Problem #7: Modeling Fetal ECOG/EEG during labor

5th problem solving workshop
@ University of Montreal

Problem proposer and consultant:

Martin Frasch, CHU St-Justine Research Centre

Statistical analysis:

***Fabrice Nonez**, Montreal Polytechnic

Antoine Saucier, Ecole Polytechnique de Montreal

***Nazim Boudjada,** Ecole Polytechnique de Montreal

Petr Plechac, University of Delaware

***extraordinary undergrads**

Mathematical modeling:

Huaxiong Huang, York University

Jonathan Wylie, City University of Hong Kong

Robert Miura, New Jersey Institute of Technology

Mary Pugh, University of Toronto

Qiming Wang, York University

Josh Chang, Mathematical Biosciences Institute

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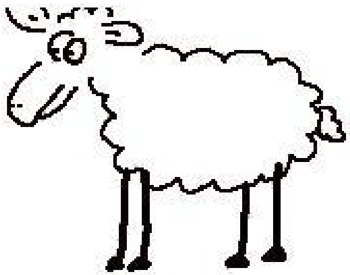
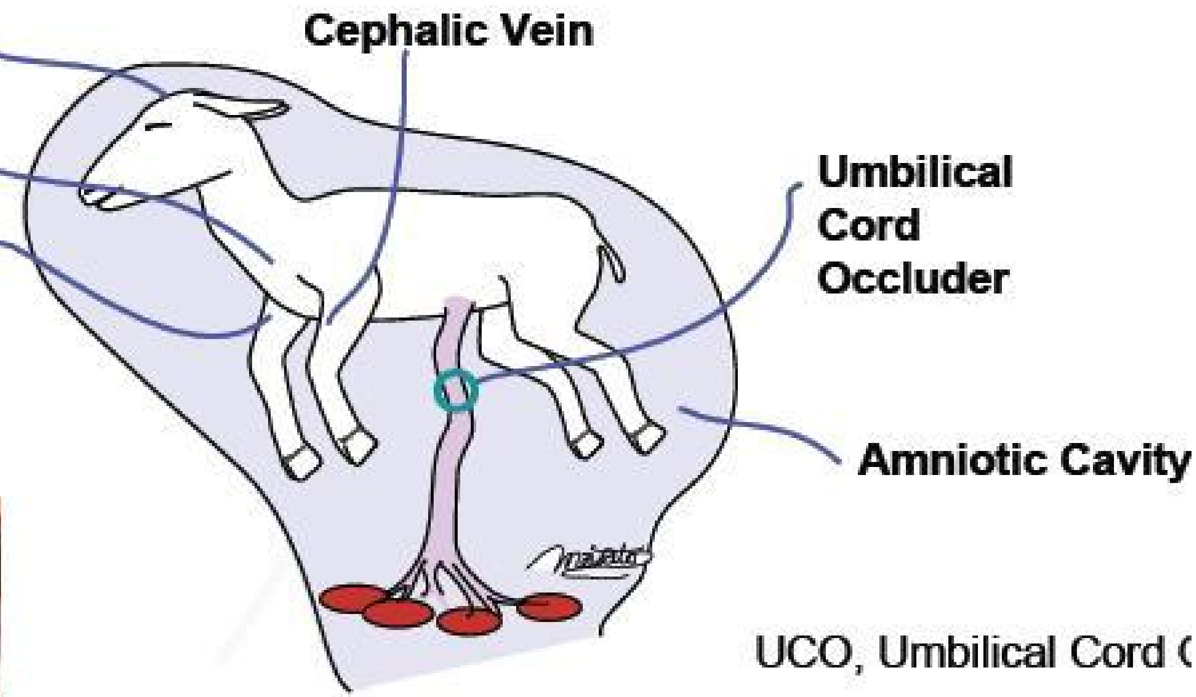
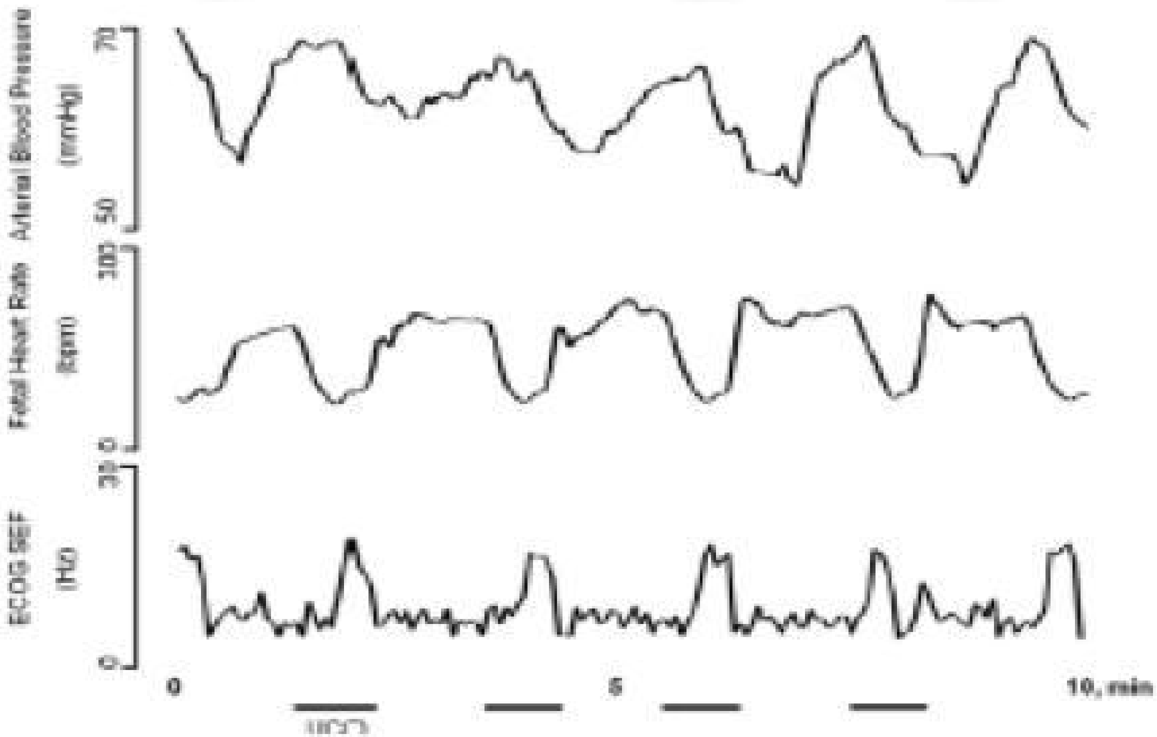


Problem under investigation …



Available data for fetal EEG monitoring

Frasch et al 2011 PloS One



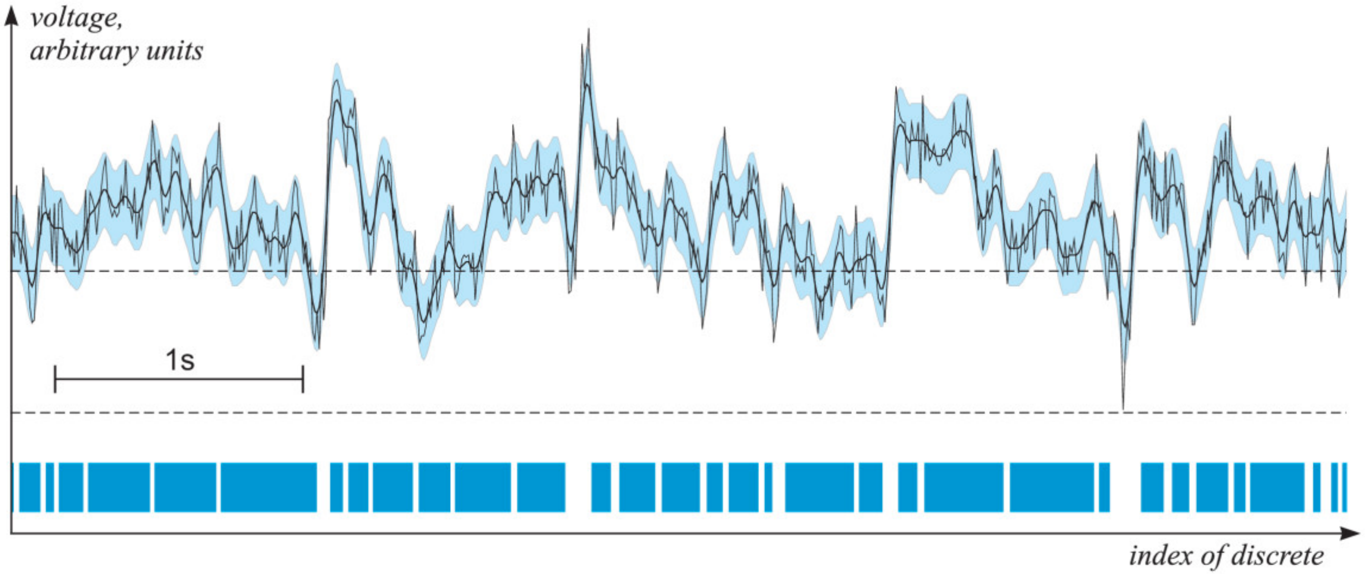
	pH	AMP, µV	SEF, Hz
ECOG	7.16 (65 min prior pH<7.00)	↓ (4 fold)	↑ (1.6 fold)
EEG	7.14 (58 min prior pH<7.00)	↓ (4 fold)	unchanged

Objective

Prevent this:

source: http://cerebralpalsy.org

By recognizing patterns in this



Insights from signal processing on the raw data

Mathematical modeling of the EEG signal?

When UCO occurs, dominant frequency shifts to lower region!

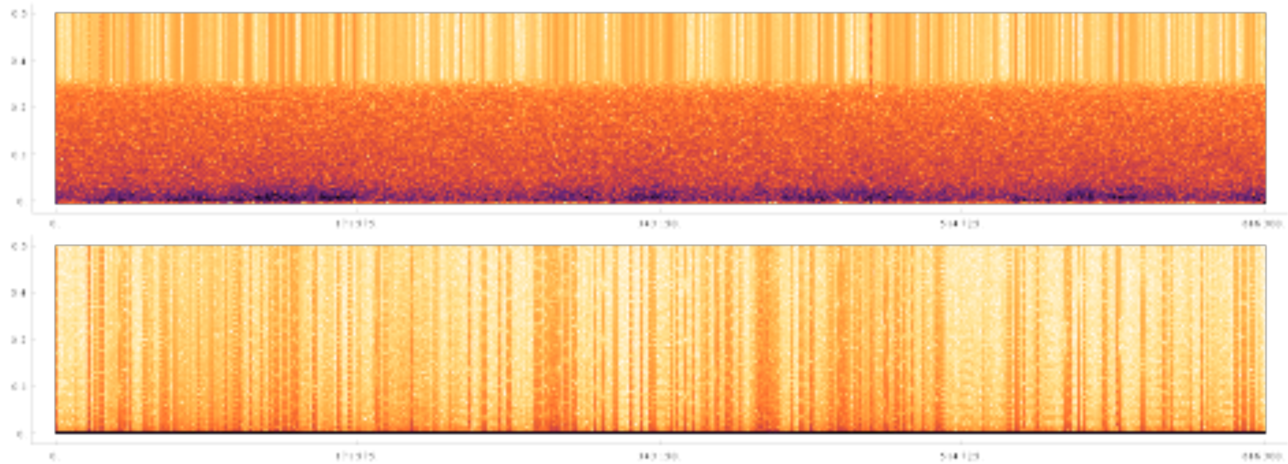


FIGURE 1 – Before the umbilical cord occlusions.

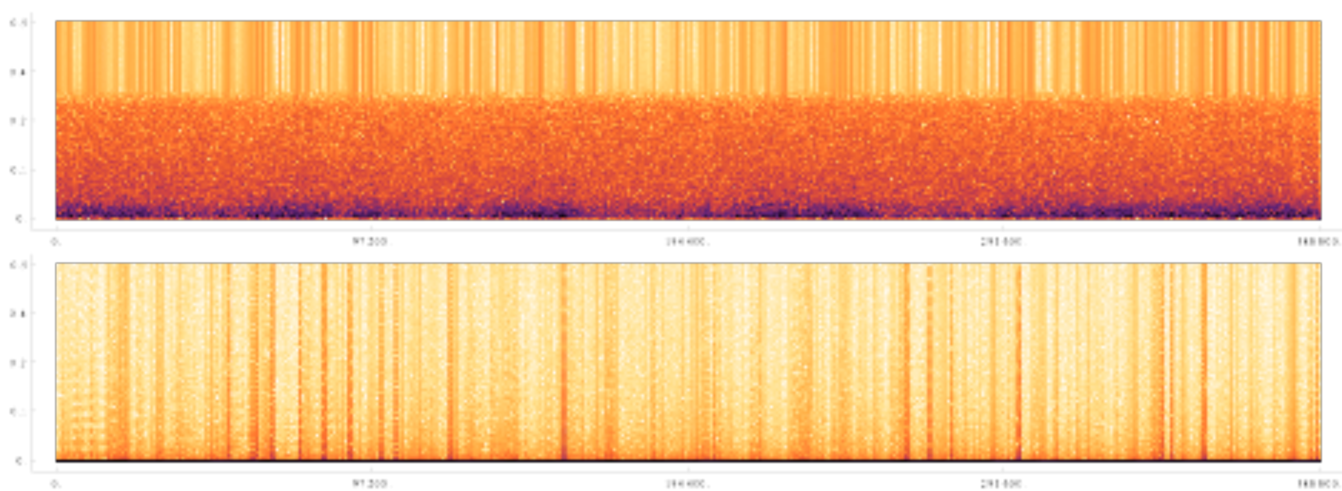


FIGURE 2 – Mild umbilical cord occlusions.

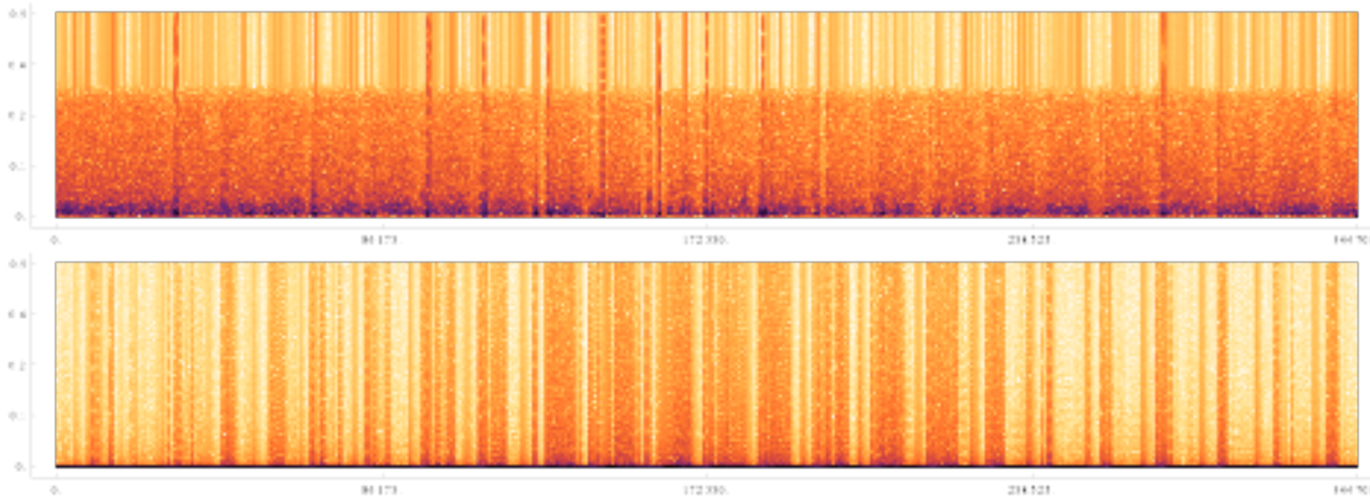


FIGURE 3 – Moderate umbilical cord occlusions.

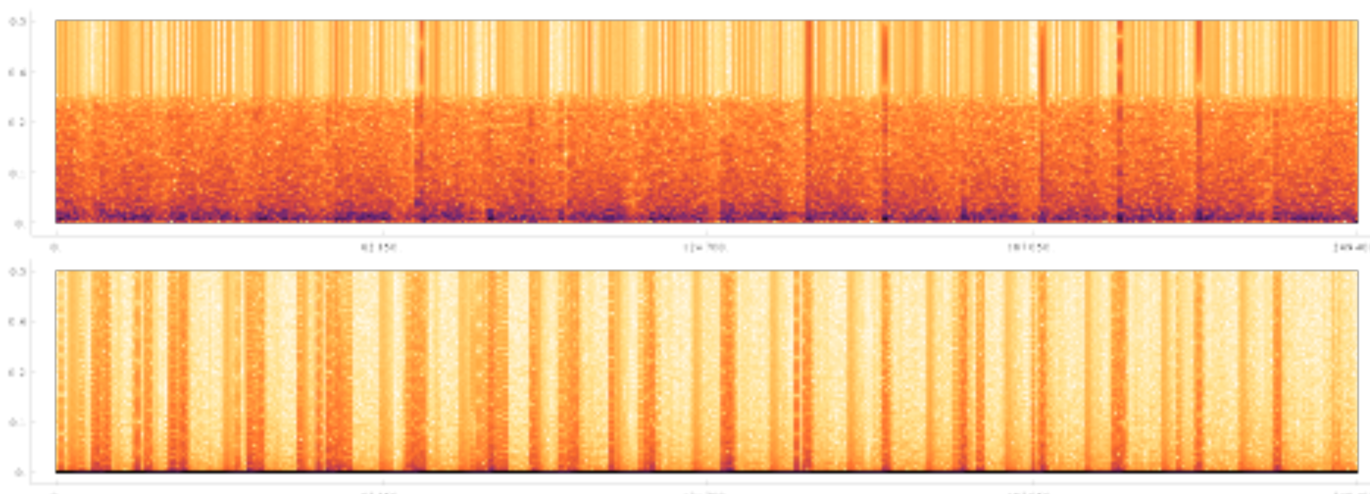


FIGURE 4 – Severe umbilical cord occlusions.

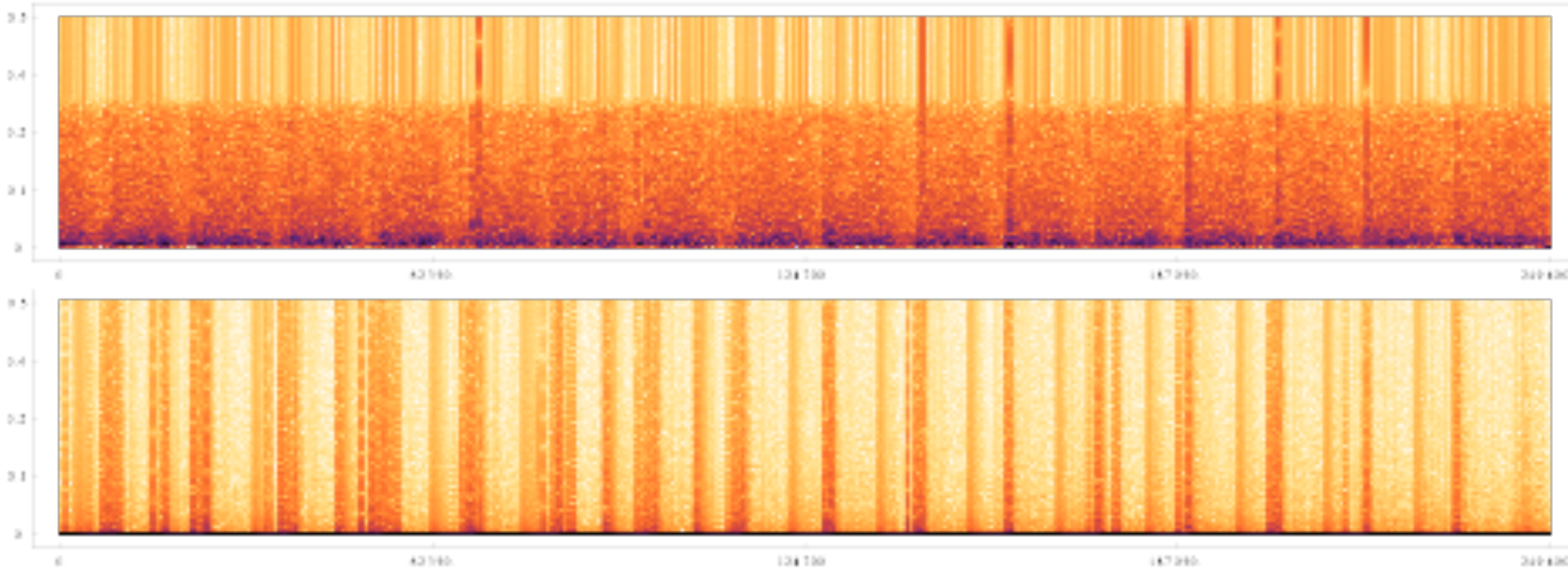
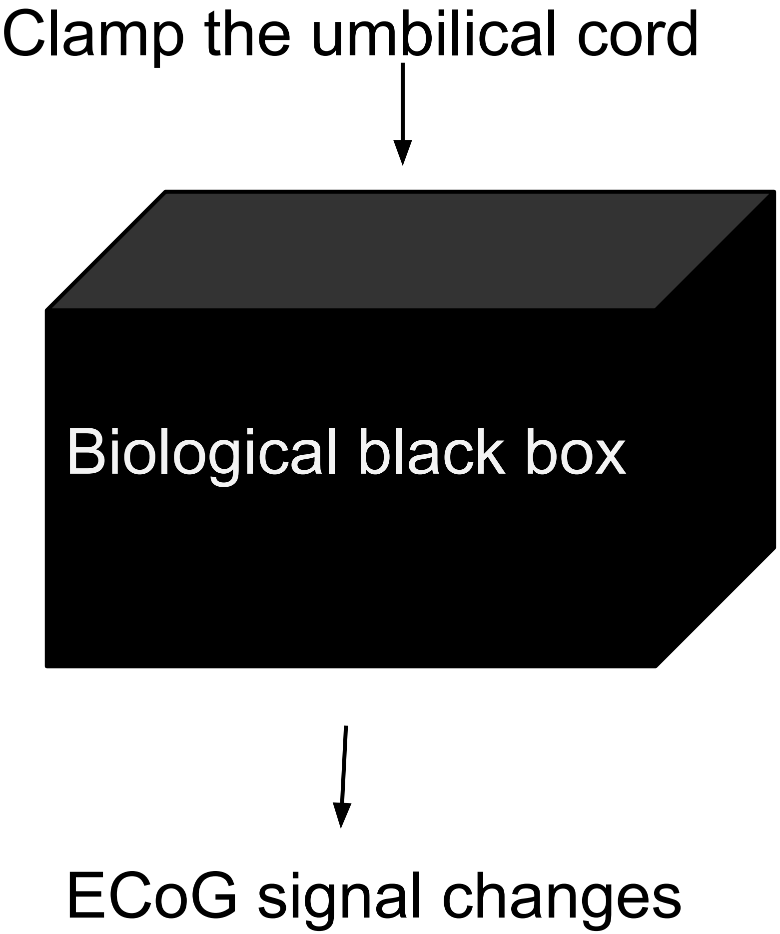


FIGURE 5 – Synchronisation of the FHR with the brain.

What's going on?



Peering into the box

Occlusion and nutrient exchange

Fetal heart rate changes

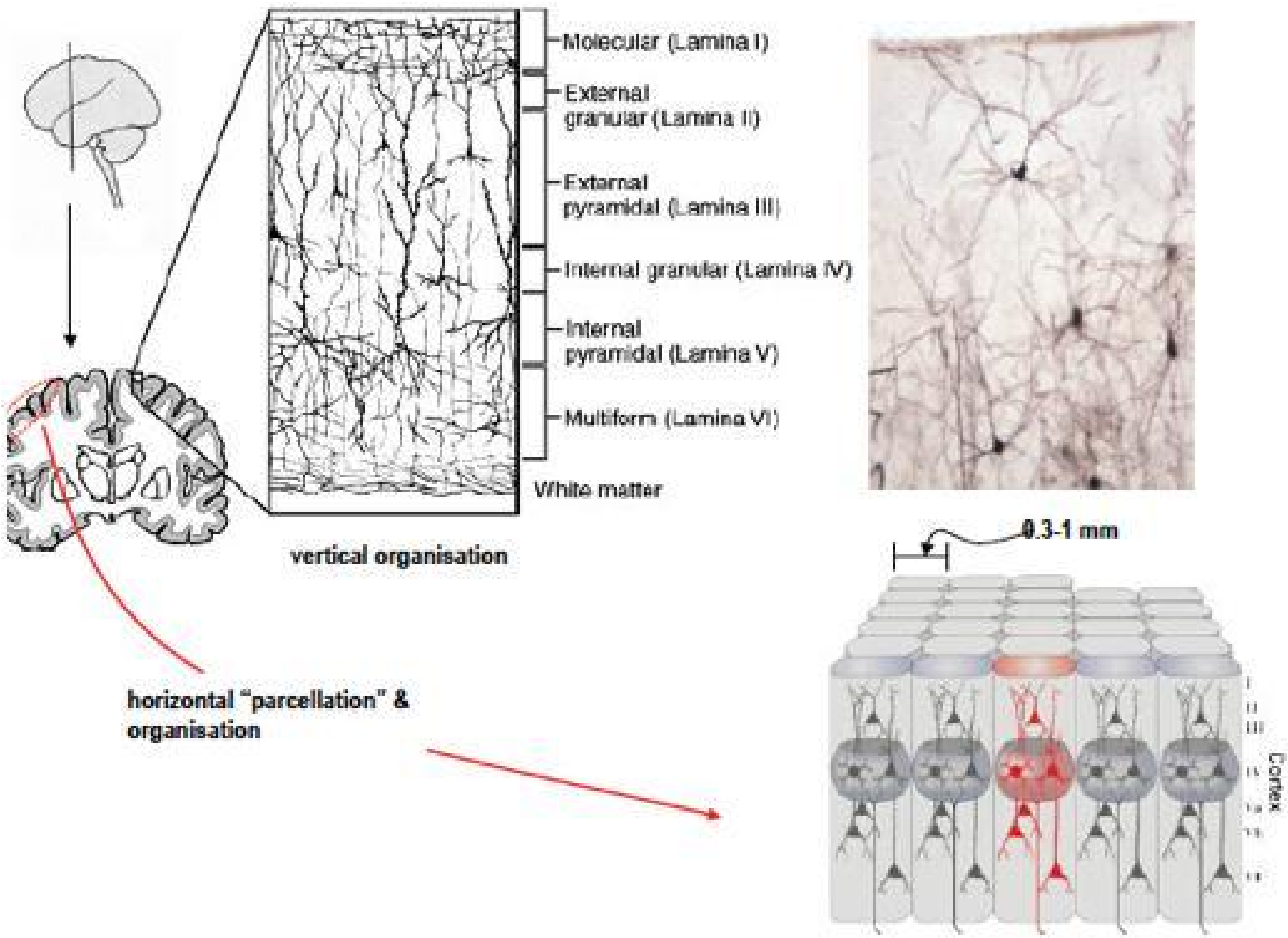
Blood flow and brain oxygenation

Oxygenation and ATP production

ATP and brain activity

Brain activity

EEG model



Molecular (Lamina I)
External granular (Lamina II)
External pyramidal (Lamina III)
Internal granular (Lamina IV)
Internal pyramidal (Lamina V)
Multiform (Lamina VI)
White matter
vertical organisation
horizontal "parcellation" & organisation
0.3-1 mm
Cortex

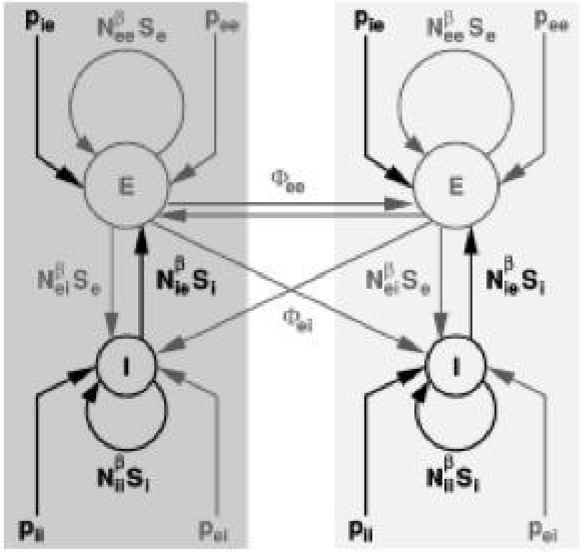
EEG model

(mean field method, critical damped oscillator):

$$\tau_k \frac{\partial h_k}{\partial t} = h_k^r - h_k + \Sigma_l \frac{h_{lk}^{eq} - h_k}{|h_{lk}^{eq} - h_k^r|} I_{lk}$$

$$\left(\frac{\partial}{\partial t} + \gamma_{lk} \right)^2 I_{lk} = e \Gamma_{lk} \gamma_{lk} \left(N_{lk}^{\beta} S_l(h_l) + p_{lk} \right)$$

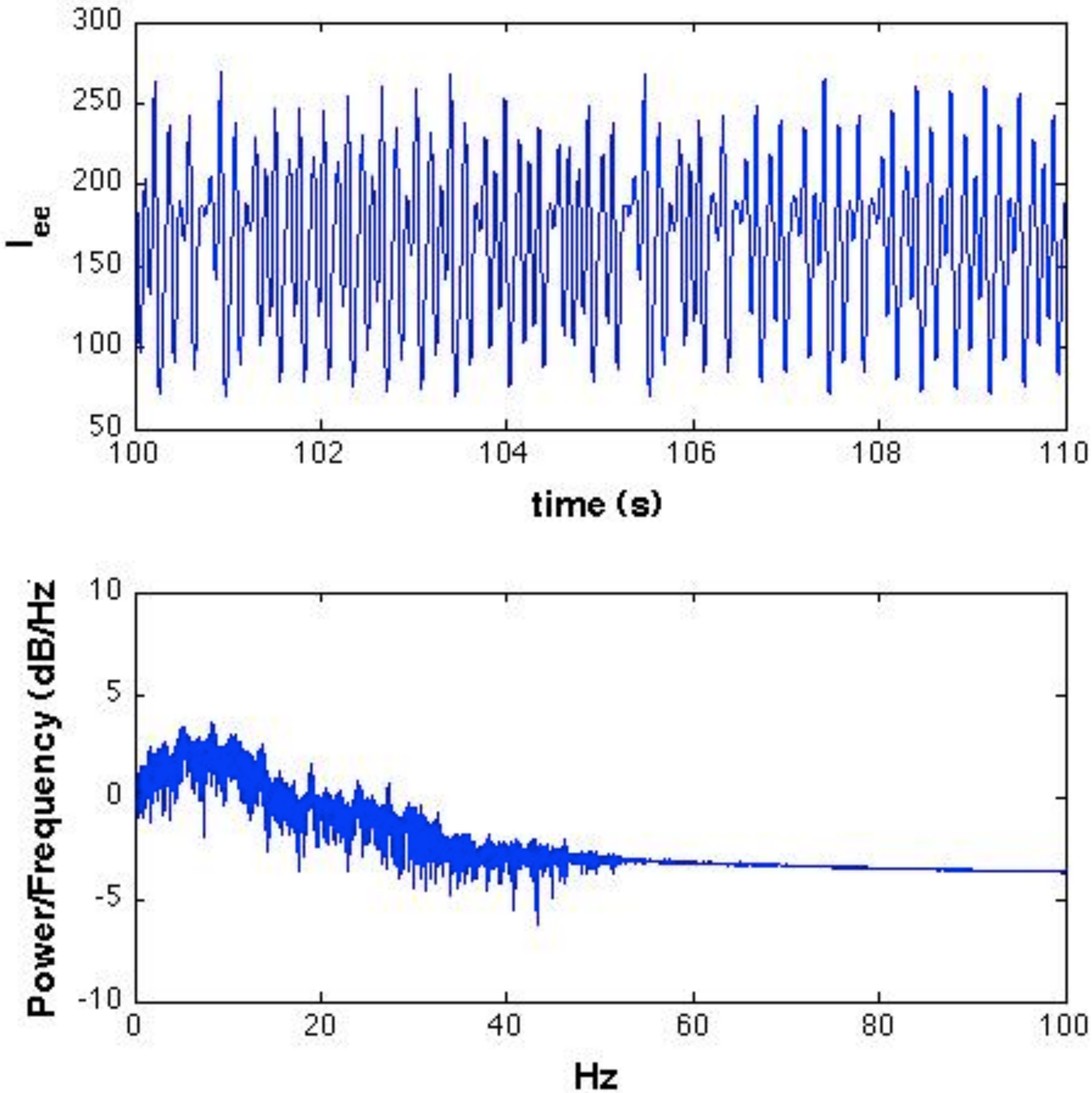
$$S_k(h_k) = S_k^{max} \left(1 + e^{-\sqrt{2}(h_k - \mu_k)/\sigma_k} \right)^{-1}$$



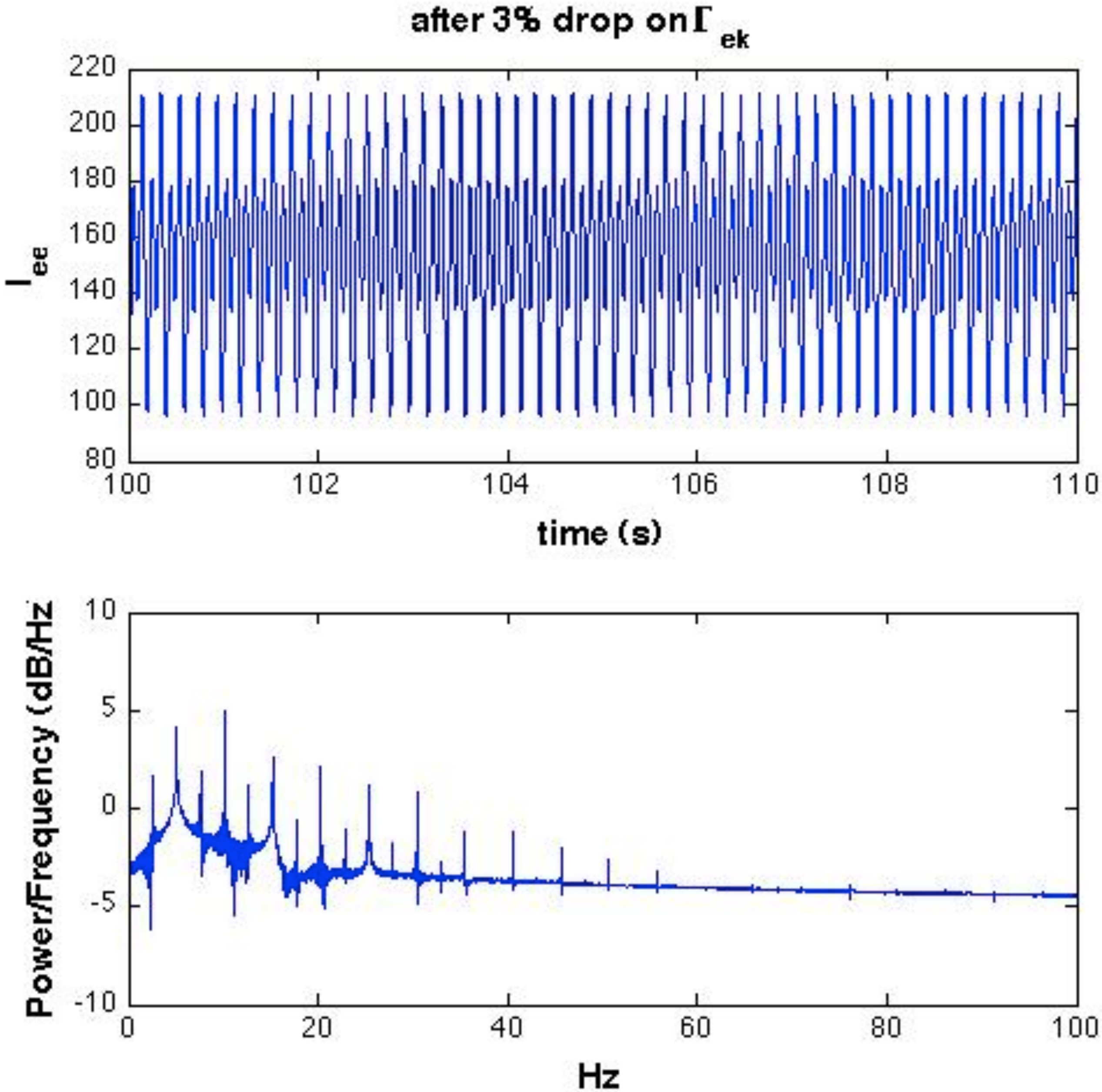
Physiological measurable parameter sets

Parameter		Min.	Max.	Parameter		Min.	Max.
Mean resting membrane potential	h_e^r	−80 mV	−60 mV	Mean Nernst membrane potential	h_{ee}^{eq}	−20 mV	10 mV
	h_i^r	−80 mV	−60 mV		h_{ei}^{eq}	−20 mV	10 mV
Passive membrane decay time const.	τ_e	5 ms	150 ms		h_{ie}^{eq}	−90 mV	$h_i^r - 5$ mV
	τ_i	5 ms	150 ms		h_{ii}^{eq}	−90 mV	$h_i^r - 5$ mV
Postsynaptic potential amplitude	Γ_{ee}	0.1 mV	2.0 mV	Postsynaptic potential rate constant	γ_{ee}	100 s^{-1}	1000 s^{-1}
	Γ_{ei}	0.1 mV	2.0 mV		γ_{ei}	100 s^{-1}	1000 s^{-1}
	Γ_{ie}	0.1 mV	2.0 mV		γ_{ie}	10 s^{-1}	500 s^{-1}
	Γ_{ii}	0.1 mV	2.0 mV		γ_{ii}	10 s^{-1}	500 s^{-1}
Total number of intracortical connections	N_{ee}^{β}	2000	5000	Total number of cortico-cortical connections	N_{ee}^{α}	2000	5000
	N_{ei}^{β}	2000	5000		N_{ei}^{α}	1000	3000
	N_{ie}^{β}	100	1000	Cortico-cortical decay scale	$\Lambda_{(ee=ei)}$	0.1 cm^{-1}	1 cm^{-1}
	N_{ii}^{β}	100	1000	and conduction velocity	v	100 cm/s	1000 cm/s
Maximum mean firing rate	S_e^{max}	50 s^{-1}	500 s^{-1}	Rate of extracortical (noise) input	$\bar{p}_{ee}(\delta p_{ee}/\bar{p}_{ee})$	0 s^{-1} (0.1)	10^4 s^{-1} (0.25)
	S_i^{max}	50 s^{-1}	500 s^{-1}		p_{ei}	0 s^{-1}	10000 s^{-1}
Firing thresholds	$\bar{\mu}_e$	−55 mV	−40 mV		p_{ie}	0 s^{-1} (fixed)	
	$\bar{\mu}_i$	−55 mV	−40 mV		p_{ii}	0 s^{-1} (fixed)	
Std. deviation of firing thresholds	$\hat{\sigma}_e$	2 mV	7 mV	Mean synaptic delay	ξ	0 ms (fixed)	
	$\hat{\sigma}_i$	2 mV	7 mV	Absolute refractory period	r_{abs}	0 ms (fixed)	

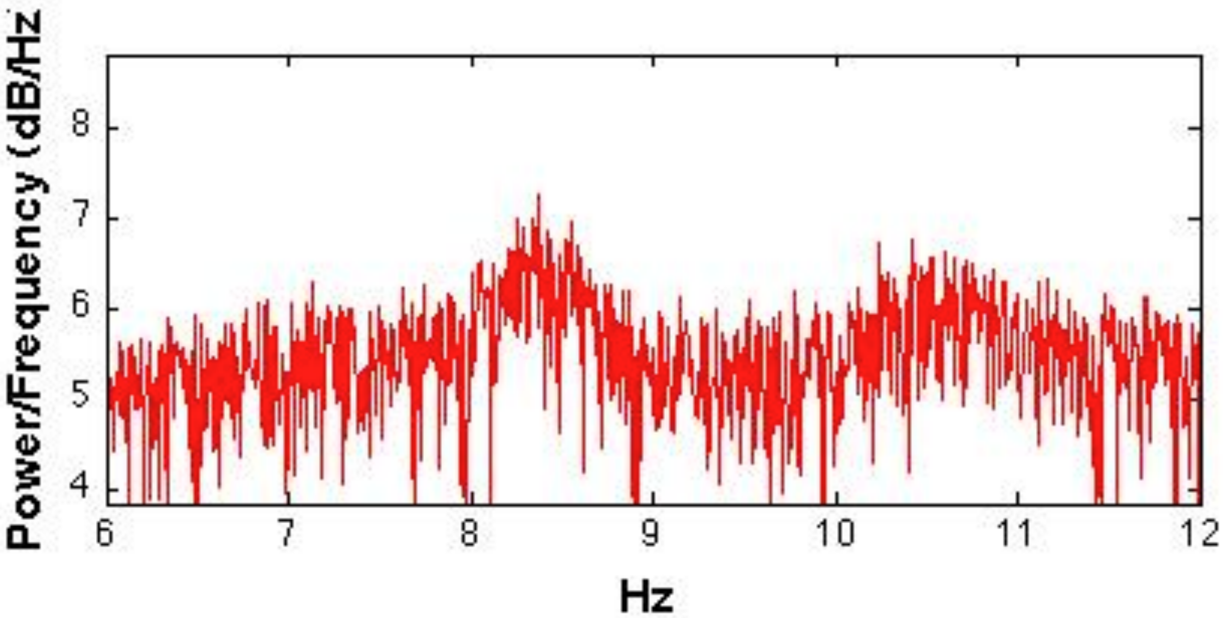
Baseline

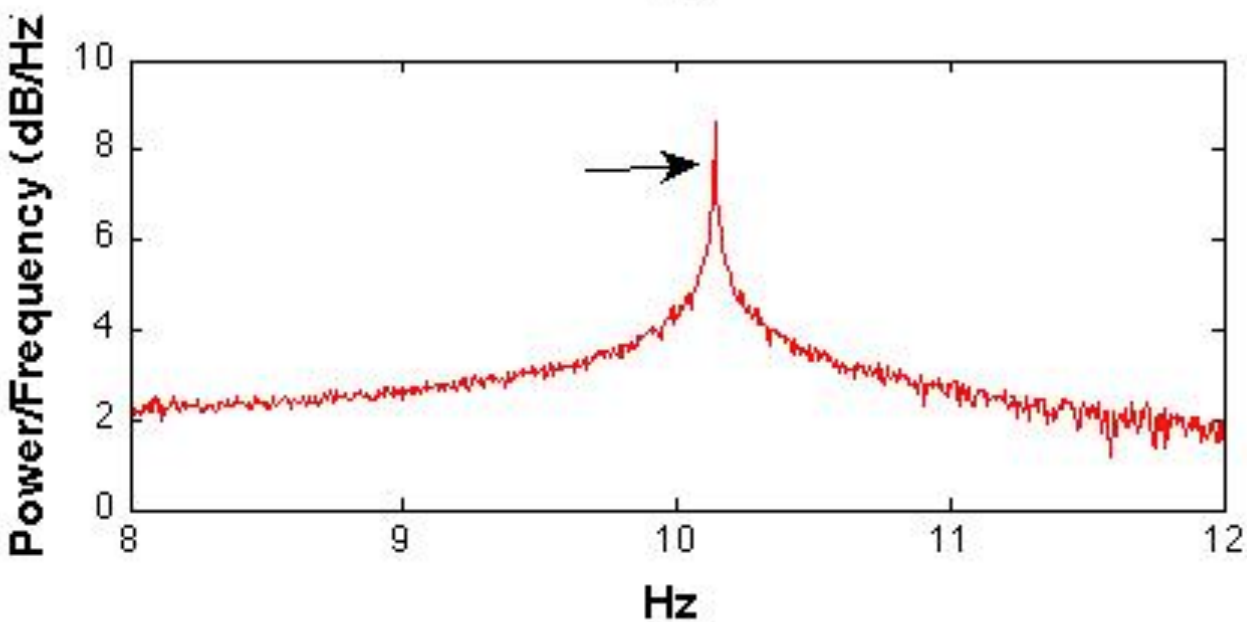


300
250
200
150
100
50
I_{ee}
100
102
104
106
108
110
time (s)
10
5
0
-5
-10
Power/Frequency (dB/Hz)
0
20
40
60
80
100
Hz



fter o2 drop


Power/Frequency (dB/Hz)
8
7
6
5
4
6
7
8
9
10
11
12
Hz


Power/Frequency (dB/Hz)
10
8
6
4
2
0
8
9
10
11
12
Hz

Metabolism in brain

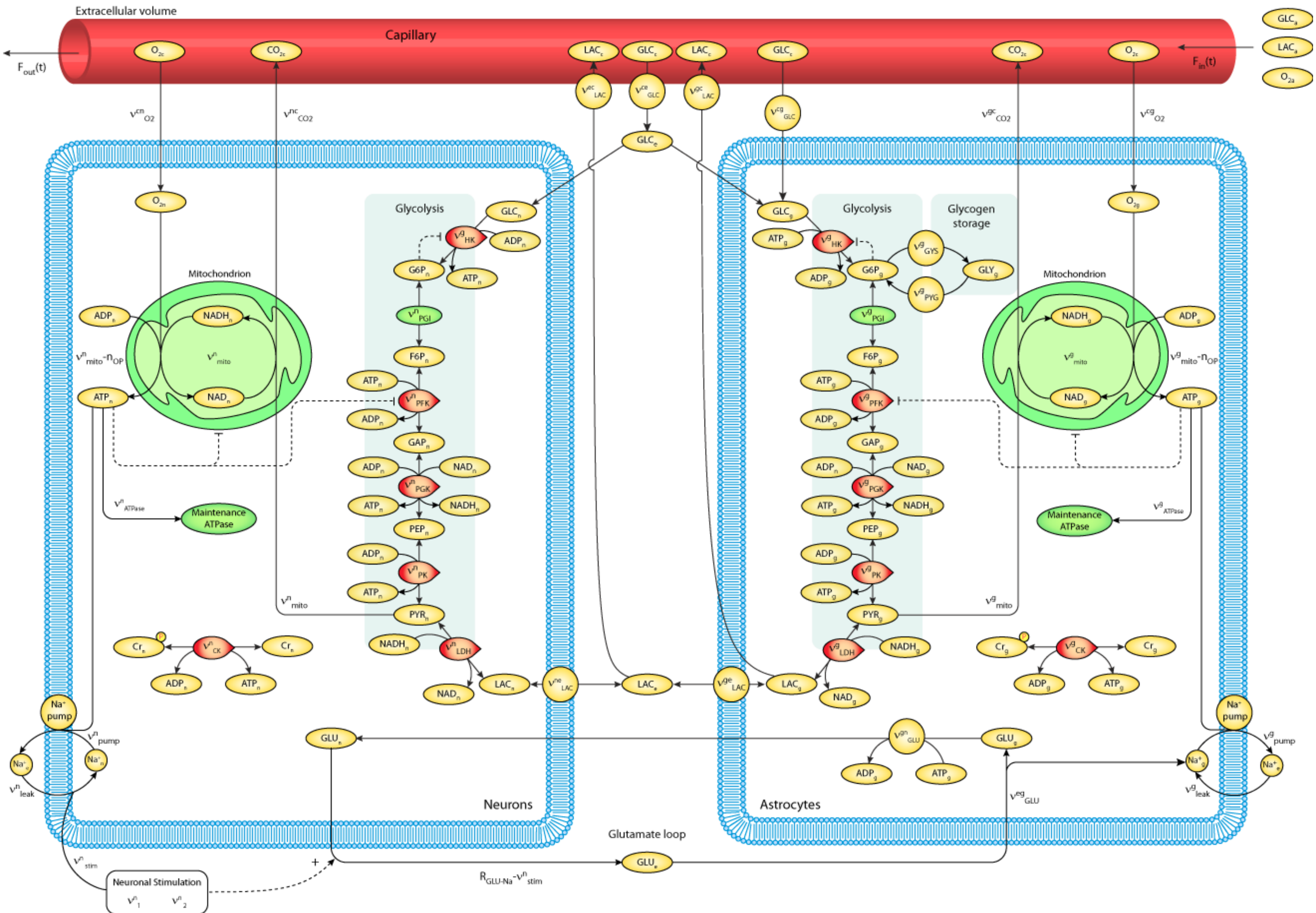
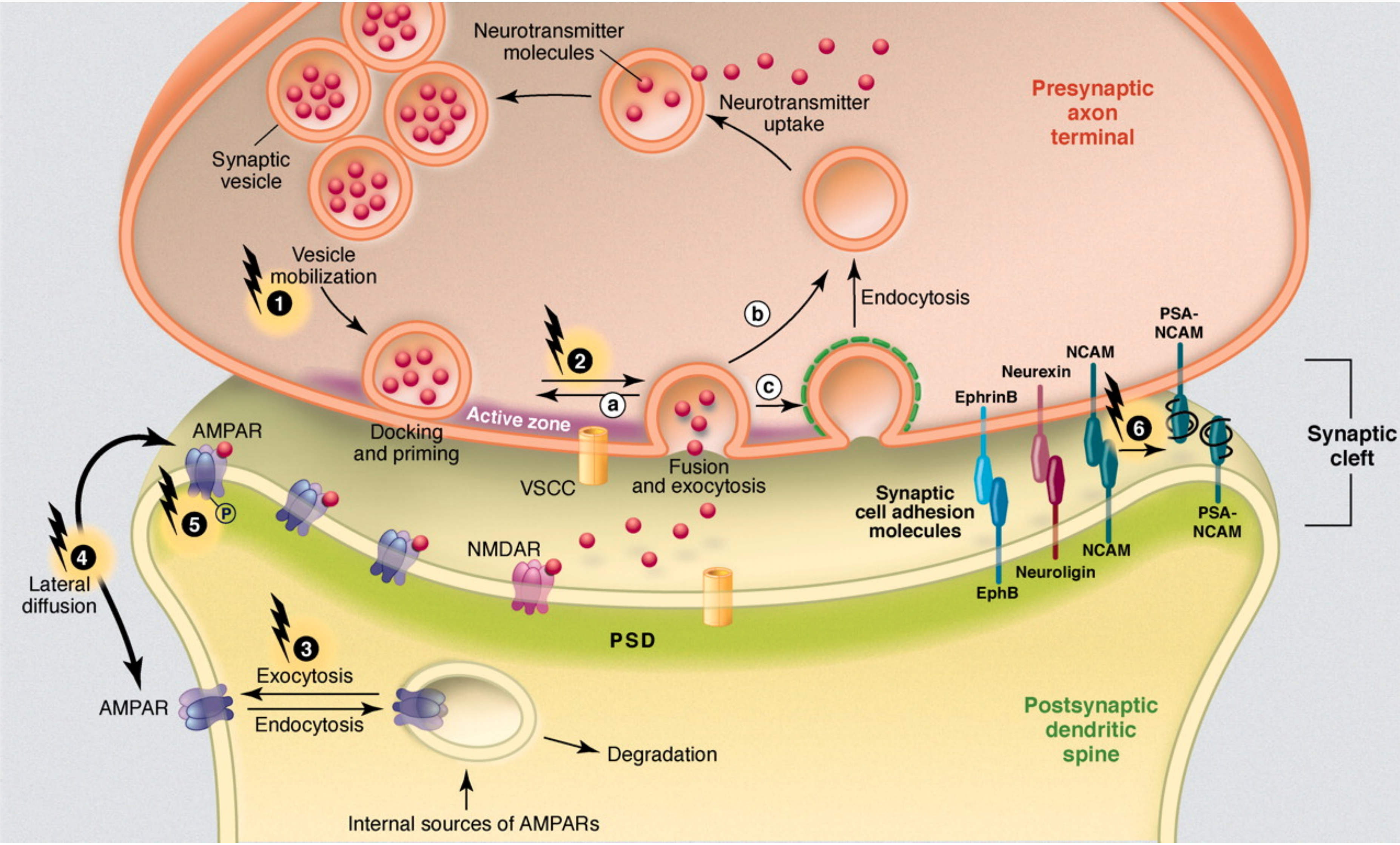


Table 4 Kinetic equations for central energy metabolism

No.	Reaction	Kinetic equation
Neuronal metabolism		
1	Hexokinase	$v_{HK}^{n} = k_{HK}^{n} \cdot ATP_{n} \cdot \left[\frac{GLC_{n}}{GLC_{n}+K_{m,GLC}}\right] \cdot [1 - f(G6Pn, 0.6, 20)]$
2	Phosphoglucose isomerase	$v_{PGI}^{n} = v_{\max,f,PGI}^{n} \cdot \left[\frac{G6P_{n}}{G6P_{n}+K_{m,G6P}}\right] - v_{\max,r,PGI}^{n} \cdot \left[\frac{F6P_{n}}{F6P_{n}+K_{m,F6P}}\right]$
3	Phosphofructokinase	$v_{PFK}^{n} = k_{PFK}^{n} \cdot ATP_{n} \cdot \left[1 + \left(\frac{ATP_{n}}{K_{I,ATP}}\right)^{nH}\right]^{-1} \cdot \left[\frac{F6P_{n}}{F6P_{n}+K_{m,F6P}}\right]$
4	Phosphoglycerate kinase	$v_{PGK}^{n} = k_{PGK}^{n} \cdot GAP_{n} \cdot ADP_{n} \cdot \left[\frac{NAD_{n}}{NADH_{n}}\right]$
5	Pyruvate kinase	$v_{PK}^{n} = k_{PK}^{n} \cdot PEP_{n} \cdot ADP_{n}$
6	Mitochondrial oxidation of pyruvate	$v_{mito}^{n} = v_{\max,mito}^{n} \cdot \left[\frac{PYR_{n}}{PYR_{n}-K_{m,PYR}}\right] \cdot \left[\frac{ADP_{n}}{ADP_{n}-K_{m,ADP}}\right] \cdot \left[\frac{O2_{n}}{O2_{n}+K_{m,O2}}\right] \cdot \left[1 - f\left(\frac{ATP_{n}}{ADP_{n}}, 20, 5\right)\right]$
7	Lactate dehydrogenase	$v_{LDH}^{n} = k_{LDH,f}^{n} \cdot PYR_{n} \cdot NADH_{n} - k_{LDH,r}^{n} \cdot LAC_{n} \cdot NAD_{n}$
8	Creatine kinase	$v_{CK}^{n} = k_{CK,f}^{n} \cdot PCr_{n} \cdot ADP_{n} - k_{CK,r}^{n} \cdot Cr_{n}ATP_{n}$
9	ATPase (excluding Na-ATPase)	$v_{ATPase}^{n} = V_{\max,ATPase}^{n} \cdot \left[\frac{ATP_{n}}{ATP_{n}-K_{m,ATP}}\right]$



Neurotransmitter molecules
Synaptic vesicle
Neurotransmitter uptake
Presynaptic axon terminal
Vesicle mobilization
1
2
a
b
c
Endocytosis
Docking and priming
Active zone
Fusion and exocytosis
VSCC
PSA-NCAM
NCAM
Neurexin
EphrinB
6
Synaptic cleft
Synaptic cell adhesion molecules
NCAM
Neuroligin
EphB
PSA-NCAM
AMPAR
P
5
4
Lateral diffusion
NMDAR
PSD
3
Exocytosis
Endocytosis
AMPAR
Degradation
Internal sources of AMPARs
Postsynaptic dendritic spine

Concluding remarks and future work

- Have tried linked the EEG model with Oxygen/ATP change
- Dominant frequency is shifted to higher region while amplitude decreases
- Probably need circulation model which can predict blood pressure to give a more physical complete understanding on how the circulation system interacts with EEG