Figure 1

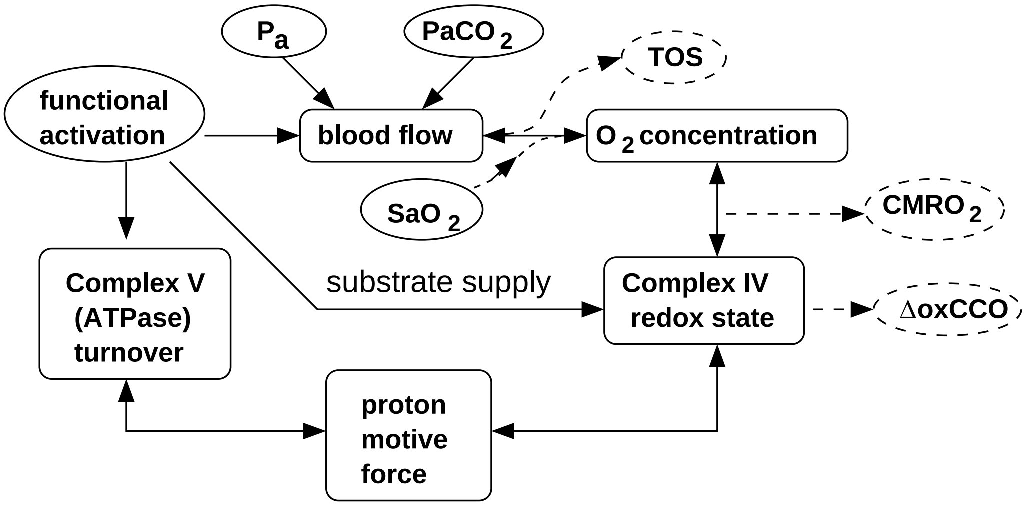

Fig. 1. **Summary of the main inputs, variables and processes in the model.** Model inputs are enclosed in solid ovals, while outputs are enclosed in dashed ovals. P_a is arterial blood pressure, SaO2 is arterial oxygen saturation level, PaCO2 is arterial CO_2 level. TOS and ΔoxCCO are NIRS signals defined in the text.

Figure 2

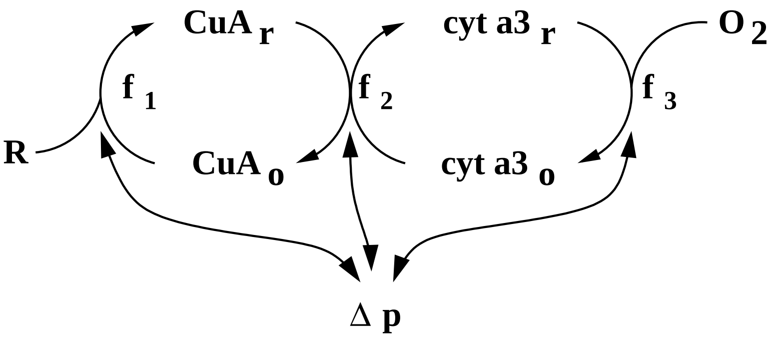

Fig. 2. **Schematic representation of the mitochondrial submodel.** The Cu_A centre is reduced by some reducing substrate, termed R. It in turn passes its electrons on to a terminal substrate, cyt a_3. Finally cyt a_3 is oxidised by oxygen. All processes can in general produce proton motive force Δp, by pumping protons out of the mitochondrial matrix. As a result, they are also inhibited by Δp. The rates of the three processes – initial reduction of Cu_A, electron transfer to cyt a_3 and final oxidation of cyt a_3, are termed f_1, f_2 and f_3 respectively.

Figure 3

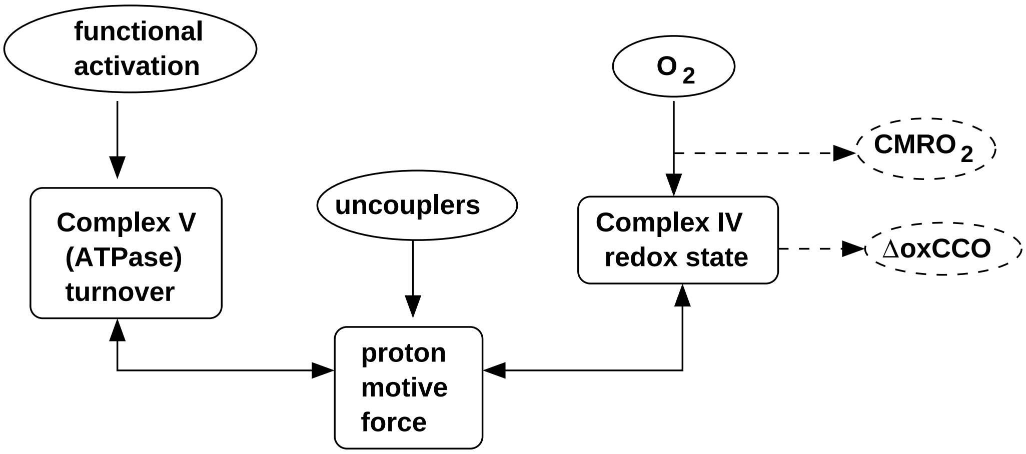

Fig. 3. **Summary of the main variables and processes in the simplified model.** As in Figure 1, inputs are enclosed in solid ovals, while outputs are enclosed in dashed ovals. Components connected with blood flow have been removed from the model. O_2 levels are now directly settable.

Figure 4

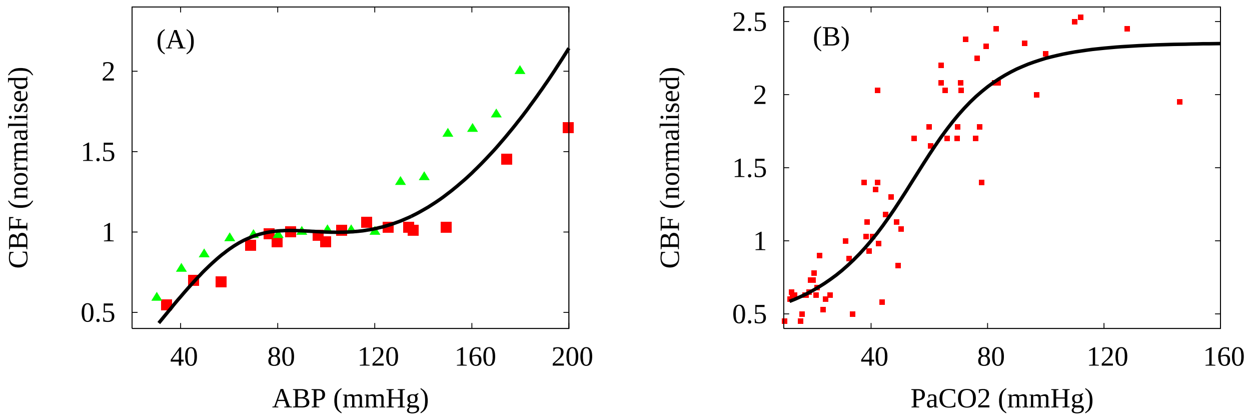

Fig. 4. **The response of model steady state CBF to blood pressure and** PaCO2 **changes.** A) Response to arterial blood pressure changes with data from [1] (red squares) and [2] (green triangles) for comparison. B) Response to PaCO2 changes with data from [3] (with normal blood flow taken as 40 ml/min/100g) for comparison.

To reproduce the model curve in Figure 4 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `pres.dat`,
(4) run the simulation and
(5) output `CBF/CBFn`.

To reproduce the model curve in Figure 4 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `co2.dat`,
(4) run the simulation and
(5) output `CBF/CBFn`.

Figure 5

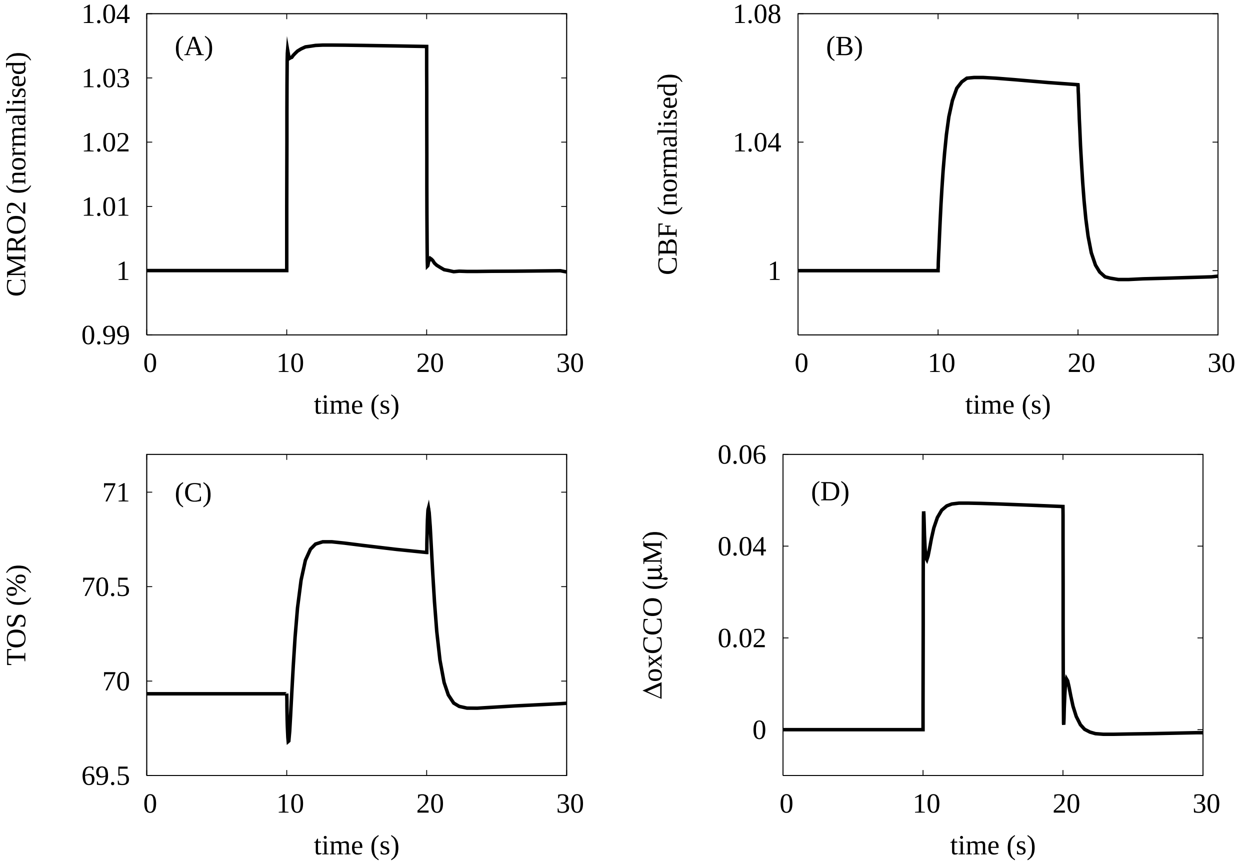

Fig. 5. **Model responses to a step up in demand.** A) Change in CMRO$_2$ (normalised). B) Change in CBF (normalised). C) Change in TOS (percent). D) Change in ΔoxCCO (μM). All parameters are held at normal values apart from u which is stepped up from 1 to 1.2 for a ten second duration, giving rise to an approximately 3.5 percent increase in CMRO$_2$ and an approximately 6 percent increase in blood flow. TOS increased by a little under 1 percent, and ΔoxCCO also increased by about 0.05 μM corresponding to an oxidation of just under 1 percent.

To reproduce Figure 5 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation.dat`,
(4) run the simulation and
(5) output `f1/f_n`.

To reproduce Figure 5 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),

(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation.dat`,
(4) run the simulation and
(5) output `CBF/CBFn`.

To reproduce Figure 5 C)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation.dat`,
(4) run the simulation and
(5) output `TOI`.

To reproduce Figure 5 D)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation.dat`,
(4) run the simulation and
(5) output `CCO`.

Figure 6

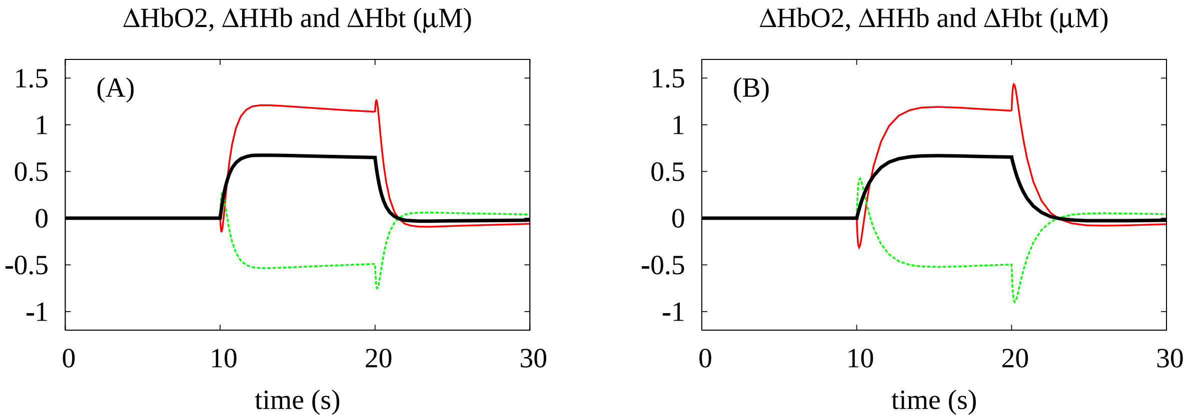

Fig. 6. **Response of haemoglobin signals to a step up in demand.** The response in μM of ΔHbO2 (red), ΔHHb (green) and ΔHbt (black) to a step up in demand. The stimulus and parameter values are as in Figure 5. In A) $\tau_u = 0.5$ s (the default value). In B) $\tau_u = 1$ s. With the slower response time, there is more pronounced transient behaviour including a clear initial decrease in ΔHbO2 before it starts to increase.

To reproduce Figure 6 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation.dat`,
(4) run the simulation and
(5) output `DHbO2: DHHb: DHbT`.

To reproduce Figure 6 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `activation_slow.dat`,
(4) run the simulation and
(5) output `DHbO2: DHHb: DHbT`.

Figure 7

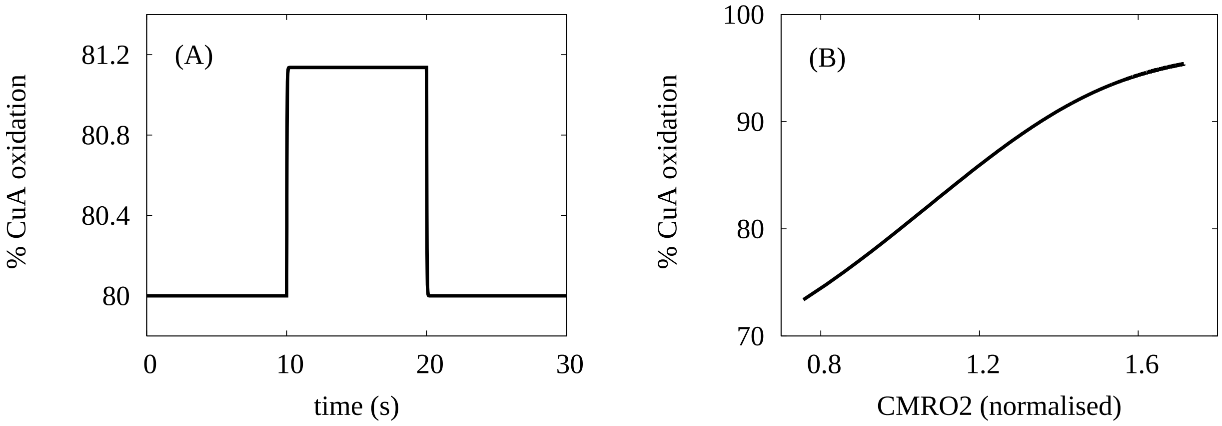

Fig. 7. **Response of $\mathrm{Cu_A}$ redox state in the simplified model to changes in u.** A) The time course of oxidised $\mathrm{Cu_A}$ in response to functional activation. As in the *in vivo* simulations, u was changed from 1 to 1.2 for a ten second duration, resulting in an approximately 1 percent increase in $\mathrm{Cu_A}$ oxidation. B) The steady state level of $\mathrm{Cu_A}$ oxidation in response to varying levels of activation. u was varied from 0.2 to 100 resulting in variation in $\mathrm{CMRO_2}$ from 80 to 170 percent of baseline. $\mathrm{Cu_A}$ oxidation increased steadily.

To reproduce Figure 7 A

(1) choose the simplified model descriptor `o2param.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `funcact_isolated.dat`,
(4) run the simulation and
(5) output `a/cytox_tot*100`.

To reproduce Figure 7 B

(1) choose the simplified model descriptor `o2param.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `funcact_u.dat`,
(4) run the simulation and
(5) output `xvar: f1/f_n a/cytox_tot*100`.

Figure 8

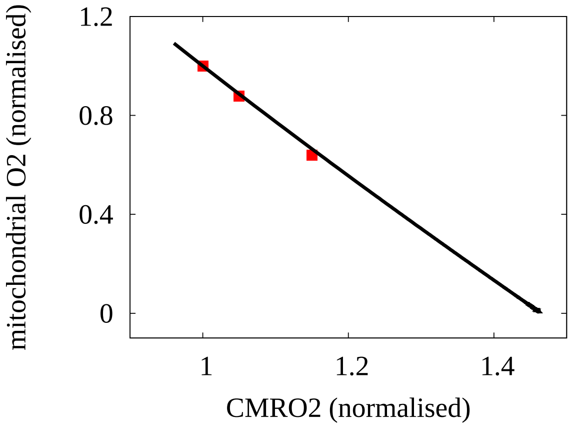

Fig. 8. **Relationship between** CMRO$_2$ **amd mitochondrial oxygen levels during activation.** The full model was run with parameter R_u set to zero so that an increase in demand had no effect on blood flow. Increasing u allowed increases in CMRO$_2$ up to approximately 145 percent of baseline. The three data points shown are calculated from Figure 2 of [4] in which predictions on how tissue oxygen levels in the "lethal corner" should vary with activation level during normoxia are presented.

To reproduce the model curve in Figure 8

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `funcact_u_CBFfix.dat`,
(4) run the simulation and
(5) output `xvar: f1/f_n O2/O2_n`.

Figure 9

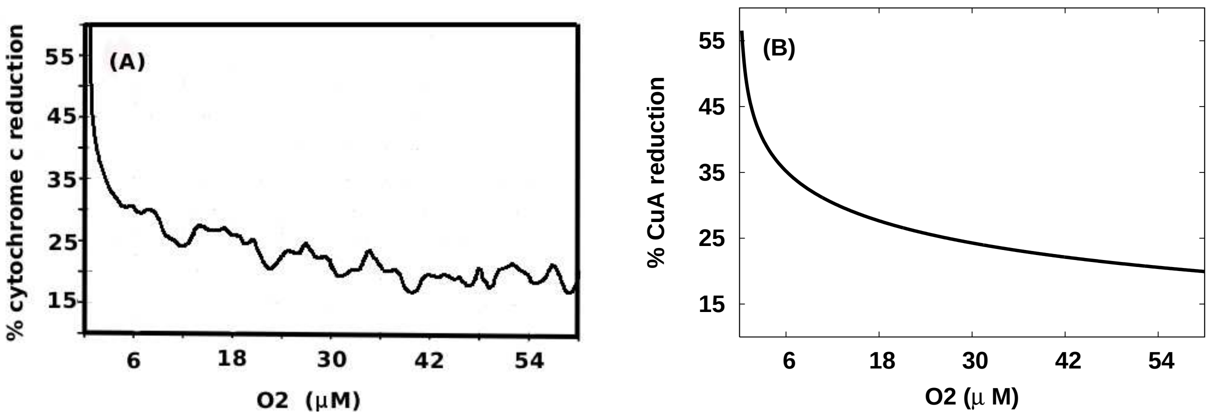

Fig. 9. **Comparison of experimentally measured and modelled CCO redox states.** A) Figure 5A from [5] is redrawn showing how the level of reduction of cytochrome c varies with oxygen concentration. B) The equivalent data for $\mathrm{Cu_A}$ from model simulations is presented. For the simulation, the reducing substrate is set to be succinate, and the demand parameter u is set to be low ($u = 0.4$) to represent a high phosphorylation potential.

To reproduce Figure 9 B)

(1) choose the simplified model descriptor `o2param.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `fwilson.dat`,
(4) run the simulation and
(5) output `xvar: 1000*O2 100*ared/cytox_tot`.

Figure 10

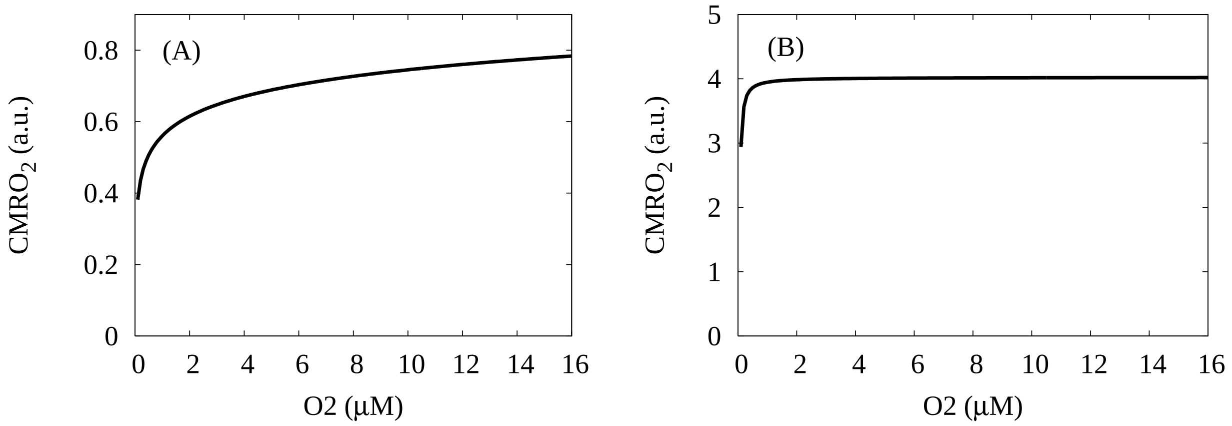

Fig. 10. **The response of steady state** CMRO$_2$ **to a drop in mitochondrial** O$_2$ **level.** CMRO$_2$ is in arbitrary units. A) In coupled mitochondria. B) Uncoupled mitochondria. As above, for both simulations, the reducing substrate is set to be succinate, so that input to the system is by electron transfer to ubiquinone, and the demand parameter u is set to be low ($u = 0.4$ in both simulations). For the uncoupled mitochondria, the parameter k_{unc} is raised from its normal value of 1 to a value of 1000. During uncoupling there is an approximately four-fold increase in maximum CMRO$_2$. The behaviour of Cu$_\mathrm{A}$ was similar to Figure 6 in [5] with baseline oxidation now at approximately 99 percent.

To reproduce Figure 10 A)

(1) choose the simplified model descriptor `o2param.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `funcact_O2wilson`,
(4) run the simulation and
(5) output `xvar: O2*1000 f1/f_n`.

To reproduce Figure 10 B)

(1) choose the simplified model descriptor `o2param.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `funcact_O2wilsuncoup`,
(4) run the simulation and
(5) output `xvar: O2*1000 f1/f_n`.

Figure 11

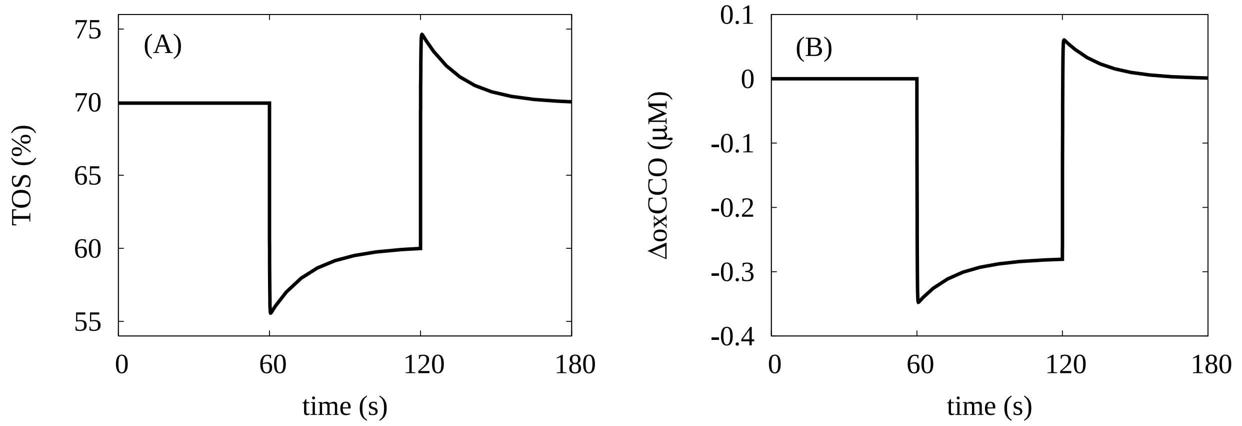

Fig. 11. **Model response of TOS and ΔoxCCO to a step down in arterial oxygen saturation.** A) Response of TOS (percent). B) Response of ΔoxCCO (μM). A hyperaemic effect is seen in both signals.

To reproduce Figure 11 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `hypoxia2.dat`,
(4) run the simulation and
(5) output `TOI`.

To reproduce Figure 11 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `hypoxia2.dat`,
(4) run the simulation and
(5) output `CCO`.

Figure 12

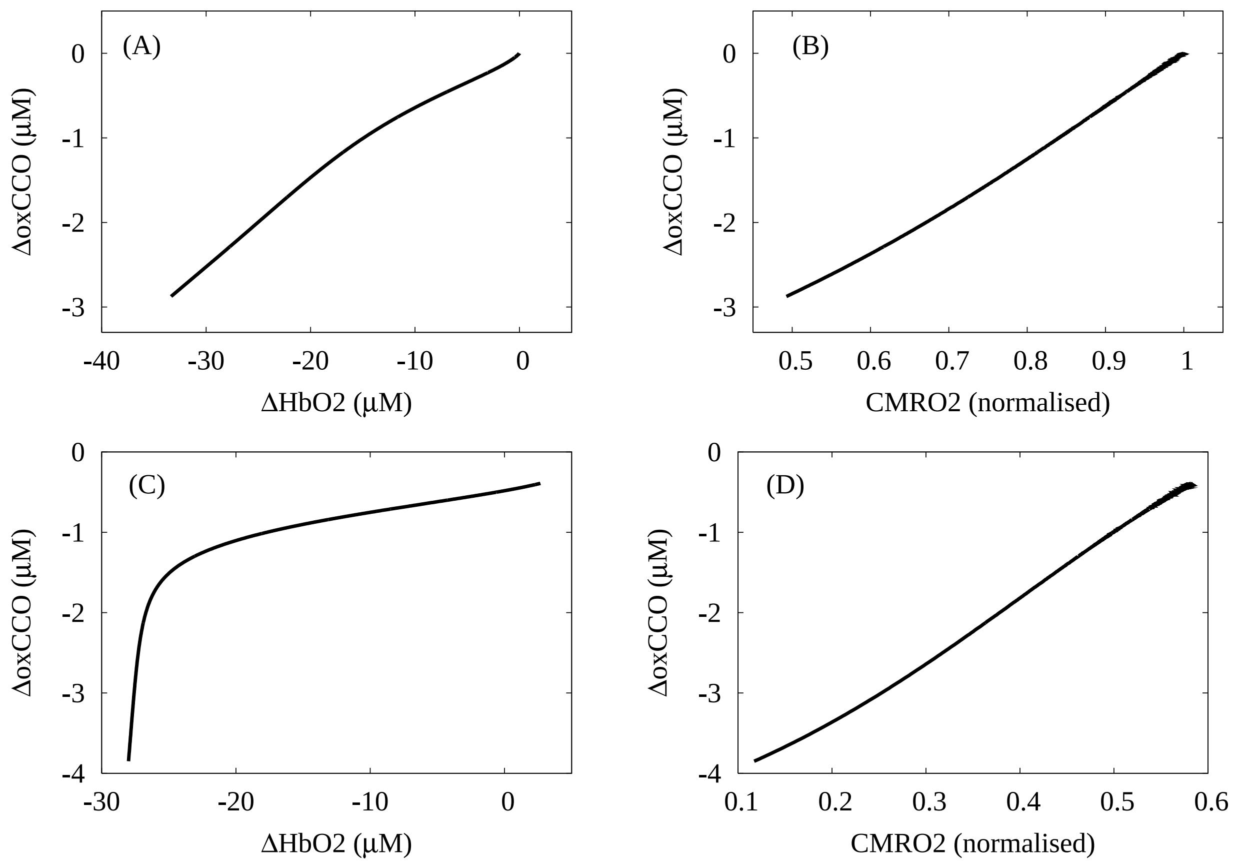

Fig. 12. **Relationship between ΔHbO2, ΔoxCCO and** $\mathrm{CMRO_2}$ **during changes in arterial oxygen saturation** A) The model was run with normal parameter values and an approximately linear relationship between ΔHbO2 and ΔoxCCO held. B) At these same normal parameter values $\mathrm{CMRO_2}$ showed an approximately linear realationship with ΔoxCCO. C) Baseline $\mathrm{CMRO_2}$ was lowered to about 60 percent of the normal model baseline, by setting $u = 0.1$, while normal CBF was also lowered by about the same amount by setting $\mathrm{CBF_n} = 0.007$ ml blood per ml brain tissue per second. A more clearly biphasic relationship between ΔHbO2 and ΔoxCCO was obtained. D) Again, at the changed parameter values, $\mathrm{CMRO_2}$ had an approximately linear relationship with ΔoxCCO.

To reproduce Figure 12 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `springett0.dat`,
(4) run the simulation and
(5) output `xvar: DHbO2 CCO`.

To reproduce Figure 12 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `springett.dat`, (this chooses the smooth approximation to `J_O2`)
(4) run the simulation and
(5) output `xvar: DHbO2 CCO`.

Figure 13

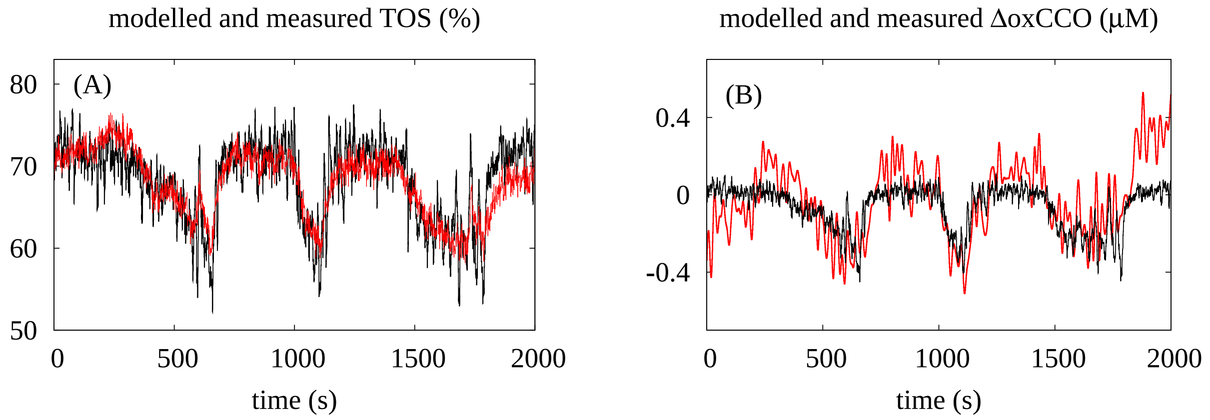

Fig. 13. **Responses of measured and modelled TOS and ΔoxCCO during a hypoxia challenge.** Measured (red) and modelled (black) responses of A) TOS (%) and B) ΔoxCCO (μM) are shown. Details are given in the text.

To reproduce Figure 13 A)

1. choose the full model descriptor `fainvivo.dat` (on the model editing interface),
2. unclick the autoreg button to get a dynamic simulation,
3. choose the input file `Hypoxia_cyt20ana1.dat`,
4. run the simulation and
5. output `TOI: TOIsup`.

To reproduce Figure 13 B)

1. choose the full model descriptor `fainvivo.dat` (on the model editing interface),
2. unclick the autoreg button to get a dynamic simulation,
3. choose the input file `Hypoxia_cyt20ana1.dat`,
4. run the simulation and
5. output `CCOsup1-0.35: CCO`.

Figure 14

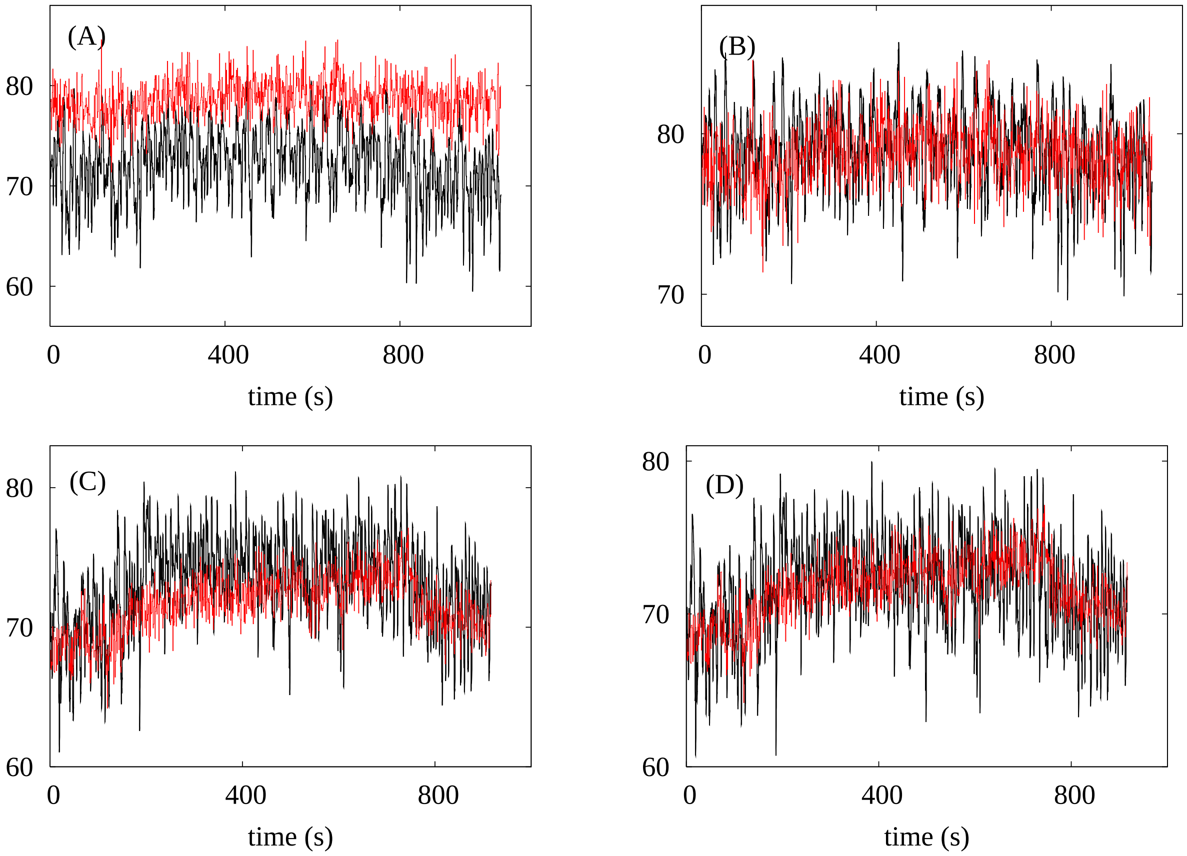

Fig. 14. **Responses of measured and modelled TOS during a hypercapnia challenge.** Measured (red) and modelled (black) responses of TOS: A) For subject 1 without optimisation. B) For subject 1 following optimisation of AVRn and R_C, which gave values of AVRn $= 0.78$ and $R_C = 1.31$. C) For subject 2 without optimisation. D) For subject 2 following optimisation of AVRn and R_C, which gave values of AVRn $= 3.5$ and $R_C = 1.62$.

To reproduce Figure 14 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `Hypdata/study17.dat`
(4) run the simulation and
(5) output `TOI: TOIsup`.

To reproduce Figure 14 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,

(3) choose the input file `Hypdata/study17opt.dat`
(4) run the simulation and
(5) output `TOI: TOIsup`.

To reproduce Figure 14 C)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `Hypdata/study09.dat`
(4) run the simulation and
(5) output `TOI: TOIsup`.

To reproduce Figure 14 D)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) unclick the autoreg button to get a dynamic simulation,
(3) choose the input file `Hypdata/study09opt.dat`
(4) run the simulation and
(5) output `TOI: TOIsup`.

Figure 4 in supplementary material

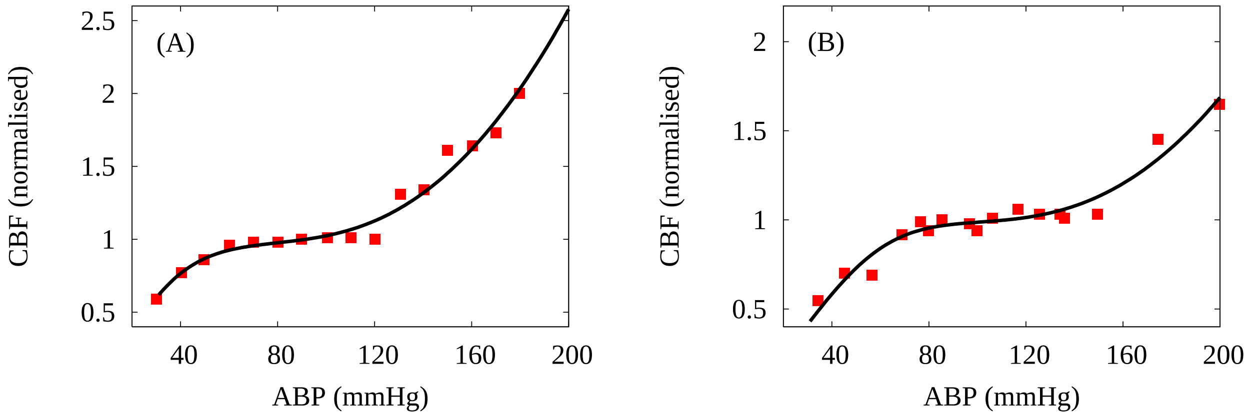

Fig. 15. [Fig. 4 in supplementary material]**The response of model steady state CBF to blood pressure changes.** A) Model autoregulation curve fitted to data from [2]. The following parameters were reset: $P_{a,n} = 91.6$, $R_P = 3.05$ and $r_0 = 0.015$. B) Model autoregulation curve fitted to data from [1]. $P_{a,n} = 112.0$, $R_P = 3.28$ and $r_0 = 0.0133$.

To reproduce the model output in Figure E.1 A)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `presharper.dat`
(4) run the simulation and
(5) output `CBF/CBFn`.

To reproduce the model output in Figure E.1 B)

(1) choose the full model descriptor `fainvivo.dat` (on the model editing interface),
(2) click the autoreg button to get a static simulation,
(3) choose the input file `presgao.dat`
(4) run the simulation and
(5) output `CBF/CBFn`.

References

[1] E. Gao, W. L. Young, J. Pile-Spellman, E. Ornstein, Q. Ma, Mathematical considerations for modelling cerebral blood flow autoregulation to systemic arterial pressure, Am J Physiol Heart Circ Physiol 274 (3) (1998) H1023–H1031.

[2] S. L. Harper, H. G. Bohlen, M. J. Rubin, Arterial and microvascular contributions to cerebral cortical autoregulation in rats, Am J Physiol Heart Circ Physiol 246 (1) (1984) H17–24.

[3] M. Reivich, Arterial P_{CO_2} and cerebral hemodynamics, Am J Physiol 206 (1) (1964) 25–35.

[4] M. A. Mintun, B. N. Lundstrom, A. Z. Snyder, A. G. Vlassenko, G. L. Schulman, M. E. Raichle, Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data, Proc Natl Acad Sci USA 98 (12) (2001) 6859–64.

[5] D. F. Wilson, W. L. Rumsey, T. J. Green, J. M. Vanderkooi, The oxygen dependence of mitochondrial oxidative phosphorylation measured by a new optical method for measuring oxygen concentration, J Biol Chem 263 (6) (1988) 2712–2718.