# A systems biology approach in solving biological and medical problems illustrated by two contrasting examples

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# Interdisciplinary approach that constitutes Systems Biology: Mathematics for Biology/Medicine or Biology/Medicine for Mathematics?

- Collaboration between 'mathematicians' and 'clinicians': do we speak the same language?
- Micro or Macro scale: one step at the time?
- 'Right' and 'wrong': both?

.......model-enriched, patent-specific systems

.......from paper via computer to the bedside

# Mathematics for Biology

- Use known mathematical methods and techniques to explore simple biological systems
- Derive analytical approximations of the longtime/relevant profiles/measurements of the corresponding variables/parameters
- Use the analytical solutions to construct relevant experiments

***...life is not that simple***

# *Biology for Mathematics*

- Well defined biological problem
- 'Mathematically' definable biological system
- Realistic set of parameters/variables that are known biologically
- Mathematical tools confirm experiments and define critical measures to be studied
- Novel biological predictions

**...real-life applied mathematics!**

# ...a little help from Computer Sciences and Data Analysts...

- More complicated mathematical systems
- Experimental data driven modlelling
- Computer simulators
- Model tested and 'real' predictions obtained
- A set of 'bed-site' relevant results

***...a solution of the biological/medical problem?***

# Illustration of interdisciplinary science

- Example I: Understanding the logic of dorsal-ventral patterning in vertebrate neural tube

  - simple mathematical framework

  - straight forward experiments

  Novel patterning logic

- Example II: Understanding brain circulation and metabolism

  - complex mathematical framework

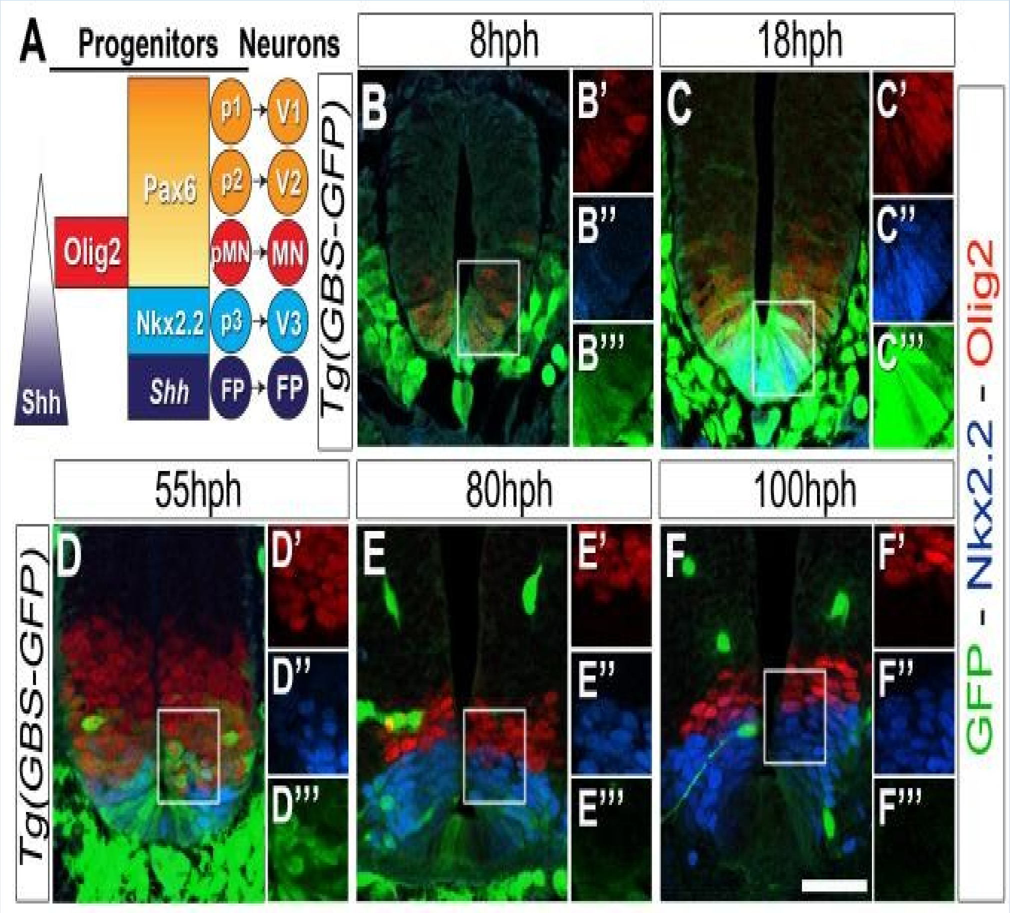
  - complicated 'bed-side' clinical work

  Interpretation of NIRS signals in patients

# Specific questions/hypothesis

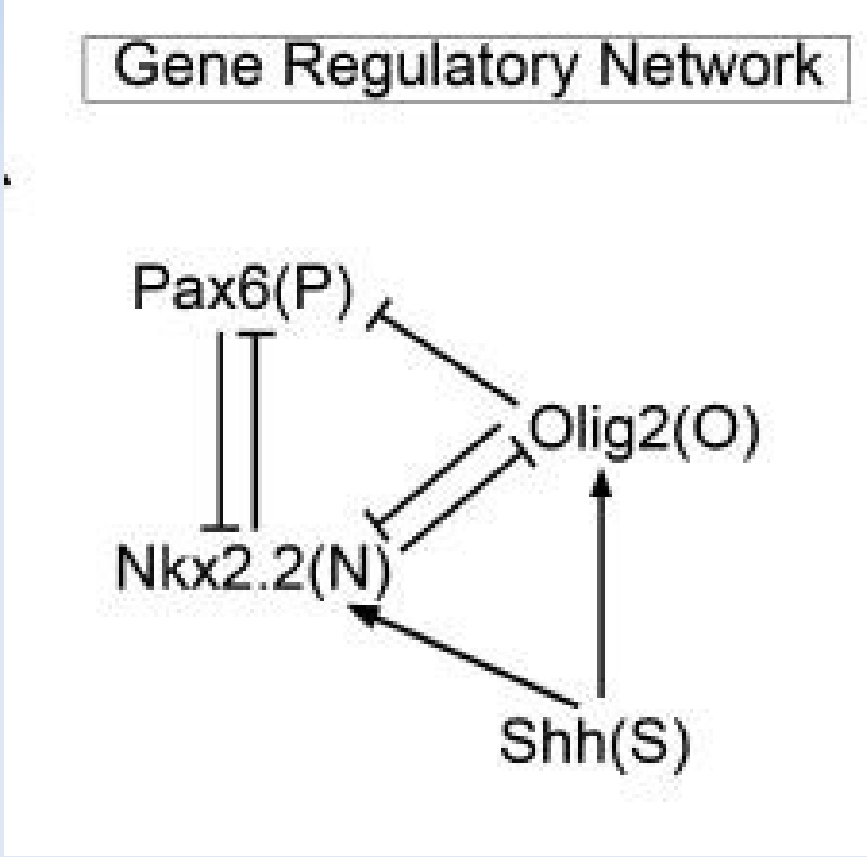
- Shhh signalling is solely responsible for the formation of French-Flag like expression pattern of progenitor cells
- Testable hypothesis:Is cross-repression important in this circuit?
- The changes in the levels oxygen and the blood pressure are important in brain metabolism
- Testable hypothesis: What is the effect of changes in blood pressure or oxygen levels on the mitochondrial metabolism?

# Example I: Explaining the logic of dorsal-ventral patterning in vertebrate neural tube




- Morphogens provide positional information that directs patterns in cellular differentiation
- In the vertebrate neural tube distinct progenitor cells arrayed along the DV axis
- Shh signalling level and duration activate expression of Pax6, Olig2 and Nkx2.2
- Genetic cross-repression is evident in the network

# Gene regulatory network: simple mathematical framework




- System of deterministic or stochastic differential equations
- Shh signal is either constant, changes in time or is described by a white noise term
- Extendable to N-node genetic network with same qualitative properties

# Interdisciplinary study: Mathematics and Biology

- Mathematical analysis and computer simulations to pin-point key features of the circuit
- Numerical simulations to explore the parameter space and confirm known experimental features
- Prediction of novel characteristics of the system
- Experimental studies to confirm numerical predictions

… a loop of joint numerical experimentally testable predictions and experimental data that can be verified numerically!

# Key results

- The dynamic behaviour mirrors the steady state behaviour so Shh signalling and both the duration and the signalling level control the pattern formation
- The response of target genes is determined by a combination of morphogen dynamics and cross-repression: challenge Lewis Wolpert's French Flag Model
- Removal of P and/or O from the model produces changes in N that mirrored the phenotype of the corresponding mouse mutants
- The circuit either confers hysteresis in the response of Nkx2.2 to Shh or transient oscillations in time at intermediate Shh values
- The cross-repression within the network buffers the noise in the circuit

# Model Extensions

- Spatio-temporal Shh profile that resembles the experimentally derived profile
- Generalise the model to N-node network
- Add extrinsic and/or intrinsic noise in the system

# Summary

- A mathematical model to complement experiments
- A general mechanism for gene regulation by the morphogen interpretation
- A novel mathematical prediction that the expression pattern is an emergent property of the network, not a consequence of sole genes' exposure to morphogen signalling
- A novel experimental confirmation of the relevance of cross-repression

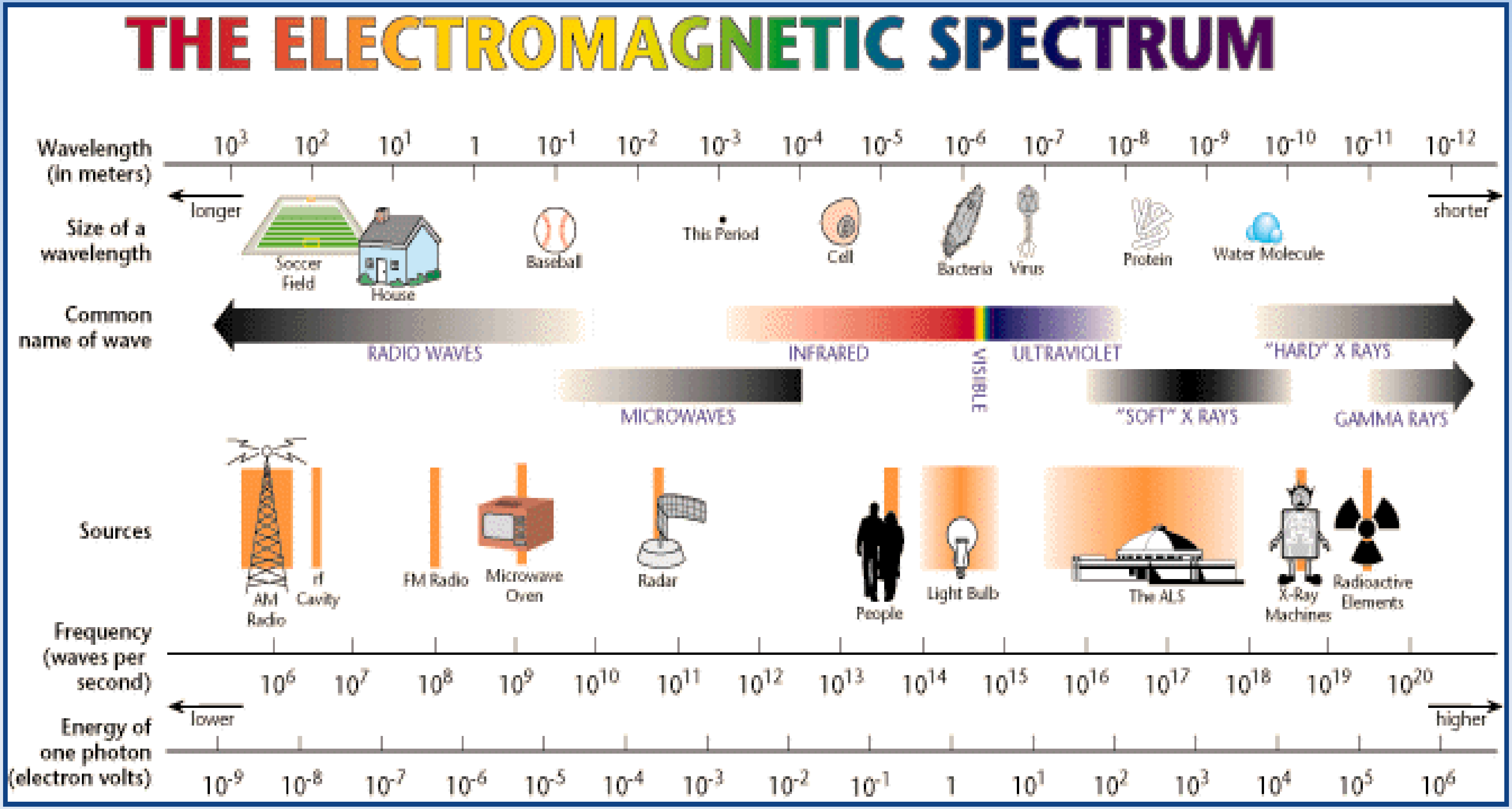
# Example II: Modelling brain circulation and metabolism

- Physiological model of brain circulation and metabolism to explain and predict quantitatively the response of 5 non-invasively measured signals to hypoxia or hypocapnia
- We simulate responses in physiological stimuli and compare with in vivo data
- Work in progres.....

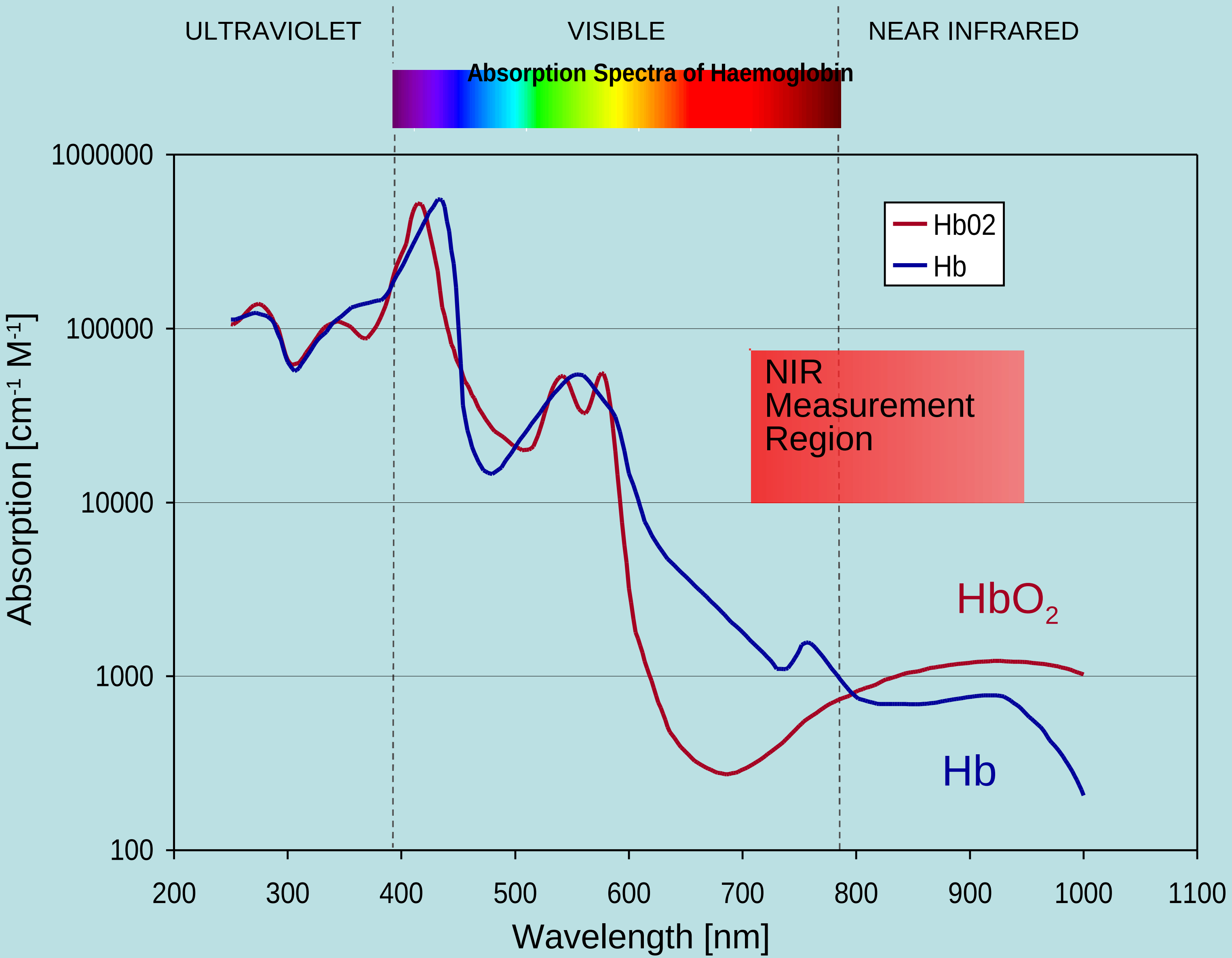
# Near-infrared Spectroscopy

- Non-invasive technique that measures the attenuation of light by tissue at multiple wavelengths
- Biological tissue is transparent to light from the near-infrared part of the spectrum
- In biological tissue there are components (e.g. the brain) where the light absorbtion is oxygenation dependent
- In brain the components which light absorbtion varies with time and oxygen status are oxyhaemoglobin (HbO2), deoxyhaemoglobin (Hhb) and oxidised cytochrome oxydise (CCO)

# Tissue Spectroscopy



# Absorption Spectrum of Blood



# Mathematical model

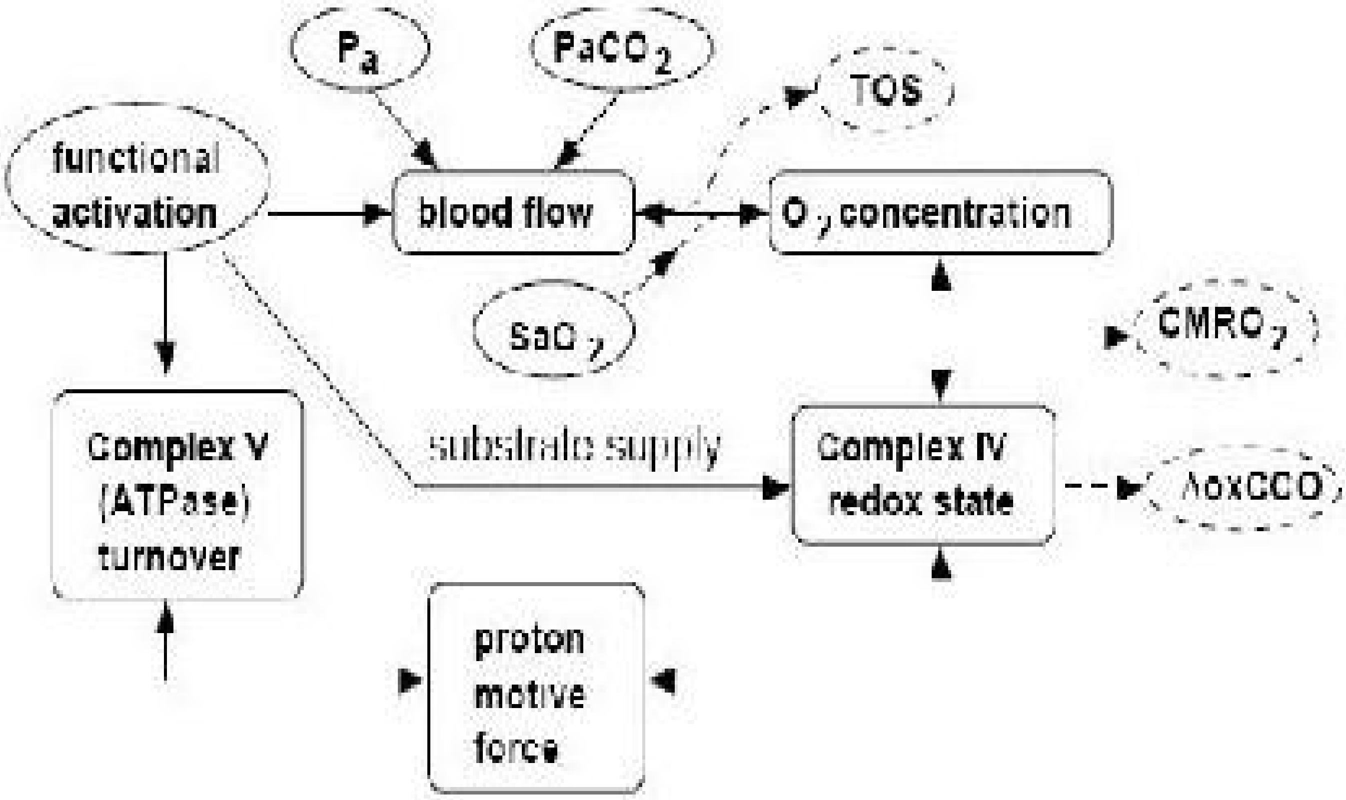



Fig. 1. Summary of the main inputs, variables and processes in the model. Model inputs are enclosed in solid ovals, while outputs are enclosed in dashed ovals. $P_a$ is arterial blood pressure, SaO2 is arterial oxygen saturation level, PaCO2 is arterial $CO_2$ level. TOS and ΔoxCCO are NIRS signals defined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

# Numerics V Experiments

- Main inputs: arterial blood pressure (Pa),arterial oxygen saturation (SaO2) and arterial carbon dioxide saturation (PaCO2)
- Main outputs: absolute tissue saturation (TOS), metabolic rate (CMRO2) and signal measuring changes in CCO signals

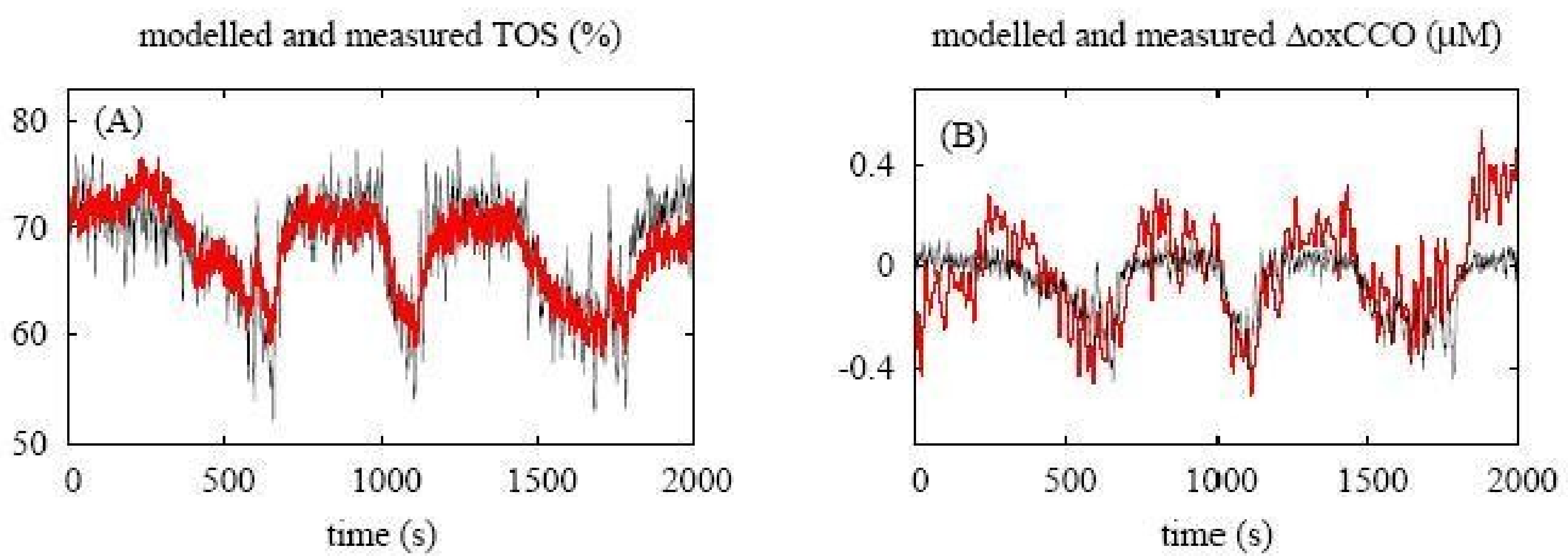



Fig. 13. **Responses of measured and modelled TOS and ΔoxCCO during a hypoxia challenge.** Measured (red) and modelled (black) responses of A) TOS (%) and B) ΔoxCCO ($\mu$M) are shown. Details are given in the text.

# A case study: multi modal monitoring on the adult neurocritical care unit

NIRS

- $\Delta$ $HbO_2$, $\Delta$ HHb,
- $\Delta$ Hbdiff ($HbO_2$ – HHb)
- $\Delta$ HbT ($HbO_2$ + HHb)

Absolute Tissue Oxygen Saturation (NIRO POX)

$\Delta$ CCO using broadband NIRS

Transcranial Doppler

Blood Flow Velocity $\Delta$Vmca (%)

Systemic

Inspired Oxygen Fraction

End Tidal $CO_2$

Arterial Oxygen Saturation

Mean Arterial Blood Pressure

Heart Rate

Invasive Monitoring

Intracranial Pressure

Brain Tissue $pO_2$

Jugular venous oximetry

Arterial Blood Gases

Cerebral Microdialysis

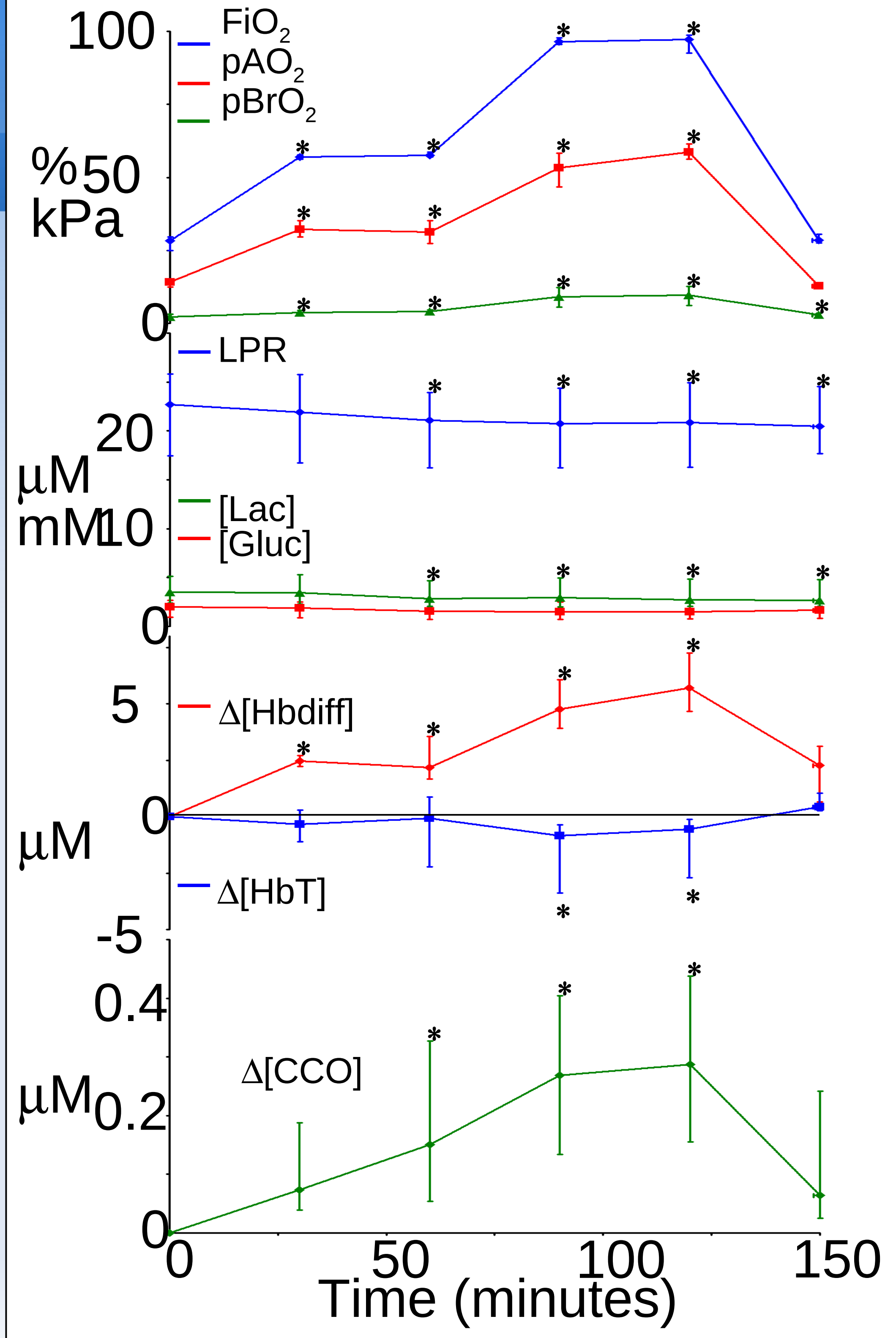
# Changes in haemodynamic and metabolism during hyperoxia in the injured brain

# Simultaneous NIRS, brain tissue $PO_2$ and microdialysis measurements

n=8

*p<0.05 for change from baseline

Tisdall et al. (2008) J. Neurosurg.



# *Systems Biology or VPH: Hand-in-hand modelling /experiments Mathematics for Biology AND Biology for Mathematics*

- Multidisciplinary studies
- Complete understanding of the micro and marco scale: simple odes to virtual simulators
- Interpretation of mathematical/numerical results in the quest to improving clinical research
- On route to building a VPH:

  - Bottom-up in hand with top-down modelling approach;

  - we all speak 'systems biology'

**Everyone is happy!**

# Thanks to

Welcome Trust

Karen Page (Department of Mathematics, UCL)

James Briscoe, Nikos Balaskas, Vanessa Ribes (Developmental Biology, NIMR)

Murad Banaji and Clare Elwell (Medical Physics and Bioengineering, UCL)

Chris Cooper (University of Essex, Colchester)

....the audience!