Middle East Technical University
Biomedical Engineering Department, Bioelectric

Dynamic Casual Modeling

Report

vol. I

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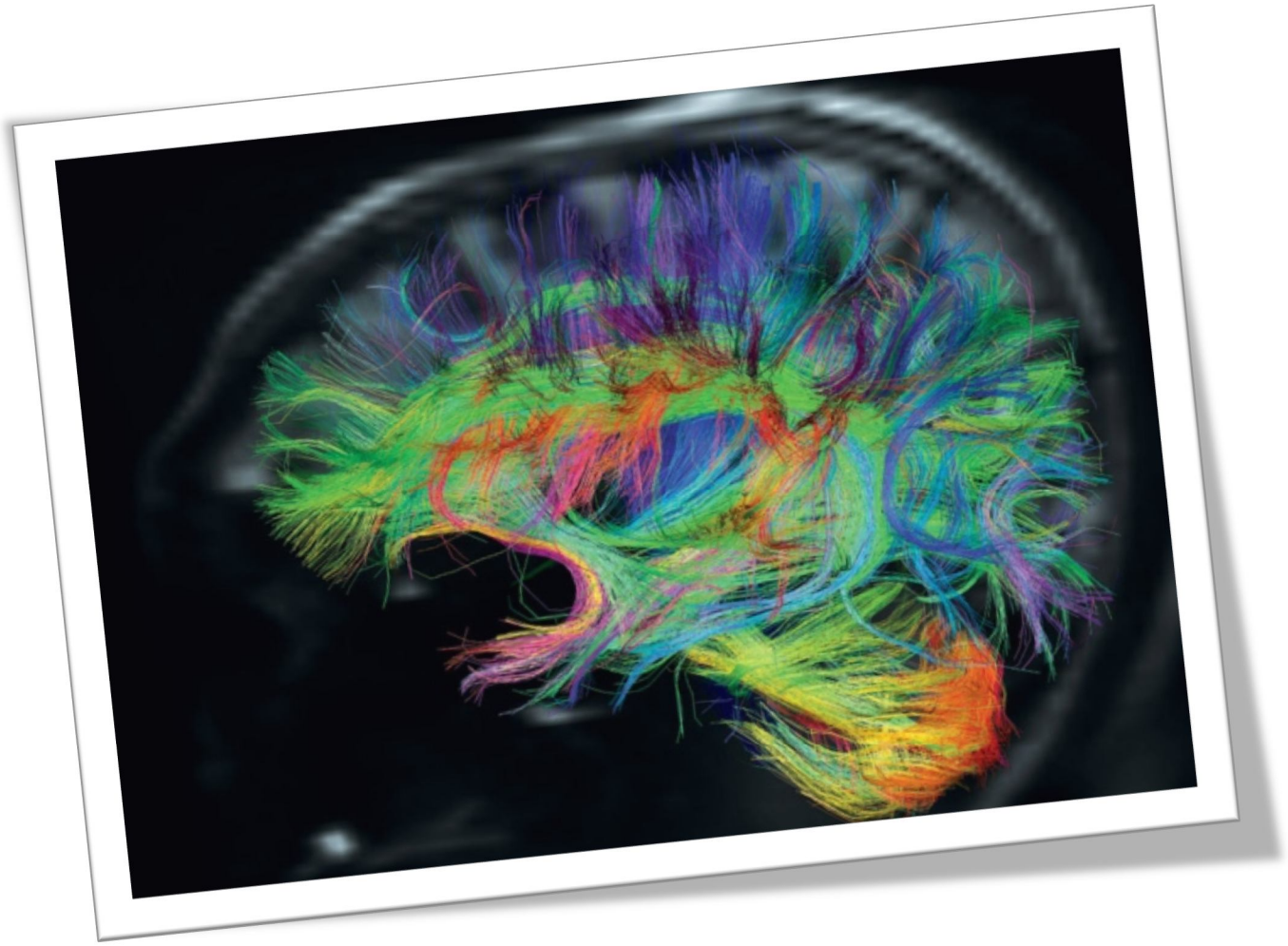


Abstraction:

In this report, I will try to explain the basic fundamentals of Dynamic Causal Modeling (DCM). It consists of the equations which are used in the **forward Hemodynamic model**, the model that is used in the DCM. You will see how the neural activities in the base level converts to the **blood oxygen level dependent (BOLD) signal** which is in the heart of fMRI and DCM. However, due to time limitation, the explanation of the **Bayesian Model Selection (BMS)** will be explained in the next report.

Introduction:

According to Christopher P. Pawela, a professor of Medical College of Wisconsin, "***Brain Connectivity*** provides groundbreaking findings in the rapidly advancing field of connectivity research at the systems and network levels". In general, we have three types of the Brain Connectivity:

I. Anatomical/ Structural Connectivity: refers to the presence of connections in the anatomical connection.
II. Functional Connectivity: tries to provide us statistical dependencies between regional time series.
III. Effective Connectivity: determines the directed influences between neurons or population of neurons.

The main difference between Functional Connectivity and Effective Connectivity is based on the direction of dependencies. In the case of Functional Connectivity, we only try to extract descriptive model which provides us the statistical dependency. On the other hand, Effective Connectivity tries to make claim about the directions of influences.

To researchers like us who interested on the Functional Magnetic Resonance Imaging (fMRI), Effective Connectivity is very interesting. The source of this interest comes from the fact that we can increase our knowledge about the neuronal regional function of brain by understanding the statistical influences and their direction between those regions.

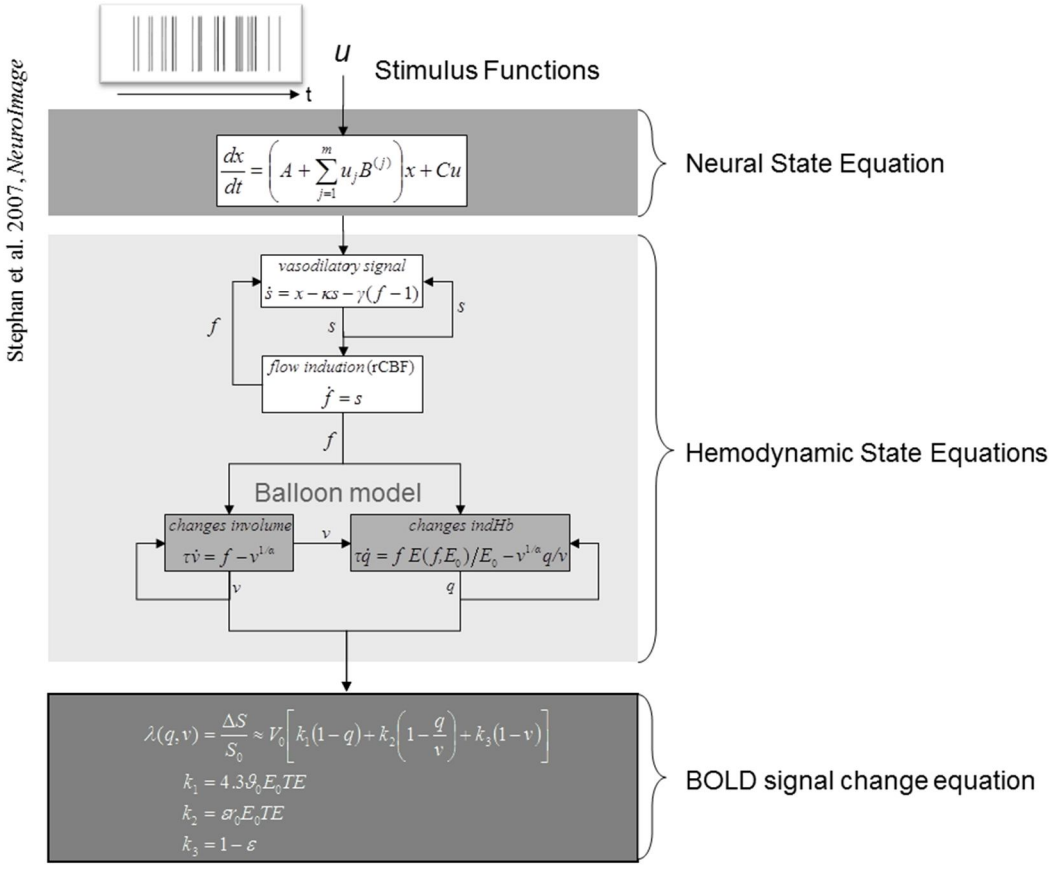
Finding a general model to extract the Effective Connectivity became a big concern since 1990's. Four types of models were developed:

I. Structural Equation Modeling (SEM)(McIntosh et al. 1991, 1994; Büchel & Friston 1997; Bullmore et al. 2000)
II. Regression Models (e.g. psycho-physiological interactions, PPIs) Friston et al. 1997
III. Volterra kernels (Friston & Büchel 2000)
IV. Time series models (e.g. MAR/VAR, Granger causality) Harrison et al. 2003, Goebel et al. 2003
V. Dynamic Causal Modelling (DCM) *bilinear:* Friston et al. 2003; *nonlinear:* Stephan et al. 2008

In this report we are going to discuss about the basic fundamentals of the Dynamic Causal Modeling (DCM) which is a part of the SPM8, and it is based on the research of Prof. Dr. Klaas Enno Stephan at the University College London who helped to development of DCM with his famous paper. [K.E. Stephan et al. 2007].

A Brief Scheme of DCM

Due to the non-invasive nature of the fMRI and EEG, Dynamic Casual Model (DCM) contains a vigor method in order to infer the correct information. We know that the relationship between neural activity and measured **blood oxygen level dependent** (BOLD) **signal** is very complicated; therefore, it is not fully understood. However, DCM uses Hemodynamic forward model which is based on the work of Buxton et.al 1998.



The figure above is the flowchart of Hemodynamic forward model. As you can see, it consists of three main parts:

I. In the first part, the challenge is to find the linkage between neural activity and regional cerebral blood flow (rCBF). This linkage is based on **linear differential equations** that model a dampened oscillator. The dampened oscillator comes from changes in neuronal activities which show an exponential decaying vasodilatory signal which is subject to the feedback-regulation by the flow it induces.

II. The second part is "**Balloon Model**", and it tries to find the dependency of BOLD signal on the **blood volume (v)** and **deoxyhemoglobin content (q)**. Two equations show these dependencies which are very important for DCM.

III. Finally, the output which is called **BOLD signal change equation**, $\lambda(q,v)$, links "v" and "q" to BOLD signal change.

Neural State Equation: Practical Perspective

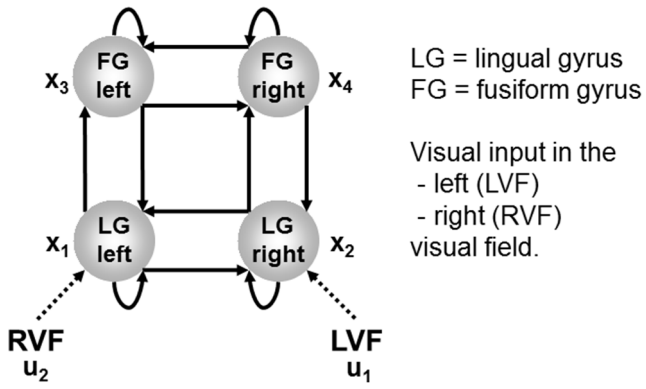
The Idea of the DCM based from the fact that we cannot directly observe the state of interest (e.g. Neuronal Activity) in the brain research. Instead, we can measure that state of interest, and convert it to the meaningful sign. For example, we use **Hemodynamic Forward Model** in the fMRI in order to covert the neural activity to the BOLD signal, or we can use **Electromagnetic Forward Model** in the case of EEG. However, we can describe the hidden Dynamics of a system in terms of Differential Equations such as

$$\frac{dx}{dt} = F(x, u, \theta)$$

which is **Neural State Equation**. As equation shows, the interested neuronal region (x) is parameterized on (θ) and some perturbation knowledge of the system called (u). Additionally, we can mathematically describe any particular neuronal sate (x) and translate it into the BOLD signal or EEG. The idea is that we can estimate the posterior distribution of given measurement based on the mathematical description by inverting and fitting the model to the estimated model.

Here, I will try to explain an example to clarify the mathematical model that we just discussed. Imagine an experiment that we presented a visual stimulus either to the left or right lingual gyrus- a part of brain that deals in the vision processing- where the subject is stated in the center. Additionally, suppose that we interested in a small system which shows the interaction of right and left gyruses and fusiform gyrus- a brain structure which deals in processing of color information, face and body recognition and word recognition.

In this example, our goal is to model the Neuronal Dynamics in the system using a few simple assumptions and some knowledge that we have about the brain. For example, as prior knowledge we know that if we present visual stimulus in the periphery of the visual field, it will receive contrariwise to the visual cortex. In other words, stimulus in the Right Visual Field will send to the Left Lingual Gyrus and vice versa. We also know some anatomical connectivity of that system. For example, monkey's studies have shown that the interested regions are connected to each other within and across the hemisphere such as figure below.



Based on that knowledge, we can make assumptions and write down mathematical equations. The first assumption could be that all things that we interested in can be summarized by single number per region. For example, this number can be mean activity of the region. For second assumption, we suppose that everything is linear. Therefore, we can write an equation for each region:

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + c_{12}u_2$$
$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{24}x_4 + c_{21}u_1$$
$$\dot{x}_3 = a_{31}x_1 + a_{33}x_3 + a_{34}x_4$$
$$\dot{x}_4 = a_{42}x_2 + a_{43}x_3 + a_{44}x_4$$

As you can see each area is represented by one number $\dot{x}_n$; $n = 1,2,3,4$, where "." means derivative in time. Therefore, $\dot{x}_1$ indicates the change in the activity of related region (in this case LG Left) as a linear combination of influences form other regions. For example, $\dot{x}_1$ equals to:

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + c_{12}u_2$$

Where,

$a_{11}x_1$: The influence of x_1 exerts on itself

$a_{12}x_2$: The influence of LG-Right exerts on LG-Left (x_1)

$a_{13}x_3$: The influence of FG-Left on LG-Left (x_1)

$c_{12}u_2$: The influence of stimuli on the Right Visual Field (RVF) on LG-Left (x_1)

Note: We have ignored other connections for simplicity. For example there should be a connection between Retina and LG-Left. We can show all these formulas in the compact form by using matrixes and vectors. I will be:

$$\dot{x}_1 = Ax + Cu \; ; \quad \theta = \{A, C\}$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & 0 & a_{24} \\ a_{31} & 0 & a_{33} & a_{34} \\ 0 & a_{42} & a_{43} & a_{44} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} + \begin{bmatrix} 0 & c_{12} \\ c_{21} & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Where,

θ: The parameters

$\dot{x}_1$: The changes in the states

A: Effective Connectivity Matrix

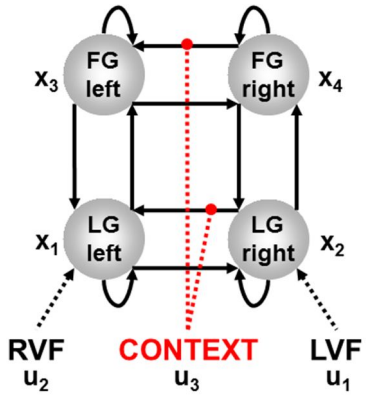
x: The current state of system

C: The parameters of input

u: External input

We can extent this formula; for example, we may wonder to determine the changes in the mathematical operation in the case of manipulating of some task. We can ask what will happen to

our mathematical system when we stimulate a "context" variable such as attention to some directions. Let suppose that we give the "context" variable between two influences as figure below:



In this case, we have to change our mathematical formula in such a way to contain these "context" variables. Mathematically,

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & 0 & a_{24} \\ a_{31} & 0 & a_{33} & a_{34} \\ 0 & a_{42} & a_{43} & a_{44} \end{bmatrix} + u_3 \begin{bmatrix} 0 & b_{12}^{(3)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_{34}^{(3)} \\ 0 & 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} + \begin{bmatrix} 0 & c_{12} & 0 \\ c_{21} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

As you can see, we added a simple matrix which is multiple by u_3. This implies the fact that when u_3=0 (no stimuli) everything will be the same as the previous term. However, when u_3=1 (there is a stimuli) we must add this matrix to our effective connectivity matrix. As a result, we can expand our pervious equation to the new form,

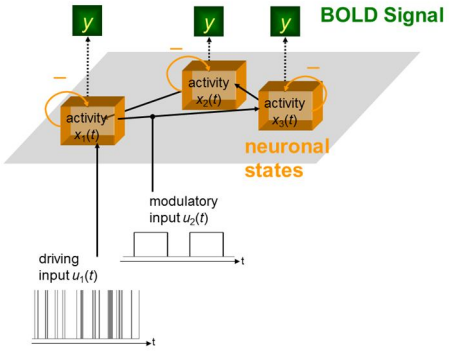
$$\dot{x} = (A + \sum_{j=1}^{m} u_j B^{(j)})x + Cu$$

Where $\sum_{j=1}^{m} u_j B^{(j)}$ is sum of the additional influences.

This is classical bilinear model that applies the DCM to fMRI. It is adaptive changes in connection strength as a function of some controlled variables (some "contexts" or task variables). Therefore, DCM allows us to define a model that describes how several populations of neurons or regions interact with each other.

DCM procedure:

In order to apply DCM on our fMRI data, first we have to define the interested regions. Then, we have to use our prior knowledge about that system to specify the connection between the regions. Third, we should specify the time of perturbation drive in such as visual stimulation as figure below shows. Finally, the specification of controlled task must be done; for example, the modulatory input $u_2(t)$ must imply.



As you can see, there are there ingredients which we have discussed as the building blocks of the equation. This equation is known as **the neuronal state equation**.

$$Neutonal\ State\ Equation \quad \dot{x} = (A + \sum_{j=1}^{m} u_j B^{(j)})x + Cu$$

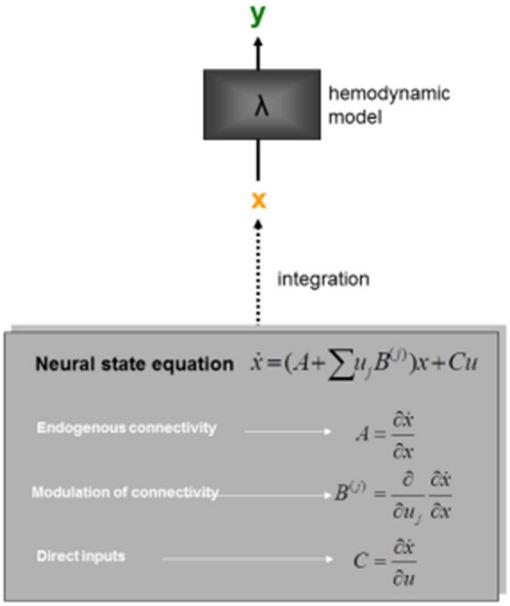
Where,

$A = \frac{\partial \dot{x}}{\partial x}$: Endogenous Connectivity and implies the strength of connection

$B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{x}}{\partial x}$: Modulation Connectivity and it allows us to change the coupling strength.

$C = \frac{\partial \dot{x}}{\partial u}$: Direct Input and it enables us to change the strength of perturbation.

After we specified the values of A, B, C, DCM integrates $\dot{x}$ to get the time series to X. At the next level, it passes X to a hemodynamic model (λ) in order to give a predictive Bold Signal. Then, DCM compares the real signal to find out the discrepancy. Based on this discrepancy, it updates parameters in the principle fashion until it cannot be able to do farther optimization.



Neural State Equation: Mathematical Perspective

If the discussed problem in the beginning of the pervious section is given to a mathematician who does not have any knowledge about the brain structure and function, he or she may model the system based on the same idea. The obvious way to build a model of a system which you do not have directly access is to use of **Taylor Series** approximation. Taylor Series is an infinite series consisting on the Partial Differential Equations (PDE). It basically approximate with increasing order to arbitrary exactness of an unknown function. However, the bilinear state equation which we discussed at the previous session can be obtained by expanding Taylor Series up to bilinear term.

Tow dimensional Taylor series (around $\mathbf{x_0=0, u_0=0}$):

$$\frac{dx}{dt} = f(x,u) \approx f(x_0,0) + \frac{\partial f}{\partial x}x + \frac{\partial f}{\partial u}u + \frac{\partial^2 f}{\partial x \partial u}ux + \ldots$$

In fact, the state equation which we are using in the DCM is a low order approximation to an unknown possible nonlinear dynamical system.

$$\frac{dx}{dt} = (A + \sum_{j=1}^{m} u_j B^{(j)})x + Cu$$

Where,

$$A = \left.\frac{\partial f}{\partial x}\right|_{u=0} \qquad B = \frac{\partial^2 f}{\partial x \partial u} \qquad C = \left.\frac{\partial f}{\partial u}\right|_{x=0}$$

The very obvious question may come to mind is: “what is the meaning of Coupling Parameters in the state of Differential Equation?” The answer of this question is that DCM parameters are just **Rate Constant**. The idea of the Differential Equations comes from the equations of Rate Constants which we have seen in the high school chemistry. The Rate Constant Equations give us (in exponential form) information about how quickly an effect is conveyed, and they are inversely proportional to the time constant of system. In other words, the speeds of the influences that feed forward in the system are similar to the speeds of the effects which are conveyed from one area to another.

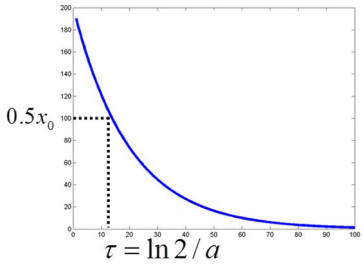
$$\frac{dx}{dt} = ax \Longrightarrow x(t) = x_0 \exp(at)$$

Where “a” is a **coupling parameter** which is inversely proportional to the half-life τ of z(t).

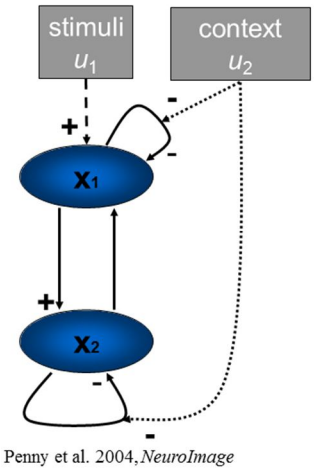
$$x(\tau) = 0.5x_0$$

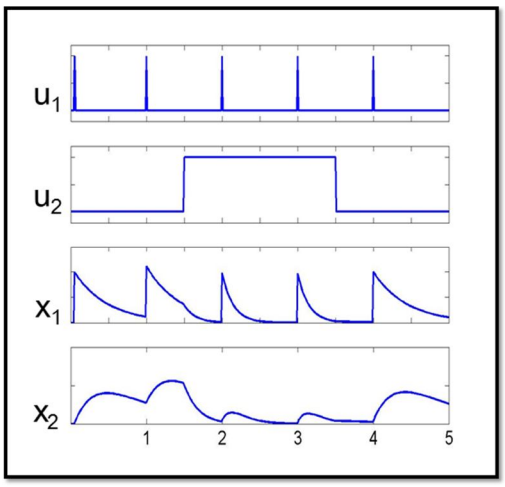
$$x(\tau) = x_0 \exp(a\tau)$$

$$a = \ln 2 / \tau$$



To clarify the concepts that we just described, lets review and example given in the Context-Dependent Decay experiment which is worked by Penny et al. 2004, NeuroImage. There are two interested regions X1 and X2 in this examle. We have a stimuli(u1) in the X1 region, and there is a context (u2) on the two regions.





As figure shows, the first one, X1, is given u1 in the equal space of time, and the interested region X1 increase suddenly and decay exponentially at each response of u1. The reason is that when first order differential equation is integrated the result is exponential form. On the other hand, The "context",u2, influences both of the X1 and X2. You can see that during the "context" the exponential decrease is very sharp in the X1 region. This decrease is even critical in the case of X2.

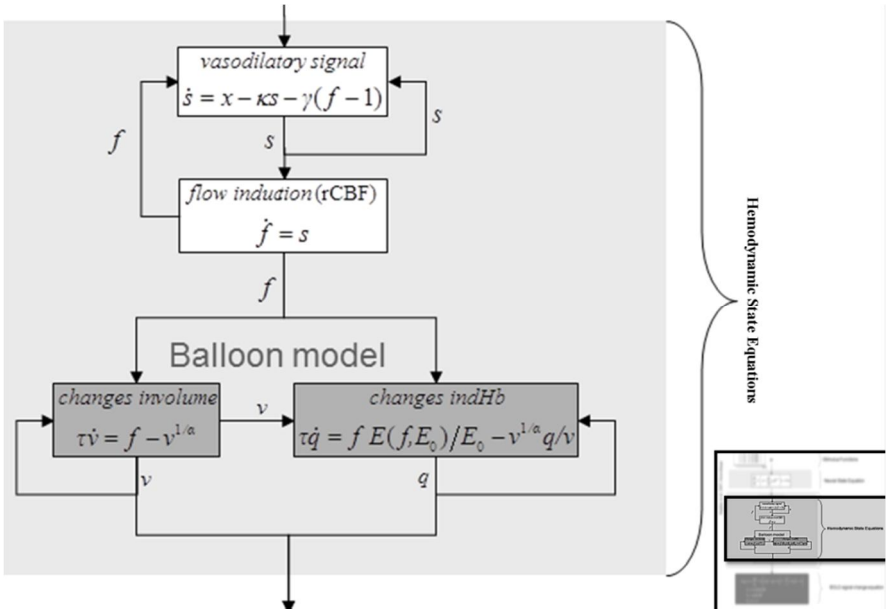
The mathematical representation of this model could be something like:

$$\dot{x} = Ax + u_2 B^{(2)} x + Cu_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & a_{12} \\ a_{21} & \sigma \end{bmatrix} x + u_2 \begin{bmatrix} b_{11}^2 & 0 \\ 0 & b_{22}^2 \end{bmatrix} x + \begin{bmatrix} c_1 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Hemodynamic State Equations:

We discussed about the first level of the DCM which was Neuronal State Equation. Now, we want to move to another level called "Hemodynamic Level" which makes DCM different from other Effective Connectivity models. The necessity in the usage of Hemodynamic is come from a study result which is done by David et al. 2008, *PLoS Biol*. David noticed a problem with the application of **Vector Auto-Regressive Model**, a model for analyzing Effective Connectivity. He used conjoin recording in rats. He simultaneously measuring fMRI and invasive recording in rat epilepsy model which is interesting model because there is a high abnormal traffic in one of the regions. This region is much more sluggish which make the region to be distinguishable from others. Then, he could show that if you apply effective connectivity model in this case Vector Auto-Regressive models to the data, you will get incorrect inference. However, he came up to the conclusion that if we add Hemodynamic Model to the top level of region such as DCM, then he could be able to get correct inference.



As figure below shows the Hemodynamic model used by DCM contains cascade of Differential equations. We will begin with **Balloon Model**, then we discuss about the **vasodilatory signal**.

Balloon Model:

The Ballon Model (1998) offers two different differential equations for evaluation of **blood volume (v)** and **deoxyhemoglobin content (q)** based on two assumptions:

I. The reaction of small past- capillary vessels to the increase of inflowing blood is like an inflating blood.
II. The extraction of oxygen is tightly related to the blood flow.

Let see how these two assumptions help us to extract the blood volume (v) and deoxyhemoglobin content (q).

According to the first assumption the changes in the blood volume (v) correspond to **differences** in inflow ($f_{in}(t)$) and outflow ($f_{out}(v)$) within a time constant (τ):

$$\tau \frac{dv}{dt} = f_{in}(t) - f_{out}(v)$$

Where,

τ is the mean transit time in blood. It directly proportional on the blood volume (V_0), but it inversely proportional to the resting blood flow (F_0):

$$\tau = \frac{V_0}{F_0}$$

$f_{out}(v)$ is outflow of blood is modulates as a function of volume with single parameter, α , which represents the resistance of venous balloon in this case the stiffness of the vessel.

$$f_{out}(v) = v^{1/\alpha}$$

Therefore, by submission of the last equation we have the final **equation for blood volume (v)**:

$$\tau \frac{dv}{dt} = f(t) - v(t)^{1/\alpha}$$

The second assumption tries to determine an equation to deoxyhemoglobin content q. The change in the q is corresponds to the *delivery of deoxyhemoglobin into the venous components* **minus** *the expulsion of deoxyhemoglobin from the venous components*. Suppose that per-capillary blood vessels contain fully oxygenated blood. The delivery of deoxyhemoglobin into the venous corresponds to the product of blood inflow and oxygen extraction fraction (E). On the other hand, the clearance of deoxyhemoglobin equals to the product of outflow and deoxyhemoglobin (q/v).

Mathematically,

$$\tau \frac{dq}{dt} = f_{in}(t) \frac{E(f_{in}, E_0)}{E_0} - f_{out}(v) \frac{q(t)}{v(t)}$$

Buxton and Frank (1997) showed that a reasonable approximation across a wide range of condition is:

$$E(f_{in}) = 1 - (1 - E_0)^{1/f_{in}}$$

By this approximation and knowing $f_{out}(v) = v^{1/\alpha}$, we would have final equation for measuring of **deoxyhemoglobin content q**:

$$\tau \frac{dq}{dt} = f(t) \frac{1 - (1 - E_0)^{1/f}}{E_0} - v(t)^{1/\alpha} \frac{q(t)}{v(t)}$$

Neurovascular State Equation:

We saw in the **balloon model** equations that both of blood volume (v) and deoxyhemoglobin content (q) are dependent of f . In other words, because v and q construct the BOLD signal, so all components of the model is based on f .

Friston and Buxton developed a model which shows that vascular response to neural activity corresponds to dampened oscillator. This means that changes in the neural activity (X) elicit an exponential decaying vasodilatory signal "s", also it subjects to feed backward regulation flow f it induces:

$$\frac{ds}{dt} = x - \kappa s - \gamma(f - 1)$$

Where,

$$s = \frac{df}{dt}$$

κ is the rate constant of signal decay

γ is the rate constant feedback regulations

Note: f is normalized flow with regard to feedback regulation term (f-1) in the equation became zero.

BOLD signal Change Equation:

The BOLD Signal Change Equation at the final level of the forward hemodynamic model of DCM links the blood volume (q) and deoxyhemoglobin content (q) together. This is done by the equation which is given in the figure below. The equation is derived in the Appendix B of K. E. Stephan et al. 2007.

$$\lambda(q,v) = \frac{\Delta S}{S_0} \approx V_0\left[k_1(1-q) + k_2\left(1 - \frac{q}{v}\right) + k_3(1-v)\right]$$

$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

$$k_3 = 1 - \varepsilon$$

BOLD signal change equation