Mathematics and brain

Filling some of the blanks between biochemistry and bioimaging

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Kaleidoscope on the brain
Brain Imaging Modalities

- **BOLD MRI**: sensitive to hemodynamics and level of deoxygenated hemoglobin
- **EEG**: measure electric field resulting from cerebral activity
- **MEG**: measure electric field resulting from cerebral activity
- **PET**: tracks marked substrates as they move through the brain
What are we looking at?
Brain Inverse Problems

• Indirect modes to detect and quantify cerebral activity assume a forward model linking observed effects to putative causes

• Contamination of data, weakening of signals, multiple possible cause for measured data is a common problem in all modalities

• Natural variation in population adds to the difficulty in interpretation of solution
Brain as a biochemical device

• Neurons and astrocytes; a complex metabolic coupling
• Cycling of neurotransmitters, essential for transmission of action potentials along axon bundles, requires energy
• Metabolic processes provide energy needed to support neural activity
Proxy for brain activity

Blood flow increase: measured by Mosso (1881) in patient doing arithmetics (8X12), and routinely via BOLD fMRI.

Changes in electric field measured on scalp (noninvasively) or in some areas of brain via grids, drilled electrodes (invasive).

Changes in magnetic field measured in region outside scalp (noninvasive).
Neuroactivity

When, Where

EEG, MEG

PET

BOLD fMRI

Metabolism

When, Where

When, Where

When, Where

Hemodynamics

When, Where
When and where?

- EEG and MEG have high temporal resolution and low spatial resolution: source localization
- PET has limited time durations – can identify location of marked substrates, specific receptors: stochastic signal
- BOLD fMRI 2-3 mm spatial resolution, sensitive to changes in blood flow, good for reproducible protocols due to averaging of signals
Combining modalities

Goal: improve spatial/temporal resolution and provide deeper understanding of cerebral activity

**MEG+EEG**: straightforward (same aspect of cerebral activity)

**MEG/EEG+fMRI**  
**fMRI + PET**  
**MEG/EEG + PET**

requires understanding the connection

Neuronal activity → Metabolic activity → Cerebral blood flow
“There is no rigid association in vivo between changes of oxygen consumption, glucose combustion, and blood flow in the human brain. The claim that cerebral blood flow rises to satisfy the demands for oxygen and glucose during neuronal excitation therefore is simplistic.”

A. Gjedde, in Handbook of Neurochemistry
Metabolism of neuronal activity

Neuron → Glu (+GABA) → Gln → Capillary

Capillary → Glucose → Pyr/Lac → 38 ATP

Astrocyte → Gln → Glu (+GABA) → K⁺ → Na⁺
Connection between metabolism and neuronal activity

Action potential transmission: directly related to EEG/MEG

Neurotransmitters enable/disable transmission of action potentials at synapses
The Blood Brain Barrier

Mathematical model of metabolism

Forward problem of metabolism

\[ \frac{dC(t)}{dt} = F(C(t), \theta, I(t)) \]

plus side constraints.

Inverse problem: Given observed concentrations (blood, tissue), estimate model parameters
Mass balances in capillary blood

\[ V_b \frac{d[A]}{dt} = \frac{Q}{F} ([A]_{\text{art}} - [A]) - J_{A, b \rightarrow ECS} + J_{A, ECS \rightarrow b} \]

\[ [A] = F[A]_{\text{venous}} + (1 - F)[A]_{\text{art}} \]

Zooming in on oxygen:

\[ [O_2]_{\text{tot}} = [O_2]_{\text{free}} + 4Hct[Hb]_{rbc} \frac{([O_2]_{\text{free}})^n}{K^n + ([O_2]_{\text{free}})^n} \]

\[ V_b \frac{d[O_2]_{\text{tot}}}{dt} = \frac{Q}{F} ([O_2]_{a, \text{tot}} - [O_2]_{\text{tot}}) - J_{O_2, b \rightarrow ECS} + J_{O_2, ECS \rightarrow b} \]
Mass balances in ECS

\[ V_{ECS} \frac{d[A]}{dt} = \sum_{x=a,b,n} (J_A, x \rightarrow ECS + J_A, ECS \rightarrow x) \]

and in synaptic cleft

\[ V_C \frac{d[Glu]}{dt} = J_{Glu, n \rightarrow c} - J_{Glu, c \rightarrow a} - \alpha[Glu] \]

\[ V_C \frac{d[Gln]}{dt} = J_{Gln, a \rightarrow c} - J_{Gln, c \rightarrow n} - \beta[Gln] \]
Mass balances in neurons and astrocytes

\[ V_n \frac{d[A]}{dt} = \sum C_{A,j} \Phi_j + J_A, \text{ECS} \rightarrow n - J_A, n \rightarrow \text{ECS} \]

Stoichiometric coeff

Reaction rate
Parametric dynamic model

Reaction type \( A \rightarrow B \)

Express reaction flux as
\[
\Phi(t) = V_{\text{max}} \frac{[A](t)}{K + [A](t)}
\]

Reaction type \( A + E \rightarrow B + F \)

Express reaction flux as
\[
\Phi(t) = V_{\text{max}} \frac{r(t)}{\mu + r(t)} \frac{[A](t)}{K + [A](t)}
\]

where \( r(t) = \frac{E(t)}{F(t)} \)
Transport rates

Diffusion based transport:

\[ J_{A, x \rightarrow y}(t) = \lambda ([A]_x(t) - [A]_y(t)) \]

Carrier facilitated transport

Ax+X → AX → Ay+X

Modelled in Michaelis-Menten form

\[ J_{A, x \rightarrow y}(t) = T_{\text{max}} \frac{[A]_x(t)}{M + [A]_x(t)} \]
## Activity model

<table>
<thead>
<tr>
<th>Neuron</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine is uptaken from cleft</td>
<td></td>
</tr>
<tr>
<td>Glutamine is transformed into glutamate</td>
<td></td>
</tr>
<tr>
<td>Glutamate collects in vesicles</td>
<td></td>
</tr>
<tr>
<td>Vesicles fuse with membrane and efflux glutamate into cleft</td>
<td></td>
</tr>
<tr>
<td>Glutamate sensitive ion channels open</td>
<td></td>
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</tbody>
</table>

### Action potential is transmitted

<table>
<thead>
<tr>
<th>Astrocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate is fast removed from cleft</td>
</tr>
<tr>
<td>Glutamate is transformed into glutamine</td>
</tr>
<tr>
<td>Glutamine is effluxed into cleft</td>
</tr>
</tbody>
</table>
Biochemical effect of activity

Assume maximum transport rate of glutamate and affinity increase with activity

\[ J_{Glu, n \rightarrow c} (t) = T(t) \frac{[Glu]_n(t)}{M(t) + [Glu]_n(t)} \]

\[ T(t) = T_0(1 + 2u(t)) \quad M(t) = M_0(1 - u(t) / 2) \]

Low activity
Increase in blood flow (why?)

\[ Q(t) = Q_{low} + u(t) \Delta Q \]

Postsynaptic ATP hydrolysis

\[ \Phi_{ATPase}(t) = \Phi_{base} + V_{max} f ([Glu]_c) \frac{[ATP]^n}{K + [ATP]^n} \]

\[ f ([Glu]_c) = \frac{[Glu]^n}{K_{Glu} + [Glu]^n} \]
Volume of blood satisfies the differential equation

\[
\frac{dV_b}{dt} = \frac{1}{\tau} \left( \frac{Q(t)}{Q_{low}} - \left( \frac{V_b}{V_{b,low}} \right)^{1/k} \right)
\]

where \( \kappa = 0.4 \) and \( \tau = 2 \) seconds

Mass balance equations in blood account for variable volume: \( m_A = [A]_b V_b \)

\[
\frac{dm_A}{dt} = Q(t) \left( [A]_{art} - \frac{m_A}{V_b(t)} \right) - J_{A, b \rightarrow ECS} + J_{A, ECS \rightarrow b}
\]
Hemoglobin and BOLD signal

Concentrations of oxy- and deoxy-hemoglobin are of interest for the coupling between neuronal activity and cerebral hemodynamic measurements.

Binding process of free O2 to the heme group

\[
O_2 + Hb_{j-1} \xrightleftharpoons[k_j]{k_{-j}} Hb_j \quad 1 \leq j \leq 4
\]

implies that at equilibrium

\[
[Hb_{j-1}][O_2]_{free} = K_j[Hb_j] \quad K_j = \frac{k_{-j}}{k_j}
\]

which, together with

\[
\sum_{j=0}^{4} Hb_j = Hb_{tot}
\]

makes it possible to determine uniquely saturation states of hemoglobin.
• **Forward problem**: large systems of coupled, nonlinear stiff differential equations which depend on lots of parameters

• Heterogeneous data – various individuals, conditions, laboratories

• Possible inconsistency between data and constraints

• Solution to parameter estimation problem needed to have a specified model may not exist, or may be very sensitive to constraints

• It would be desirable to quantify the expected variability of model predictions over population under given assumptions

• Proceed to do a Bayesian recasting of problem, where parameters, hence model predictions, are random variables

  Prior+likelihood \[\rightarrow\] posterior
Saturation levels
Time constants
Concentration info
A priori estimates

\[ \Phi = V_{\text{max}} \frac{C}{K + C} \]
Predictive envelopes

Glycolytic activity in astrocyte and neuron

Astrocyte

Glycolysis, astrocyte

Neuron

Glycolysis, neuron
Lactate trafficking

from astrocyte ....

...... into neuron
Lactate dehydrogenase (from pyruvate to lactate)

Astrocyte

Neuron
Flux of pyruvate into Krebs cycle

Astrocyte

PDC+TCA, astrocyte

flux [mmol/min]

0.3
0.4
0.45
0.5
0.55

time [min]

5
10
15
20

Astrocyte (much higher)

PDC+TCA, neuron

flux [mmol/min]

1.2
1.4
1.6
1.8
2
2.2

time [min]

5
10
15
20
Simple v.s. detailed models

<table>
<thead>
<tr>
<th>Simple models:</th>
<th>Detailed models</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fewer parameters to determine, easier to identify from data</td>
<td>• Need additional information to identify large number of parameters</td>
</tr>
<tr>
<td>• Computationally easier to handle</td>
<td>• Computationally cumbersome</td>
</tr>
<tr>
<td>• May fail to explain all data (overdetermined systems)</td>
<td>• May provide better interpretation of data</td>
</tr>
</tbody>
</table>
- Paramagnetic and diamagnetic properties of oxy- and deoxy-hemoglobin, together with increase in blood volume couple cerebral metabolic rate of oxygen with intensity of BOLD signal.
- It has been observed that CBF changes in response to activation: it is not yet fully understood what is the (local) metabolic controller of the (global) blood flow.
- Indirect nature of BOLD signal stresses the importance of the model in interpretation.
Need for distributed models

- Anatomical and physiological properties of brain change according to location
- Interactions between different regions and metabolic and vascular variations require a spatially distributed model
- Railways arrangement: cells are independent stations communicating with the same railway system carrying/removing substrates at different rates depending on location
A railway inspired model of distributed brain: cells communicate through ECS
Challenges of spatial distribution

• From ODEs to PDEs: the computational resources needed for a detailed spatially distributed model may be formidable
• Information about brain connectivity and locality may be needed to identify model
• Similar model which were developed for hepatocytes may be adapted for brain
• More investigation is still needed
Collaborators

Erkki Somersalo (Case Western Reserve University)
Rossana Occhipinti (Case Western Reserve University)

Amy Kuceyeski (Cornell Medical Center)
Jenni Heino (Aalto University, Finland)

Joseph LaManna (University Hospital)
John Mosher (Cleveland Clinic)
Michelle Puchowicz (University Hospital)
Gerald Saidel (Case Western Reserve University)
• D. Calvetti and E. Somersalo: *Dynamic activation model for a glutamatergic neurovascular unit*, submitted


Software: **METABOLICA**
http://www.case.edu/artsci/math/Software.htm