Occam's Knife-Fight

Matthew Caldwell, BORL — 20 May 2015

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part one is “context”, for which read: weeping generalisations, caricatures, wild surmise, circular arguments, gross oversimplifications, thinly disguised prejudice and…

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Handwaving

All models are wrong but some are useful

— *George Box*

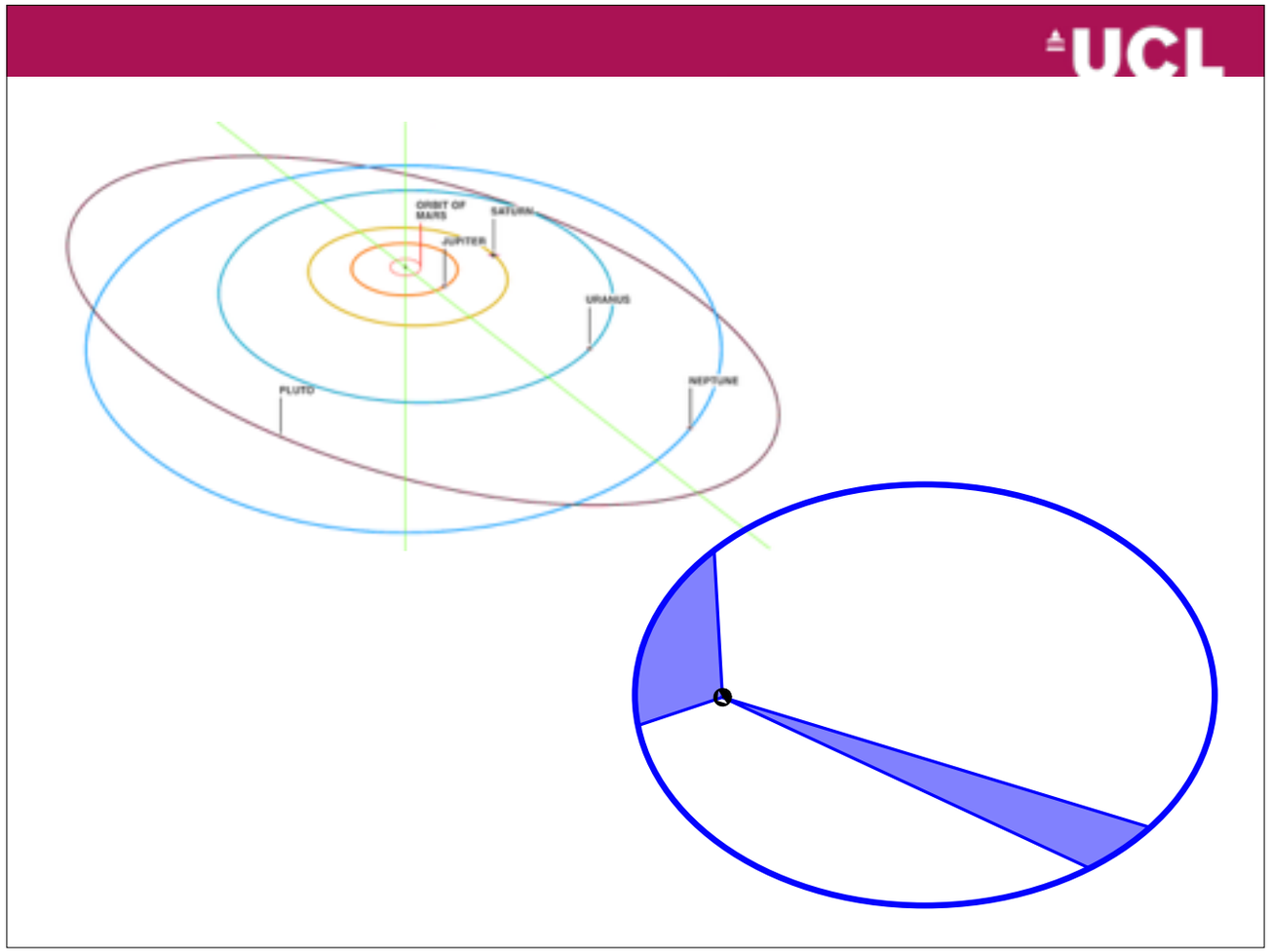
statistician vs mathematician or physicist

don’t assume this means: useful despite being wrong

very often a model is useful because it is wrong

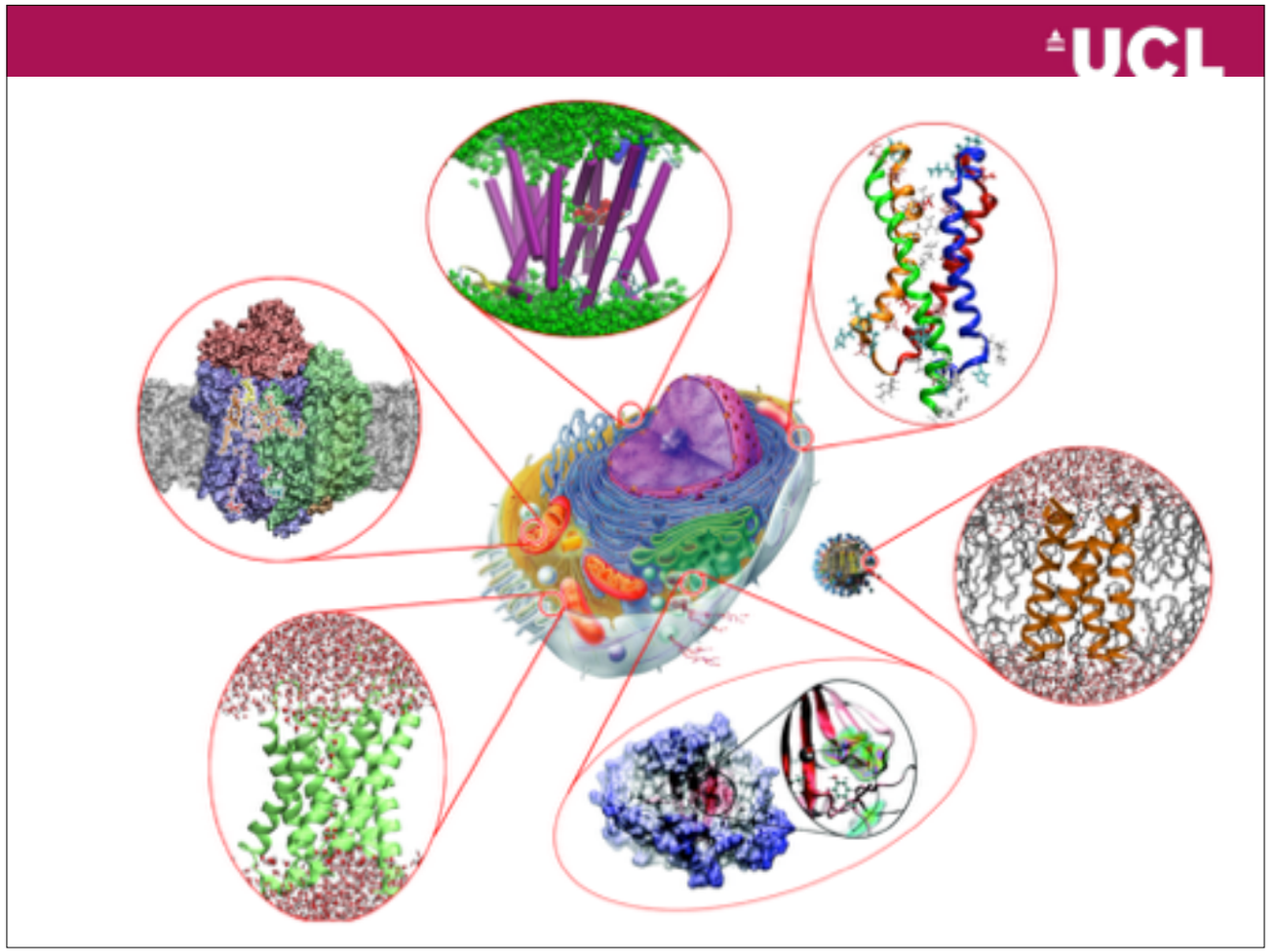
$$F = G\frac{m_1 m_2}{r^2}$$

in disciplines such as physics one may well encounter situations where a model is a very very very good approximation to real world behaviour still glosses over some thorny details, but they are legitimate things to gloss



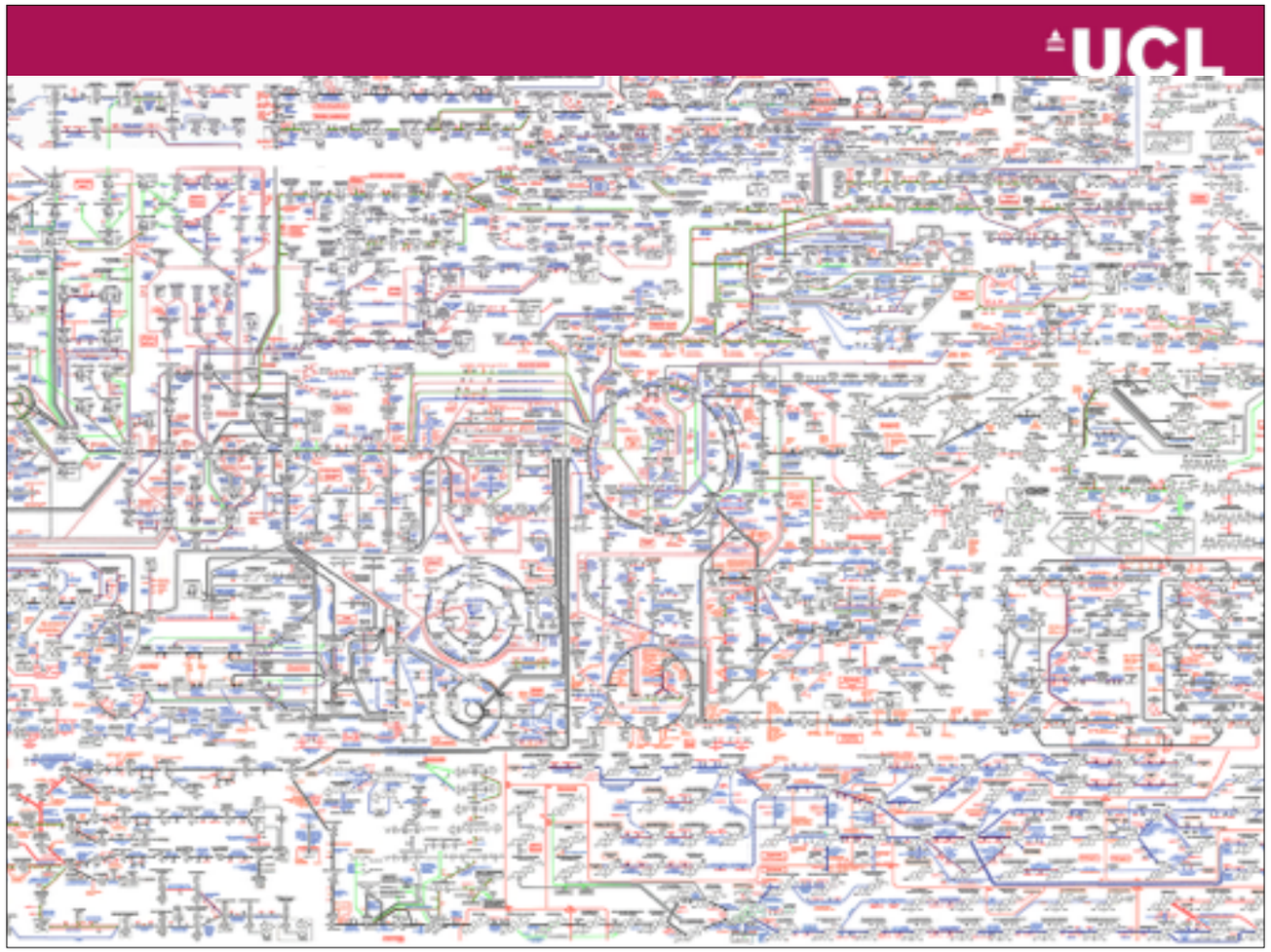
with such examples as planetary motion, gas laws, and indeed Beer Lambert, to go on

one might conclude that an inability to model biological systems with similar elegance and fidelity is evidence of JUST NOT TRYING HARD ENOUGH



but biological systems usually cannot be treated in isolation to the same extent

they are complex and interconnected and contingent — and they often can’t be readily represented by comprehensible models



one approach is just to pile on detail upon detail

unfortunately, this tends to mean losing sight of Box's principle

winding up with models that were still axiomatically wrong, but also sorely lacking in usefulness due to their bewildering complexity

Every time you add something
(a variable or parameter or process)
to a model
it gets **worse**

due to increased uncertainty, more sources of error, incomprehensibility, loss of explanatory power, etc — cf Occam's Razor, AIC etc

With four parameters I can fit an elephant, and with five I can make him wiggle his trunk

— John von Neumann

with that in mind, here is the BEST MODEL EVAH, and with that we can all go home

$$y = 0$$

Ta-da! Perfect. No pesky parameters, no difficult numerical solutions.

It can account for everything, as long as you assume that any behaviour you actually observe is essentially measurement error.

Every time you add something
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Since that is obviously not sufficient though, we must temper the previous assertion

Every time you add something
(a variable or parameter or process)
to a model
it gets worse

…but it may get better **more**

this is basically the tension melodramatically represented in the talk title

Better or worse?

trivial models cannot (typically) explain non-trivial phenomena (though there are exceptions)

complexity must be justified by a commensurate increase in explanatory power

— and we can’t really say much more useful without getting into more concrete examples

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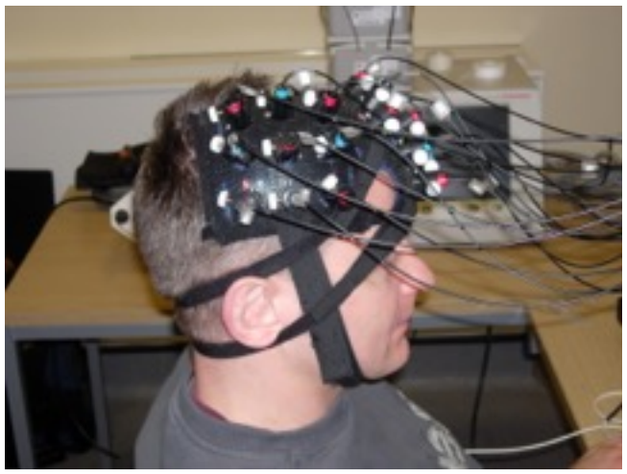
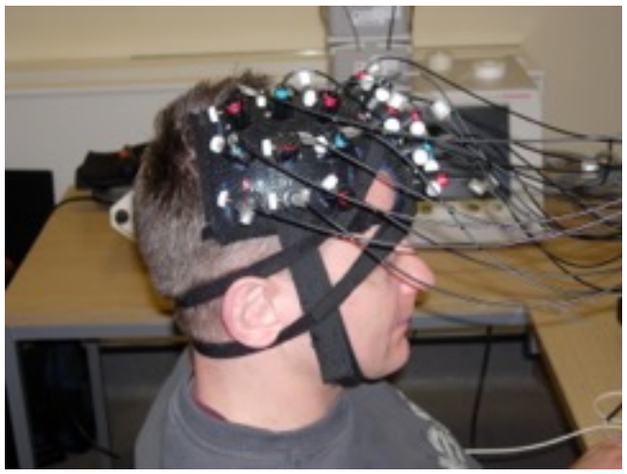
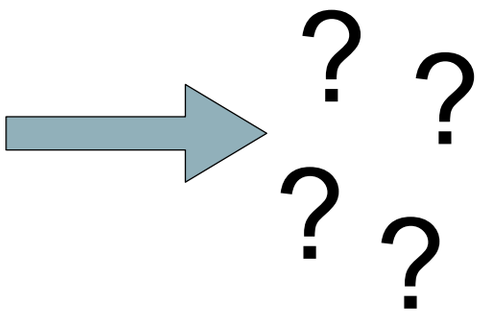
Brass Tacks

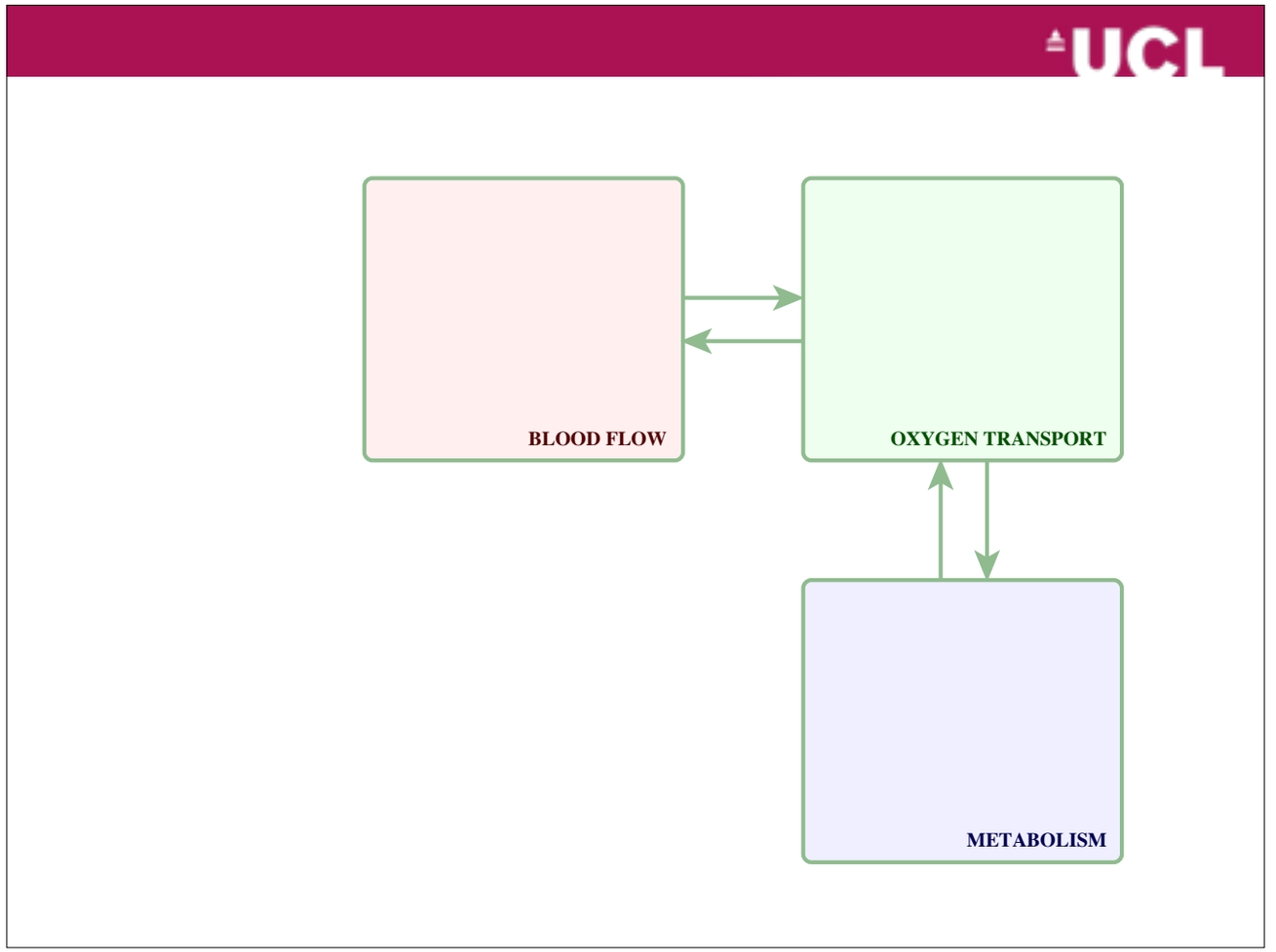


instrumentation such as NIRS gives us information about what's going on internally, but only in a proxy, cryptic form

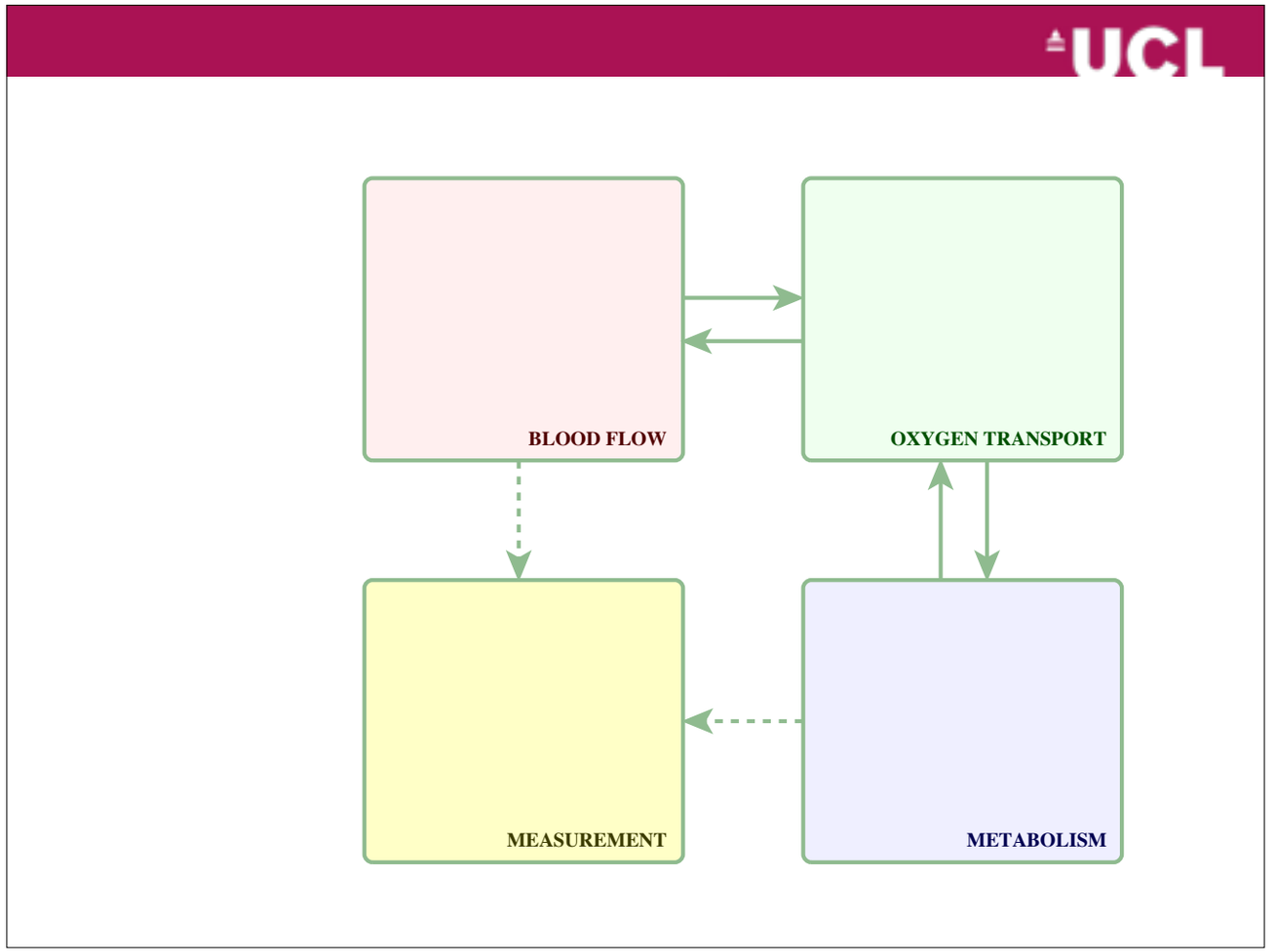




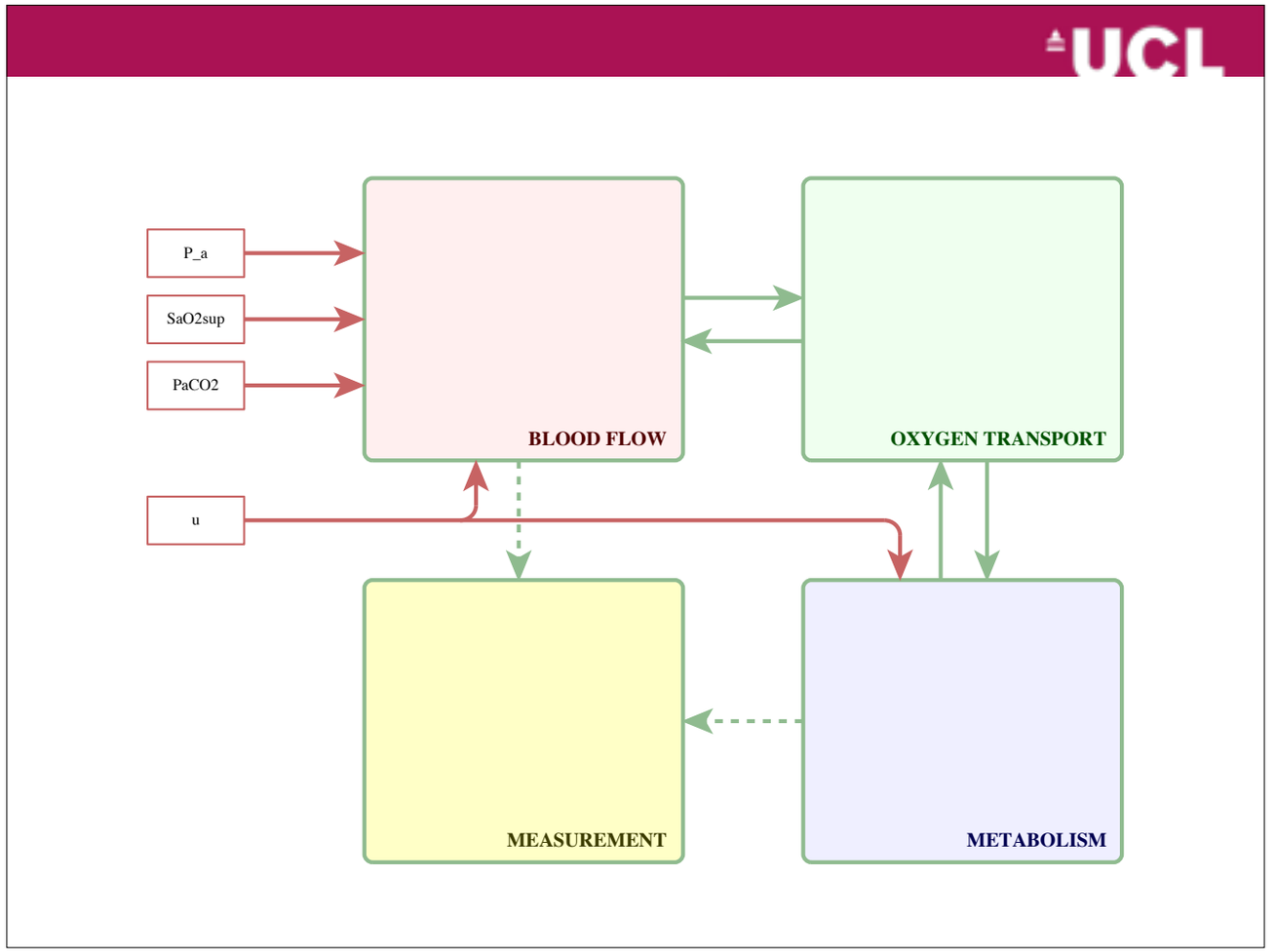
to estimate internal states we need to have models of how those relate to measurable quantities



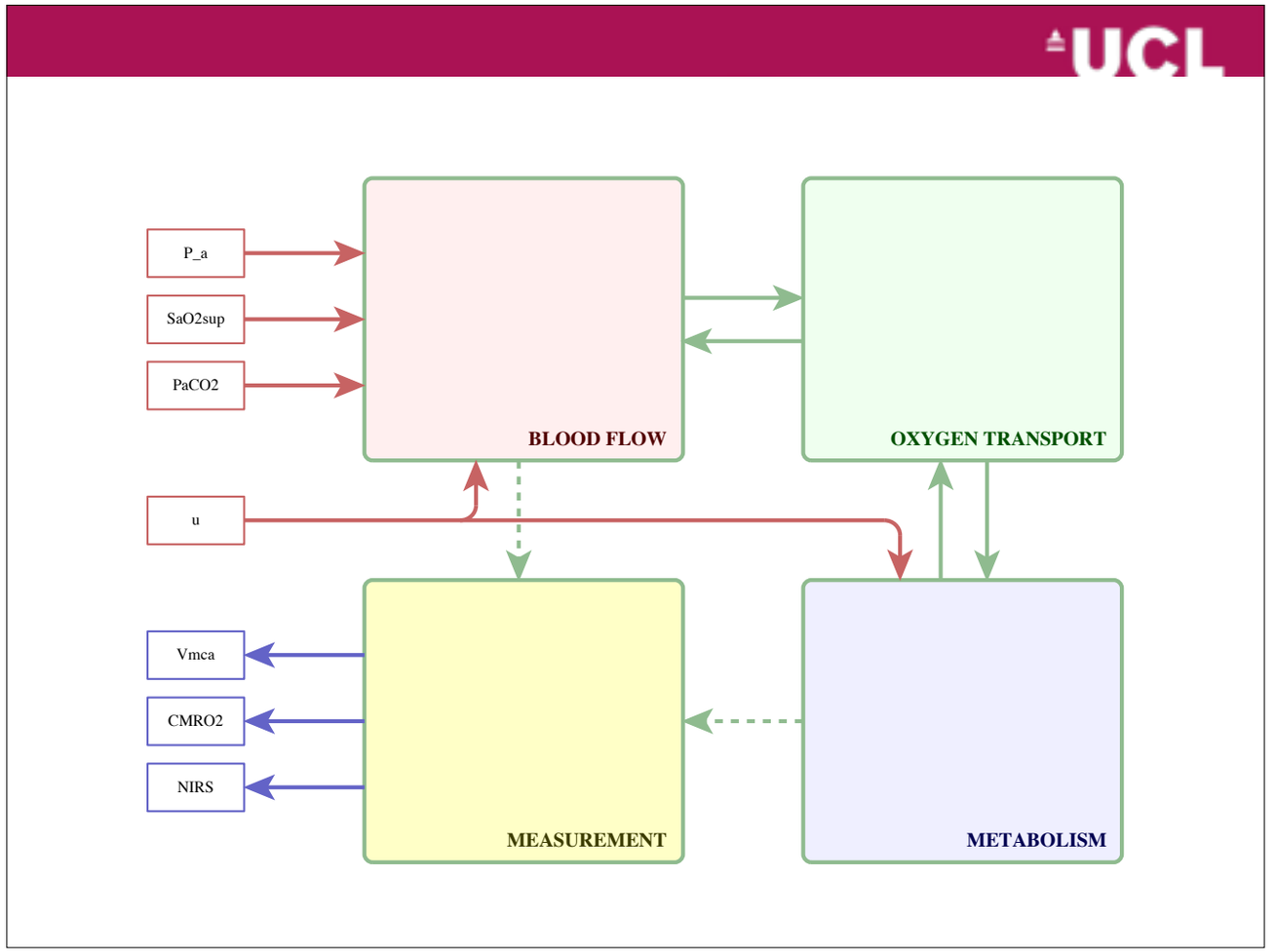
these are abstracted models of physiological activity in several compartments



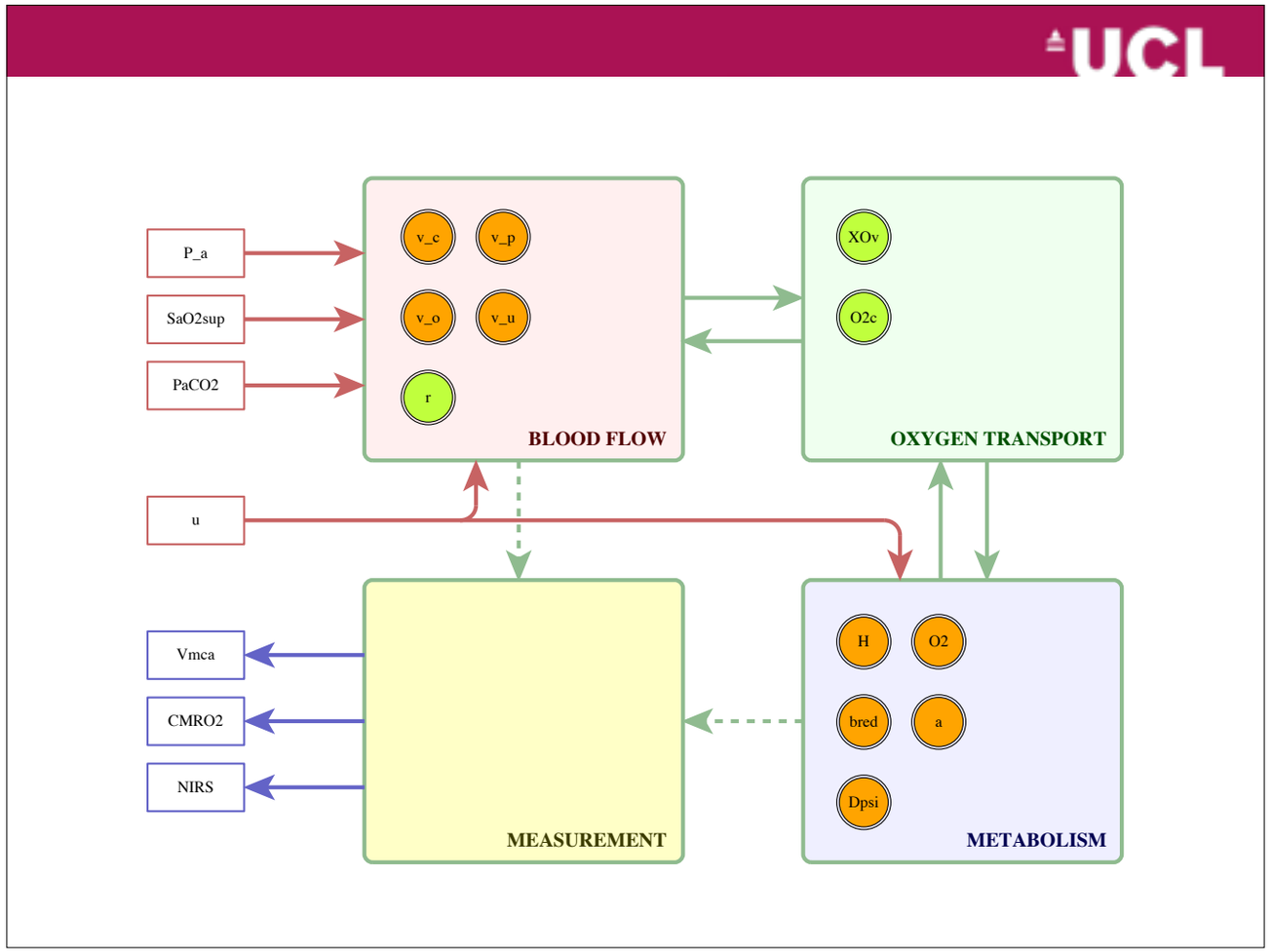
plus a measurement model that maps the internal state to an estimate of the signals we observe



the model is driven by a small number of measurable inputs, plus an (at present) non-measurable made up one represented “demand”

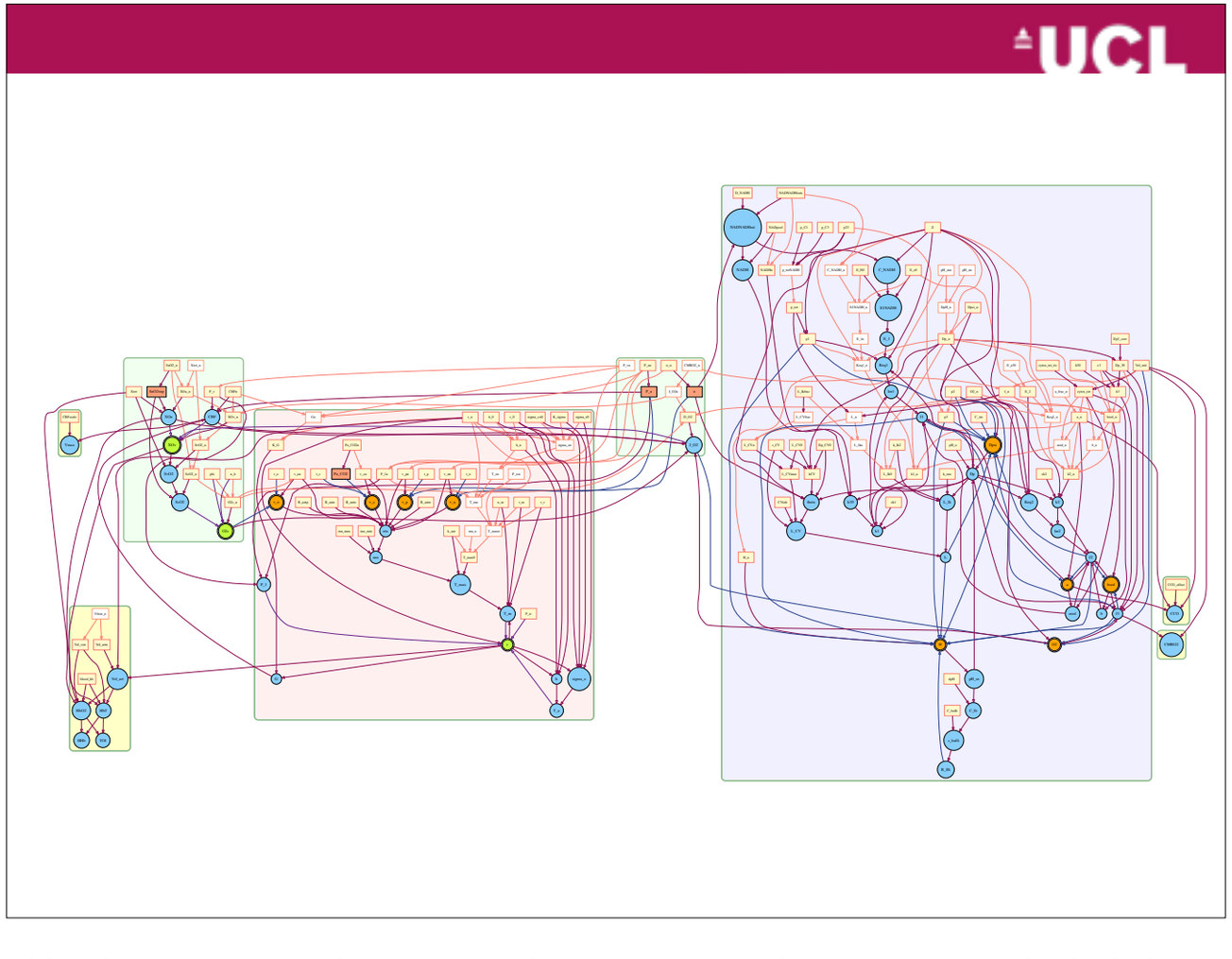


and produces a number of outputs, otherwise measurable or not, including NIRS

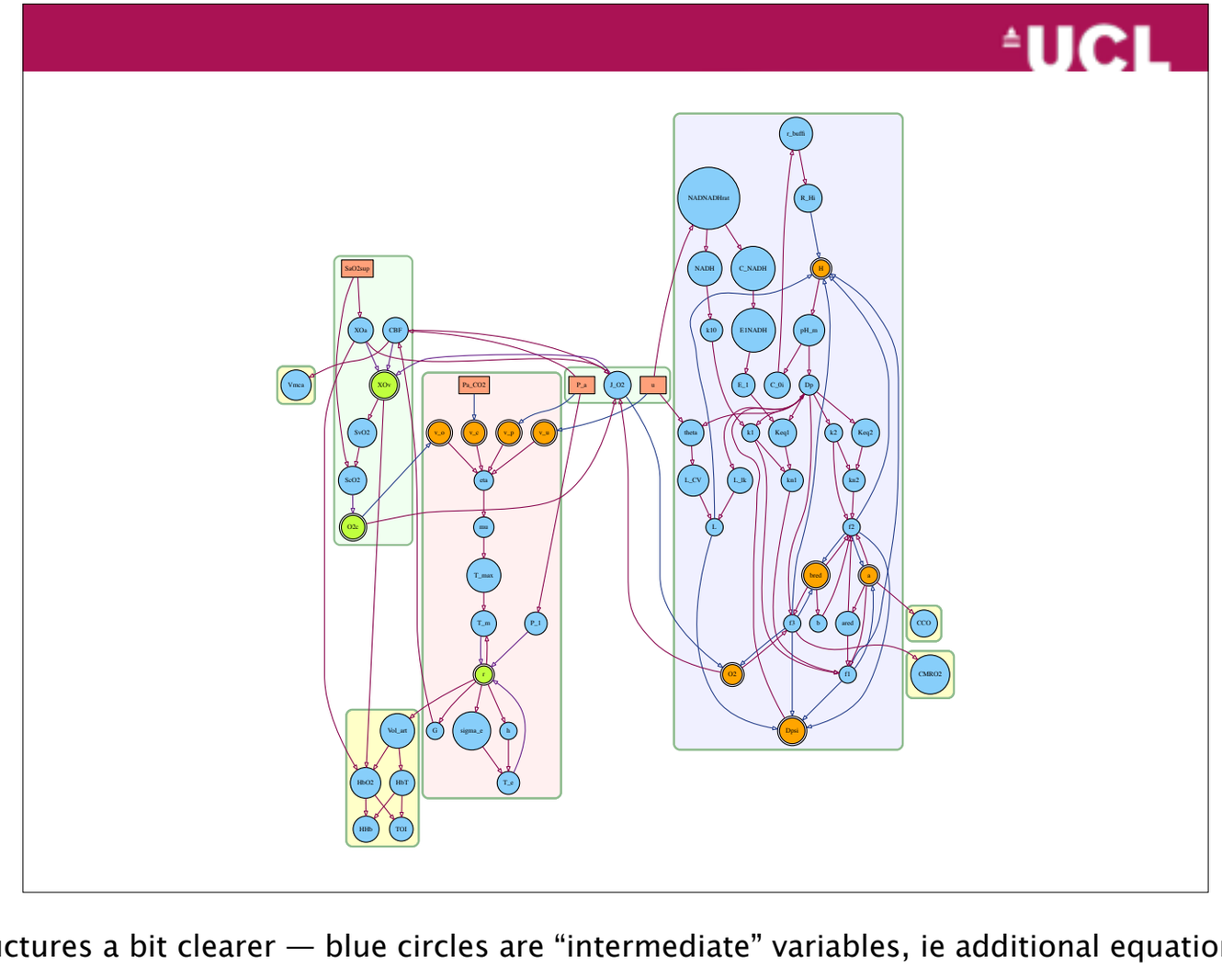


a number of model variables represent the internal state; note that there are none in the measurement model, since it does not influence behaviour

this is a simplified representation



the actual implementation looks more like this (represented as a network of interacting data entities) — the little boxes are parameters — there are LOTS



omitting parameters makes the structures a bit clearer — blue circles are “intermediate” variables, ie additional equations in the model spec

Supplementary material for "A model of brain circulation and metabolism"

A Model equations

Apart from the equations defining the first-order filtered regulatory stimuli, v_{P_a}, v_{O_2}, v_{PaCO2} and v_u, the model has only five dynamic variables, $\Delta\Psi$ and the four mitochondrial concentrations: CuA_o, $a3_r$, [H], and $[O_2]$. A minimal set of equations describing the model are provided below:

$$\frac{dv_x}{dt} = \frac{1}{\tau_x}(x - v_x), \qquad x = P_a, O_2, PaCO2, u \tag{A.1}$$

$$\frac{d\,CuA_o}{dt} = 4(f_2 - f_1) \tag{A.2}$$

$$\frac{d\,a3_r}{dt} = 4(f_2 - f_3) \tag{A.3}$$

$$\frac{d\,[H]}{dt} = (-p_1 f_1 - p_2 f_2 - p_3 f_3 + L)/Vol_{Hi} \tag{A.4}$$

$$\frac{d\,\Delta\Psi}{dt} = \frac{p_1 f_1 + p_2 f_2 + p_3 f_3 - L}{C_{im}} \tag{A.5}$$

$$\frac{d\,[O_2]}{dt} = J_{O2}/Vol_{mit} - f_3 \tag{A.6}$$

$$f_1 = k_{1,n}\frac{NADH}{NADH_n}\exp(-c_{k1}(\Delta p - \Delta p_n))\left[CuA_o - \frac{CuA_r}{10^{-(p_1\Delta p/4 - E_1(NADH))/Z}}\right] \tag{A.7}$$

$$f_2 = k_{2,n}\exp(-c_{k2}(\Delta p - \Delta p_n))\left[CuA_r\,a3_o - \frac{CuA_o\,a3_r}{10^{-(p_2\Delta p/4 - E_2)/Z}}\right] \tag{A.8}$$

$$f_3 = k_{3,0}[O_2]a3_r\,\frac{\exp(-c3\Delta p)(1+\exp(c3\,\Delta p_{30}))}{1+\exp(-c3(\Delta p - \Delta p_{30}))} \tag{A.9}$$

$$L = L_{CV,max}\left(\frac{1-\exp[-k_{CV}(\Delta p - \Delta p_{CV0} + Z\ln(u))]}{1 + r_{CV}\exp[-k_{CV}(\Delta p - \Delta p_{CV0} + Z\ln(u))]}\right) + k_{unc}L_{lk0}(\exp(k_{lk2}\Delta p) - 1) \tag{A.10}$$

$$Vol_{Hi} = \frac{1000\ C_{buffi}\ Vol_{mit}\ dpH}{[H]\ (1 - 10^{-dpH})} \tag{A.11}$$

$$J_{O2} = \min\{D_{O2}([O_{2,c}] - [O_2]),\ CBF[HbO_{2,a}]\} \quad \text{with smooth approximation} \tag{A.12}$$

$$J_{O2} = c - \frac{\sqrt{(x+c)^2 + \epsilon^2} - (x+c)}{2} \quad \text{where}$$

$$c = CBF[HbO_{2,a}],\ \ x = D_{O2}([O_{2,c}] - [O_2]),\ \ \epsilon = CBF_n[HbO_{2,a,n}]/10 \tag{A.13}$$

$$CBF = K_G(P_a - P_v)r^4 \tag{A.14}$$

$$[O_{2,c}] = \phi\left(\frac{2SaO2 - J_{O2}/(CBF\ [Hbtot])}{2 + J_{O2}/(CBF\ [Hbtot])}\right)^{\frac{1}{n_h}} \tag{A.15}$$

$$r = \frac{(\sigma_{r0}(\exp(K_\sigma(r - r_0)/r_0) - 1) - \sigma_{cstl})h + T_{max0}(1 + k_{aut}\mu)\exp\left(-\left|\frac{r - r_m}{r_t - r_m}\right|^{n_m}\right)}{(P_a + P_v)/2 - P_{ic}} \tag{A.16}$$

$$h = \sqrt{r^2 + (r_0 + h_0)^2 - r_0^2} - r \tag{A.17}$$

$$\mu = \frac{\mu_{min} + \mu_{max}e^\eta}{1 + e^\eta} \tag{A.18}$$

$$\eta = R_P\left(\frac{v_{P_a}}{v_{P_a,n}} - 1\right) + R_O\left(\frac{v_{O_2}}{v_{O_2,n}} - 1\right) + R_C\left(1 - \frac{v_{PaCO2}}{v_{PaCO2,n}}\right) + R_u\left(1 - \frac{v_u}{v_{u,n}}\right). \tag{A.19}$$

In the case of the simplified model Equations A.1, A.6 and A.12-A.19 are omitted, mitochondrial oxygen $[O_2]$ is a controllable parameter, and f_1 (Equation A.7) takes the form

$$f_1 = k_{1,n}\frac{UQH_2}{UQH_{2,n}}\exp(-c_{k1}(\Delta p - \Delta p_n))\left[CuA_o - \frac{CuA_r}{10^{-(p_1\Delta p/4 - E_1(UQH_2))/Z}}\right]. \tag{A.20}$$

Note that several of the equations are implicit or need to be solved simultaneously. Apart from CBF above, important model output variables (or observables), which can potentially be used to compare model behaviour to measured quantities *in vivo* are

$$SvO2 = SaO2 - \frac{J_{O2}}{CBF[Hbtot]} \tag{A.21}$$

$$CMRO_2 = Vol_{mit}f_3 \tag{A.22}$$

$$TOS = \frac{AVRn(r/r_n)^2SaO2 + SvO2}{(AVRn(r/r_n)^2 + 1)} \tag{A.23}$$

$$\Delta Hbt = \frac{1000}{4}\left(Vol_{art,n}\left(\frac{r}{r_n}\right)^2 + Vol_{ven}\right)[Hbtot]Vol_{blood,n} - Hbt_n \tag{A.24}$$

$$\Delta HbO2 = \frac{1000}{4}\left(Vol_{art,n}\left(\frac{r}{r_n}\right)^2 SaO2 + Vol_{ven}SvO2\right)[Hbtot]Vol_{blood,n} - HbO2_n \tag{A.25}$$

$$\Delta HHb = Hbt - HbO2 - HHb_n \tag{A.26}$$

$$\Delta oxCCO = 1000\,Vol_{mit}\,(CuA_o - CuA_{o,n})\,. \tag{A.27}$$

the main equations look like this, from the original publication
(a bunch of the intermediates are referred to but not defined here)

Note that several of the equations are implicit or need to be solved simultaneously.

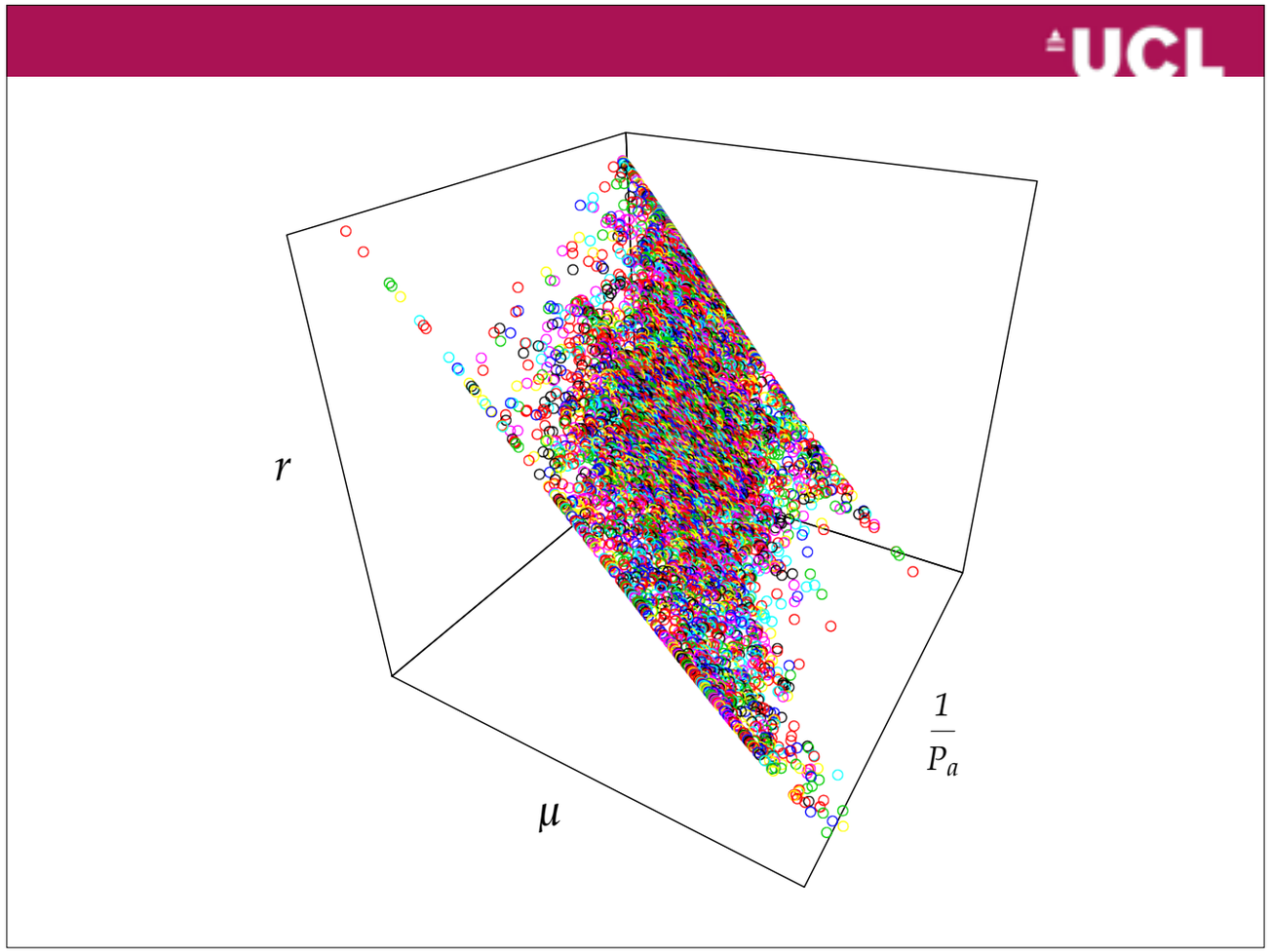
note this sentence:

Note that several of the equations are implicit or need to be solved simultaneously.

i.e., we cannot represent the model in the sort of nice functional form that we would ideally like

$$r = \mathrm{f}\left(P_a, \mu, \ldots\right)$$

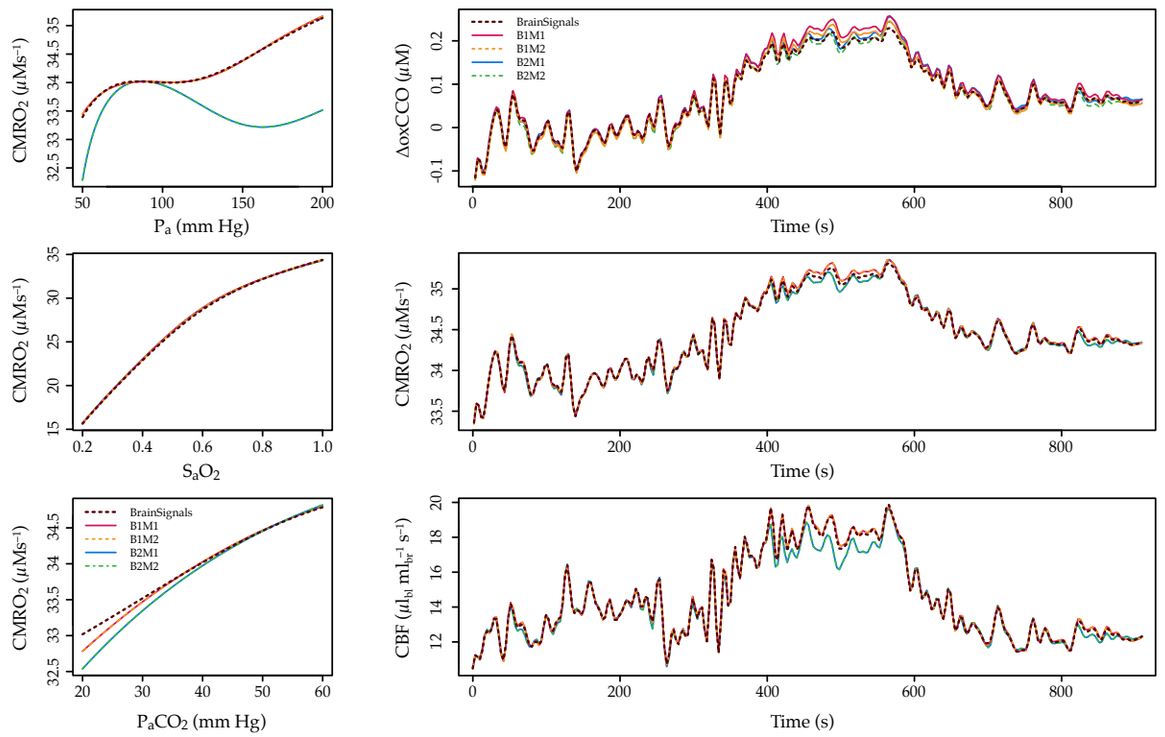
…which would be directly representing state variables, such as r here, in terms of the inputs (and intermediate variables calculated from them)



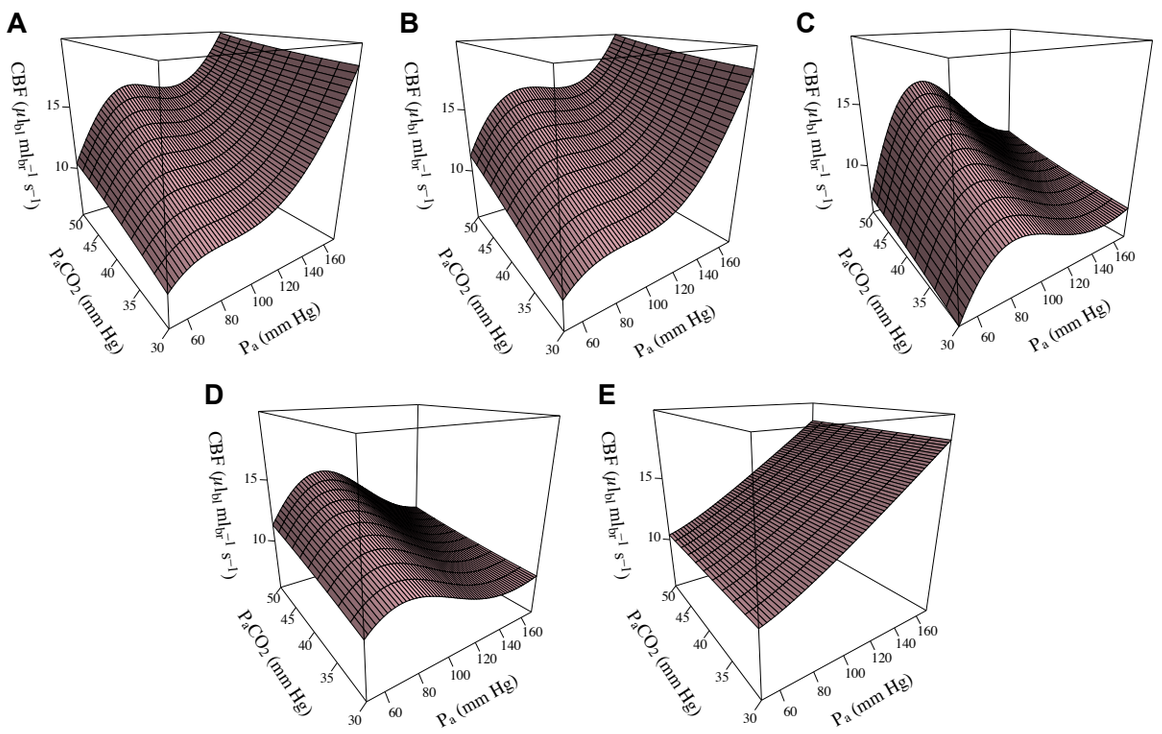
driving model with a wide range of inputs we find regions of behaviour that are well-described by linear relationships

$$r = \lambda_0 + \lambda_1 \frac{1}{P_a} + \lambda_2 \mu + \lambda_3 \frac{\mu}{P_a}$$

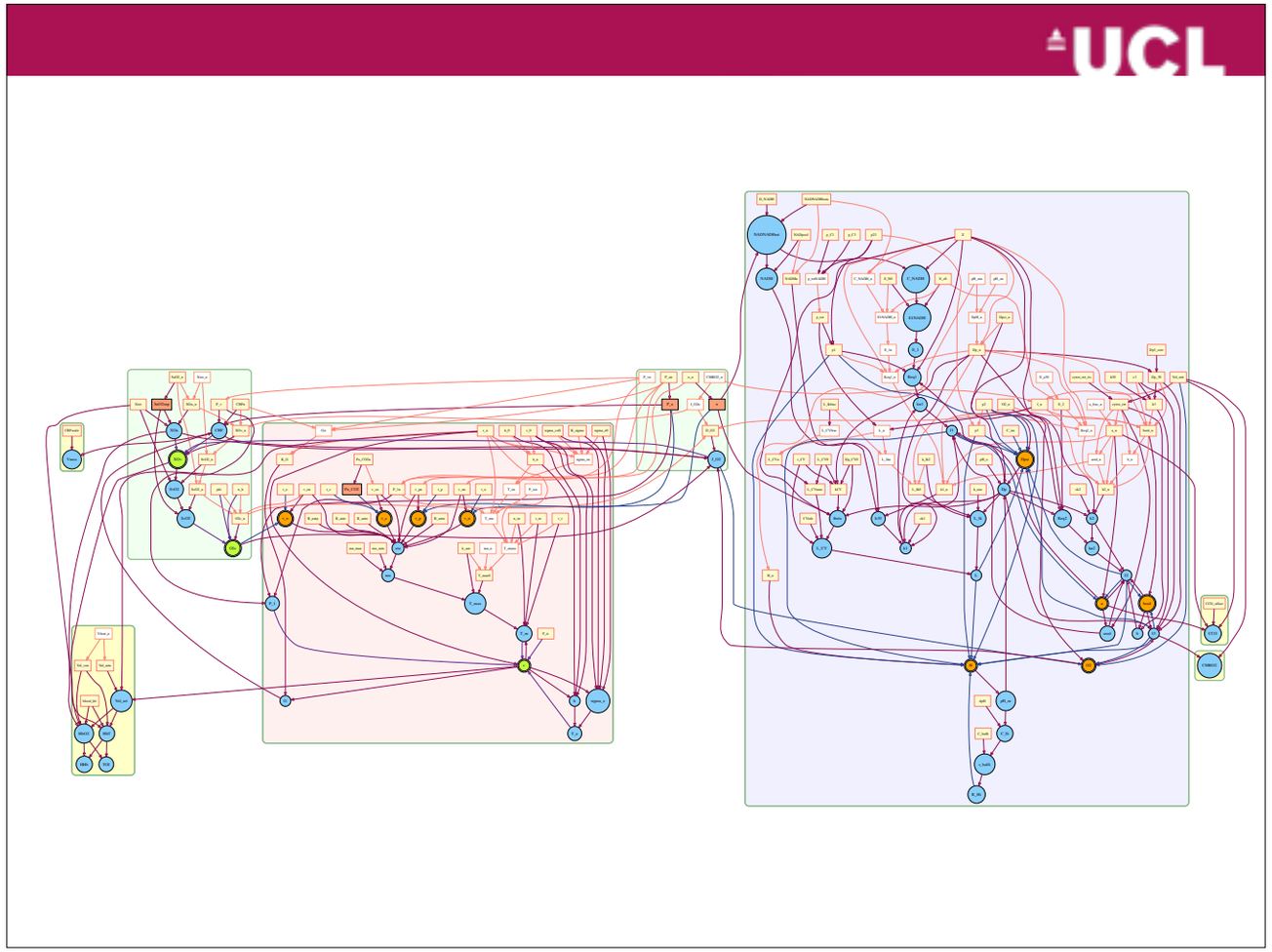
so let’s pretend we *can* express them this way, and fit a simple linear model



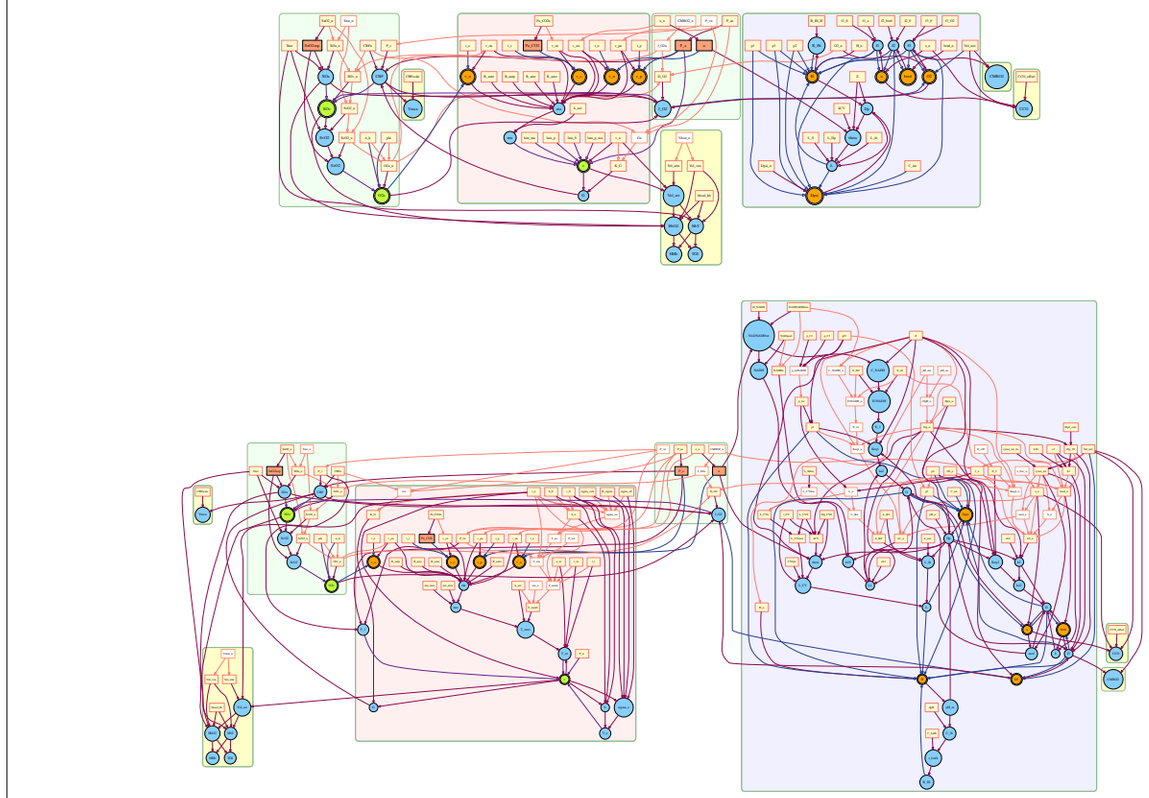
we find that overall model behaviour can be well approximated in simplified form



obviously we cannot just discard relationships arbitrarily and maintain behaviour — there is some minimum level of interaction that must be included — if we lose too many terms the model no longer captures the behaviours we're interested in



compare the original model…



...to the simplified one. it is certainly smaller and simpler. But...

Better or worse?

is it actually any better? it’s more nuanced than that: the simplification brings benefits, but also costs. utility depends on what you want to do with the model. for our purposes… well, it’s not yet clear…