bvp function in the scipy package. The code was optimised to run in parallel on 16x3.3GHz Intel Xeon cores with a total of 32GB RAM on the Linux operating system. The run-time varied depending on the size of the Krogh cylinder, from a few minutes to over an hour for the largest geometries considered.

The code was written to allow for variation in both the structural input parameters (length and width of the capillary and capillary radius) and the model parameters (diffusivity, blood flow velocity, $CMRO_2$, P_aO_2 and haemoglobin). For this model we assumed that diffusivity was fixed across the microscopic model volume, however cellular architecture may mean that it is not entirely homogeneous.

The model output variables were mainly local PO_2, which was used to calculate global $P_{bt}O_2$ and jugular venous saturations ($S_{Jv}O_2$). There was no unique solution of input parameters that resulted in a set of $P_{bt}O_2$ and $S_{Jv}O_2$ therefore we chose physiologically appropriate values that resulted in $P_{bt}O_2$ and $S_{Jv}O_2$ values that corresponded with clinical data obtained for this purpose (see below).

The Krogh cylinder radius was adjusted to give the desired $P_{bt}O_2$ reflecting the change in mean intercapillary distance associated with obliteration of capillaries seen after TBI,[8, 14] producing results with a range of $P_{bt}O_2$. We then used these results as a starting point to explore the dependence of $P_{bt}O_2$ on the different parameters such as CBF, $CMRO_2$, P_aO_2 and haemoglobin concentration (Hb) reflecting clinically relevant interventions.

In addition to the $P_{bt}O_2$, we also calculated the amount of tissue that is potentially hypoxic (hypoxic fraction). The threshold for hypoxia was set according to previous studies using [18F]fluoromisonidazole positron emission tomography binding.[14] We were therefore able to calculate the volume of hypoxic tissue and explore its dependence on the input parameters.

The geometry and parameterisation does not result in an accurate representation of real-life physiology, however the model is a characterization of a microscopic process. The input parameters, e.g. CBF and $CMRO_2$ are "lumped" or aggregated global parameters that represent the overall brain tissue.

Amongst the simplifications in this model, we do not discuss the microvascular changes that may occur due to oxygen reactivity, metabolic by-product generation or nitric oxide which may compete competitively for oxygen at the mitochondrion. Such processes are not sufficiently quantitatively understood to include directly without a large number of additional, unknown, free parameters. Whilst this is a limitation, at the same time there is a conceptual benefit from adopting a more parsimonious model such as ours as this better highlights the underlying physics and physiology.

Clinical data:

In order to obtain the parameters that inform our model and validate the results, we recruited patients with severe traumatic brain injury requiring ventilation and invasive multimodal monitoring as part of their routine clinical care. Patients were recruited from the neuroscience and trauma critical care unit (UK national research ethics reference number 12/LO/0074) at Addenbrookes Hospital. Four patients (age between 18 and 64 years, three male and one female) were recruited in the period between June and September 2013. All of them were recruited in the first three days post-injury. A standardised protocol to establish the effect of increasing P_aO_2 on $P_{bt}O_2$ was used whilst simultaneously measuring ipsilateral transcranial Doppler velocity and near-infrared tissue oxygenation index (TOI) as surrogates for CBF changes and jugular bulb saturation respectively.

The F_IO_2 was increased from baseline in steps of 10 percent to 100 percent and sufficient time was allowed for equilibration of $P_{bt}O_2$ after each change. The flow velocity, TOI and $P_{bt}O_2$ were measured in addition to the standard parameters of saturations, arterial blood pressure, end-tidal CO_2 and ICP. F_IO_2 was calibrated against P_aO_2 using blood gas analysis. During the experiment the other parameters were held as close as possible to constant by adjusting inotropic support and ventilation.

Results:

Fitted model parameters:

The final fitted model parameters from combining the clinical and literature data are shown in Table 1.

Table 1

Structural parameters:	
Capillary radius	3 µm
Krogh cylinder radius	20 µm to 35 µm
Capillary length	200 µm[15]
Model parameters:	
P_aO_2	200 mmHg [a]
Hb	10 g/dl [b]
$CMRO_2$	3 mlO_2/(100g min) [16]
CBF – velocity	15 mm/sec [17]
Diffusivity	4 * 10^{-4} cm^2/sec [18]

a: 26.6 kPa assumed to be a clinically appropriate P_aO_2. b: assumed to be a clinically appropriate Hb level

Model parameters: These are the structural and physiological parameters used in the model. Most are taken from established literature or set to clinically representative values.

Model fits to the clinical data are displayed in Fig 2 to show the change in $P_{bt}O_2$ with change in PaO2 with increasing F_IO_2. The variation in response when increasing F_IO_2 for the four patients is reflected in the different slopes of the curves. While we are able to generate a similar relation of $P_{bt}O_2$ with P_aO_2 at the low end of P_aO_2, at the higher P_aO_2 the clinical data shows a more rapid increase with P_aO_2 than our model.

As discussed above, our computational model cannot not take into account regional variation in the brain but is a microscopic representation that provides an average for the whole brain. The use of clinical data was to demonstrate that our 'lumped' parameter simplified model behaves appropriately compared to clinical data.

Figure 2

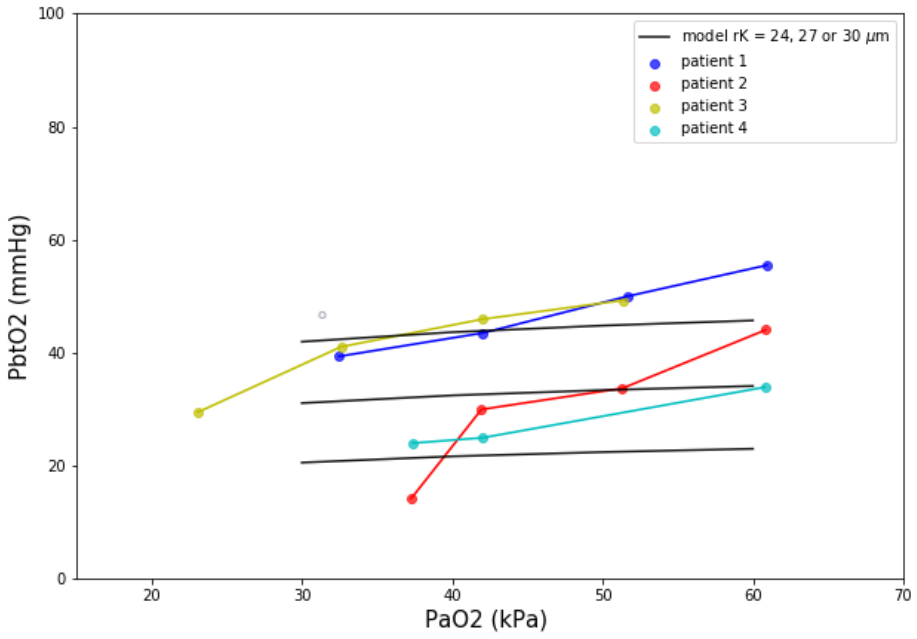

Figure 2:

$P_{bt}O_2$ versus P_aO_2 for the patient data with simulation results: Patient data is shown with model data superimposed in black. We used a range of inter-capillary distances and calculated the $P_{bt}O_2$ for the range of P_aO_2 that patients had been exposed to.

PbtO2 dependence on mean capillary spacing:

The top plot in Fig 3 shows the distribution of local PO_2 for model parameters / r_K chosen to give $P_{bt}O_2$ = 15mmHg, typically regarded as being a clinical threshold for dangerous hypoxia.[2] The resulting local tissue PO_2 distribution showed a clear dependence of the oxygen tension on both longitudinal distance along and radial distance from the capillary.

Figure 3

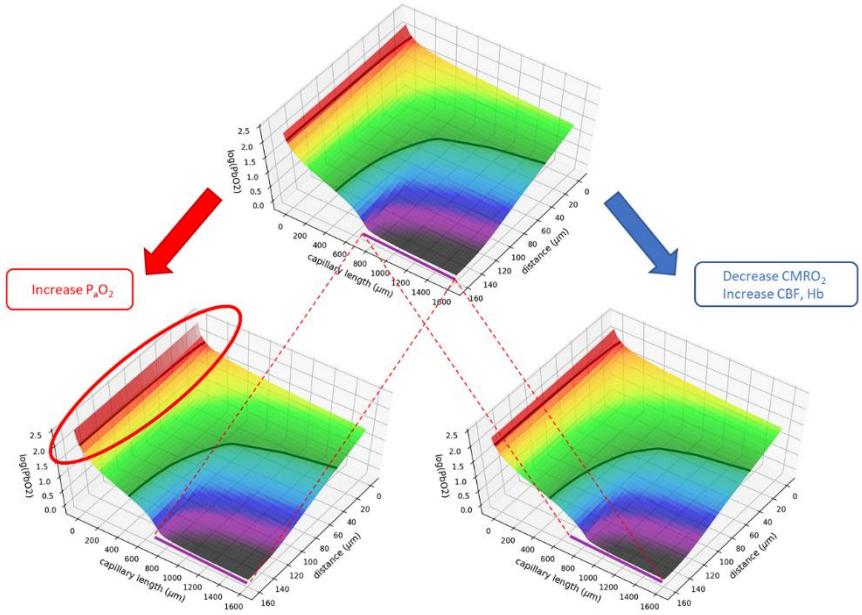

Figure 3:

Spatial distribution of oxygen tension for 3 representative scenarios. Top: distribution of oxygen pressure for r_K chosen so that $P_{bt}O_2$=15mmHg. Whilst much of the tissue is well oxygenated, the low PO_2 is mediated by a `hypoxic corner' (purple scale-bar) of very low PO_2 distant to the capillary and towards the venous end. Right-lower: Equivalent plot but for any of CBF (or equivalently Hb or $CMRO_2$) adjusted to cause a 10% improvement in $P_{bt}O_2$. The hypoxic fraction is now notably smaller than the purple scale-bar. Left-lower: Plot for an equivalent 10% improvement in $P_{bt}O_2$, but this time mediated by increasing PaO2 or F_IO_2. In this case the hypoxic fraction is unchanged with the apparent improvement in $P_{bt}O_2$ being instead mediated by a new region of hyperoxic tissue (red circled area).

As described above, we consider the development of brain tissue hypoxia after TBI to be primarily a consequence of increasing mean inter-capillary distance, which is equivalent to increasing r_K. Fig 4 shows the calculated dependence of the important clinically measurable parameters $P_{bt}O_2$ and $S_{Jv}O_2$ on changing inter-capillary distance as well as the volume fraction of hypoxic tissue. All other input parameters such as P_aO_2, CBF, $CMRO_2$ and haemoglobin (Hb) concentration were assumed kept constant. The equivalent calculated relationship between hypoxic fraction and varying $P_{bt}O_2$ is shown in Fig 5.

Figure 4

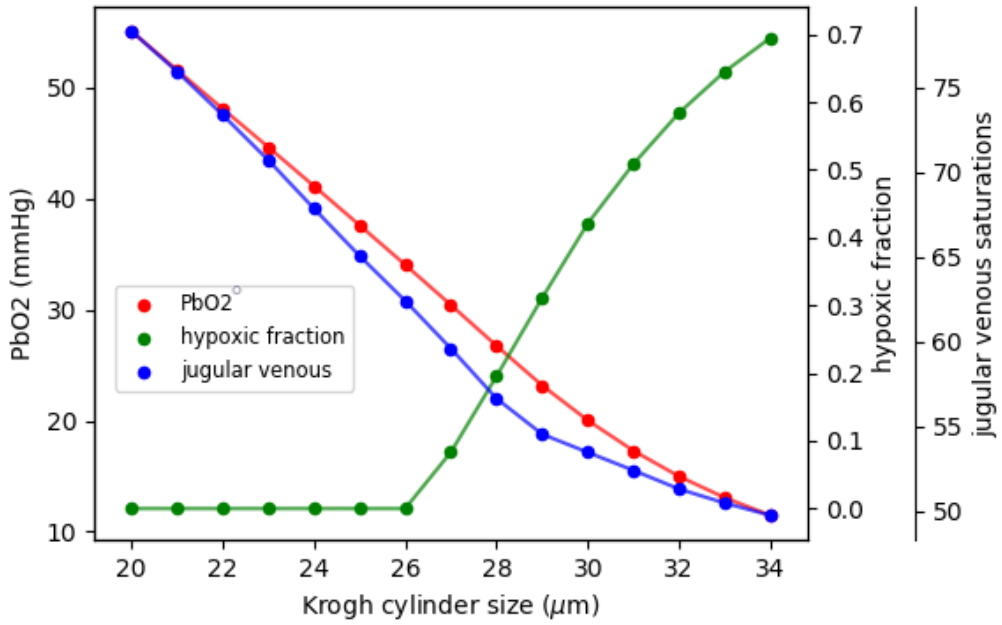

Figure 4:

Dependence of $P_{bt}O_2$, $S_{Jv}O_2$ and hypoxic fraction versus on inter-capillary distance. $P_{bt}O_2$ and jugular venous saturations fall with increasing cylinder size in a very similar manner. We identify a critical r_K: For low r_K, the hypoxic fraction remains relatively constant and cerebral oxygenation is supply limited. For r_K higher than about 26 µm in our simulations, the hypoxic fraction increases and cerebral oxygenation becomes diffusion limited instead.

Figure 5

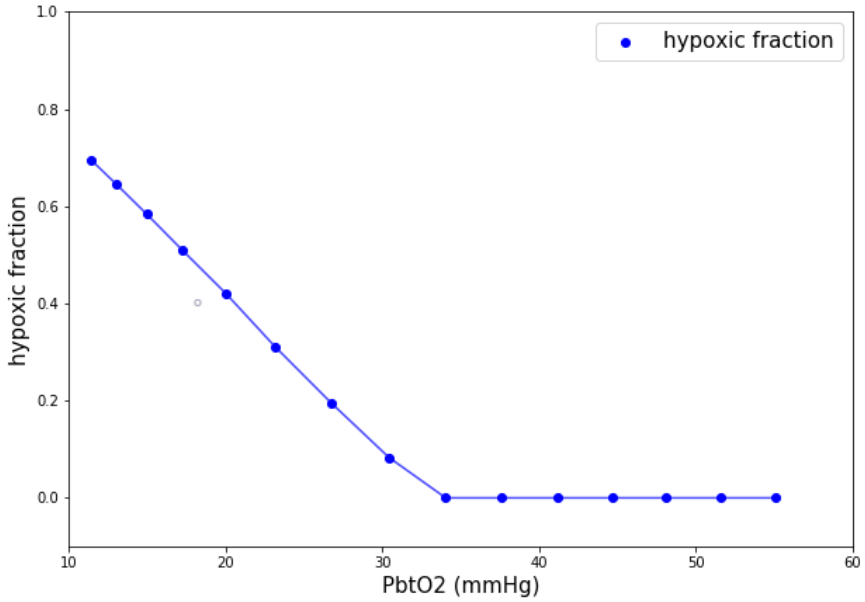

Figure 5:

Illustration of hypoxic fraction: Hypoxic fraction displays similar behaviour when shown versus varying $P_{bt}O_2$ obtained by varying inter-capillary distance (equivalent to varying r_K). There is a critical value of $P_{bt}O_2$ (32mmHg with the chosen parameters in this case) below which there is a significant increase in the fraction of hypoxic tissue.

Effect of clinically relevant rescue strategies on PbtO2 and hypoxic fraction:

To compare the relative effectiveness of clinically relevant rescue strategies, we investigated the percentage change in CBF, $CMRO_2$, Hb concentration or P_aO_2 needed to cause a 10% improvement in $P_{bt}O_2$ for different starting $P_{bt}O_2$. This data is shown as a function of starting $P_{bt}O_2$ in Fig 6.

Figure 6

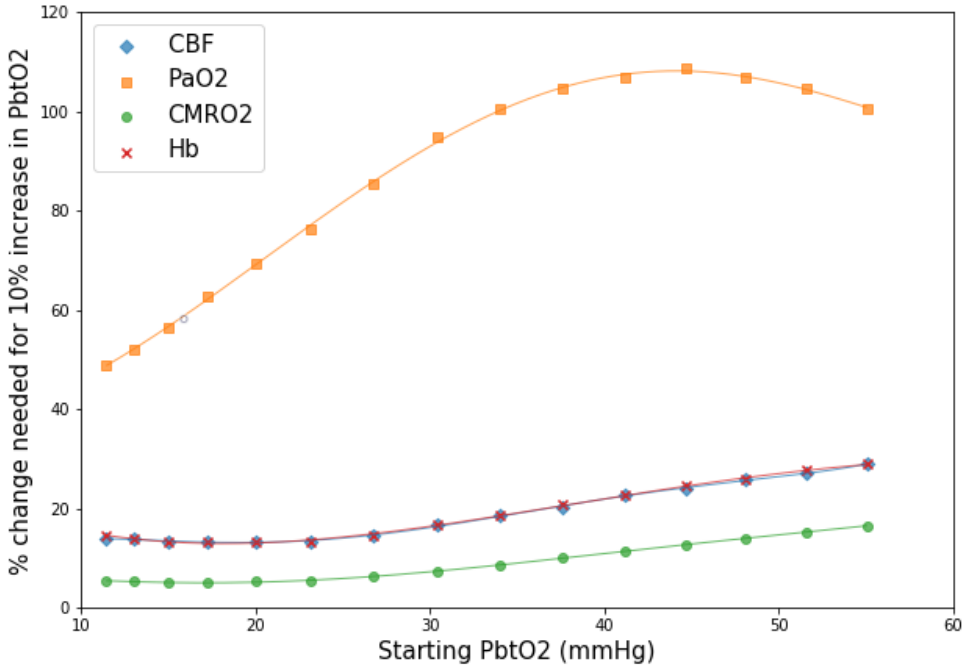

Figure 6:

Relative effectiveness of rescue strategies for a 10% change in $P_{bt}O_2$. Percent change in P_aO_2 , blood flow velocity, $CMRO_2$ or Hb to achieve a 10% improvement in $P_{bt}O_2$. The change in P_aO_2 required to achieve the 10% change in $P_{bt}O_2$ is clearly higher than for the other variables. CBF and Hb have the same effect as they both represent oxygen delivery.

Furthermore, we calculated the hypoxic fraction for each of the models to look more closely at the effects and the distribution of tissue oxygenation. Fig 7 shows the percentage decrease in hypoxic tissue volume for a 10% improvement in $P_{bt}O_2$ brought about by increasing CBF, Hb, P_aO_2 or reducing $CMRO_2$ by an appropriate amount.

Figure 7

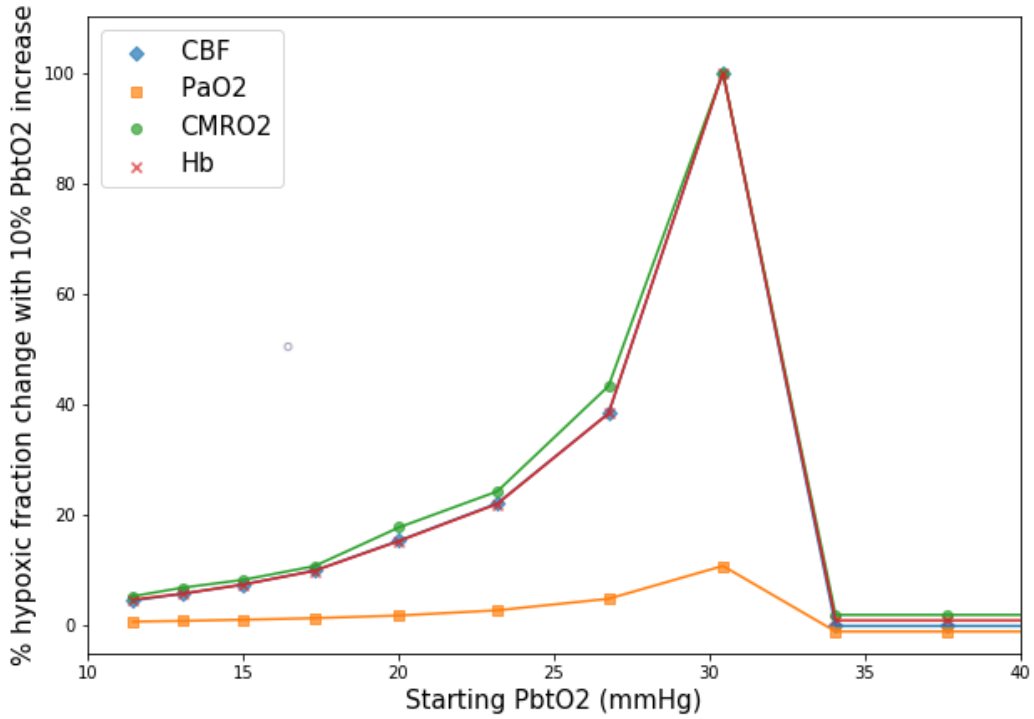

Figure 7:

Percent change in hypoxic fraction when $P_{bt}O_2$ is increased by 10%. Change is shown as a percentage of the original hypoxic fraction. The curves for CBF and Hb are again overlapping. Changes in CBF, Hb and $CMRO_2$ are seen to decrease the amount of hypoxic tissue significantly more than changes to P_aO_2.

Discussion:

From Fig 4 we see that as r_K increases, representing an increase in mean inter-capillary spacing due to capillary collapse, there is a steady decrease in both $P_{bt}O_2$ and $S_{Jv}O_2$ reflecting an increasing degree of diffusion hypoxia as expected, although their behaviour is not identical.

At the same time, the hypoxic fraction increases above a threshold r_K. This is also well demonstrated in Fig 5 which shows that there is $P_{bt}O_2$ at which the hypoxic fraction may in fact be increasing rapidly even for modest reductions in measured oxygen tension. Detecting this point would be of clinical interest since it is precisely the presence of such hypoxic tissue that we wish to identify

clinically and ameliorate with any intervention. However the change in $P_{bt}O_2$ in Fig 4 does not show any discontinuity demonstrating that a significant hypoxic fraction may be developing even with an apparently modest drop in measured brain tissue oxygen and it important to realise that, because of its spatially averaged nature, neither invasive brain tissue oxygen tension measurements nor jugular bulb oximetry are directly sensitive to this aspect of physiology. In passing, it is interesting to note that $P_{bt}O_2$ and $S_{Jv}O_2$ are not completely equivalent in Fig 4 and indeed diverge maximally around this critical point suggesting that the discordance between these parameters could be a surrogate for the development of a sizable fraction of hypoxic tissue.

Fig 6 demonstrates that clinically relevant rescue interventions are in fact not all equally effective in improving $P_{bt}O_2$.[5] We found that suppression of $CMRO_2$ was the most effective. Improving CBF or Hb concentration were indistinguishable strategies, which is understandable as both equivalently increase the rate of cerebral oxygen delivery. Increasing P_aO_2 was found to be the least effective strategy.

For example Fig 6 shows that to improve a $P_{bt}O_2$ of 19mmHg by 10% the P_aO_2 has to be increased by 32% from 220 mmHg to 264 mmHg, however to achieve the same change in $P_{bt}O_2$ with a change in blood flow velocity it only needs to be increased by 15%. Although the difference was less pronounced at lower (and therefore more critical) $P_{bt}O_2$ presumably since diffusion limitation and the development of a hypoxic fraction is dominant in this domain, P_aO_2 nevertheless remained relatively ineffective strategy.

Of the four variables investigated the percentage change to improve $P_{bt}O_2$ is lowest for suppression of $CMRO_2$. Only a 5% decrease is needed around $P_{bt}O_2$ of 20mmHg. These results show that model reflects the effects seen by the common methods used clinically to try and improve cerebral oxygenation. The increase in Hb needed to change $P_{bt}O_2$ by 10% ranged between 11 and 35% (see Fig 6) depending on the starting $P_{bt}O_2$, which corresponds to increasing Hb to 11.2 to 13.6g/dL from a base value assumed to be 10g/dL.

Fig 7 shows that the extent to which these proposed rescue strategies influences the hypoxic fraction depends strongly on the starting $P_{bt}O_2$. At high $P_{bt}O_2$, there is no hypoxic fraction and therefore no effect. Similarly at very low $P_{bt}O_2$ where there is a large region of profoundly diffusion limited tissue, the effectiveness of all of the interventions becomes limited. However, what is clear is that P_aO_2 is globally far less effective at improving the hypoxic fraction for a given observed improvement in $P_{bt}O_2$.

The spatial oxygen tension distribution plots in Fig 3 show that the hypoxic fraction is located, as expected, in tissue regions that are distant from the capillary radially and towards the venous end of the model geometry. The upper right plot in Fig 3 shows that the size of this region may be reduced by strategies that improve $P_{bt}O_2$ by increasing the balance of oxygen delivery to consumption (increase CBF, Hb or reduce $CMRO_2$). The lower right panel shows the oxygen tension for an equivalent 10% improvement in measured $P_{bt}O_2$, but this time produced by increasing P_aO_2 instead. In this case, the size of the hypoxic fraction is unchanged: The increase in $P_{bt}O_2$ occurs instead as a result of the development of a small region of hyperoxic tissue at the arterial end of the capillary. Although this area is small, its extremely high local oxygen tension is sufficient to increase the mean tissue oxygen tension over the volume.

The model assumed a simplified geometry with a single capillary and cylindrical symmetry. This simplification allowed us to investigate oxygen diffusion at microscopic scales and better understand the effects of changing individual parameters. The limitations of this model are both in its geometry – a more realistic model would include branching and variation in shape and size of both the capillary and its surrounding tissue – and the simplified input parameters – we use blood flow velocity as a surrogate for any change in CBF no matter what the cause of it.

Another consequence of this microscopic scale model is that when calculating the $P_{bt}O_2$ we assume the whole brain is composed of a large number of these regions. However, realistically there would be areas of higher and lower P_aO_2, especially when considering patients with traumatic brain injury.

Our model therefore can be thought of as a representation of a capillary in a specific region with the calculated $P_{bt}O_2$ showing the expected value for that region.

Taken together, these results indicate that increasing P_aO2 (whether through F_IO_2 or PEEP) is not only a relatively ineffective strategy for improving $P_{bt}O_2$ but also does not ameliorate local hypoxia. Furthermore, inducing local hyperoxia could lead to harmful increases of oxidative stress. Although several studies have shown that hyperoxia can improve oxygen utilization and cytotoxic oedema in pericontusional tissue,[19, 20] other evidence indicates worse outcomes with arterial hyperoxia and increased glutamate in microdialysis.[21, 22] Two recent meta-analyses concluded that hyperoxia seems to be associated with increased in-hospital mortality.[23, 24]

Our data are only approximately quantitative and derived critical thresholds for the development of hypoxic tissue must be interpreted with great caution since it is important to remember that the exact numerical calculations obtained will vary with the choice of geometry and parameters used in the model. For instance the Krogh geometry, whilst attractive due to being mathematically tractable, is a poor representation of true brain capillary microarchitecture which is fractal in nature, conferring a degree of protection against hypoxia as the tissue is topologically more `connected'. Nevertheless, whilst we cannot claim that our calculations are fully quantitative, there is no reason to suggest that the qualitative physiology demonstrated in our model does not hold. As such, the exact parameter estimates and geometrical approximations are to an extent immaterial.

In our model, we have considered the various interventions as independent which is almost certainly not the case in reality. For example we cannot account in our model for changes in rheology that may occur as a result of transfusion, nor the cerebral vasodilation that may occur as a result of improving oxygen delivery. Such considerations may be very complex-- for example the effect of cerebral vasodilation on cerebral haemodynamics may depend on intracranial compliance through effects on intracranial pressure. This limitation of our model is, at the same time, potentially a

strength as a only a *ceteris paribus* approach can give insights into such complex physiological system.

Conclusions:

We have demonstrated that *in silico* modelling can be effective as a tool to understand complex physiology not amenable to direct clinical measurement and can be applied to determine the effectiveness of clinically relevant rescue strategies for patients with TBI. We have shown that whilst manipulation of CBF, transfusion, $CMRO_2$ or increasing P_aO_2 may all improve $P_{bt}O_2$, these strategies are not equivalent. In particular, increasing P_aO_2 (either through increasing F_IO_2 or PEEP) is relatively ineffective. Furthermore, this strategy improves apparent brain oxygenation by causing periarteriolar hyperoxia without any improvement in hypoxic tissue and cannot be recommended on the basis of our model. Such considerations may be of significance both at the bedside and in developing future prospective studies using brain tissue oxygen targets as part of clinical care.

Conflict of interest:

No conflict of interest exists for any of the authors.

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