Using mathematical models & approaches to quantify BRAIN (dynamic) Positron Emission Tomography (PET) data

Imaging Seminars Series
Stony Brook University, Health Science Center
Stony Brook, NY – January 29th, 2013

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Application of mathematical models & approaches to PET data (Time Activity Curves - TACs) to estimate PET OUTCOMES of interest.

Stats (e.g., group analysis)

Reconstruction

Co-registration

Motion correction

The role of modeling in PET

[11C]DASB
[11C]PIB
[18F]FDG
[11C]WAY
[11C]CUMI
[11C]PE2I
[11C]ABP
...

MDDs
PTSDs
ADs
...

Application of mathematical models & approaches to PET data (Time Activity Curves - TACs) to estimate PET OUTCOMES of interest.
“To be useful in clinical investigations, PET needs to be quantitatively correct: the information collected by the camera (i.e., the “pictures” of the radioligand distribution in the brain) must be translated into numbers that relate to well-defined biologic entities. Short of a validated quantitative analysis, the information is of little value for clinical investigations.”

What is a mathematical model?

MODEL = a representation that includes only some “relevant” aspects of reality

REALITY = a biological/physiological system, whose complexity and (indirect) measurements issues (e.g., in vivo) make the use of models appealing

MATHEMATICAL MODEL = set of mathematical equations describing the relationships existing between the variables of the real system

X SYSTEM

Questions about X

Answers for X

M MODEL

Questions about M

Answers from M

To DESCRIBE - QUANTIFY - INTERPRET - PREDICT
The system under investigation in brain PET
The system under investigation in brain PET

RADIOligand in brain tissue that interacts with the receptors
PET data @ the Region Of Interest (ROI) level

PET images

TISSUE ROI TAC

MODEL

ESTIMATES
blood flow,
glucose uptake,
potential binding...

NUMBERS!!!
PET data at the voxel level

**TISSUE VOXEL TAC**

**ESTIMATES** blood flow, glucose uptake, potential binding...

**PARAMETRIC MAPS!!!**
**ROI vs. voxel**

**ROI**

- ✓ **High Signal-to-Noise Ratio (SNR)**
- ✓ **Limited number (< 100) of ROIs**: computationally-demanding analysis can be applied
- ★ **Original spatial resolution lost**
- ★ **Affected by the methods used for ROIs delineation, PET-MRI co-registration etc.**
- ★ **Heterogeneity issue**

**voxel**

- ★ **Low SNR**
- ★ **Elevated number (~10^5) of voxels**: need for faster & “simpler” methods of analysis
- ✓ **Original spatial resolution preserved**
- ✓ **Exploratory analysis (in absence of a priori hypothesis on ROIs)**
- ✓ **Heterogeneity issue lessens**
The system under investigation in brain PET

**INPUT**

RADIOLIGAND IN ARTERIAL PLASMA AVAILABLE TO BIND

**OUTPUT**

RADIOLIGAND IN BRAIN TISSUE THAT INTERACTS WITH THE RECEPTORS
Input Function (IF) & metabolites

IF & metabolites-corrected IF (cIF)
Input Function (IF) & metabolites

Metabolite Corrected Plasma Fit

Metabolite Corrected Plasma Fit Linear
Invasive PET

Full arterial & metabolites analysis

✓ “Gold-standard”: to measure how much radioligand is “supplied” to the brain tissue to properly quantify the “uptake” amount

★ Arterial sampling: invasive, costly, time-consuming, risky & uncomfortable for subjects, unfeasible in clinical practice
- tends to deter subjects’ participation
- requires highly specialized medical staff & labs (blood analysis)

★ (tech note) Mathematical problems related to the presence of noise in the measured arterial data
The system under investigation in brain PET

- **INPUT**
  - Radioligand in arterial plasma available to bind

- **OUTPUT**
  - Radioligand in brain tissue that interacts with the receptors
The third component

INPUT

RESPONSE FUNCTION

OUTPUT

\[ \text{RESPONSE FUNCTION} \otimes \text{RESPONSE FUNCTION} \]
How can we describe the response of a system?

DATA MODELS
(IN-OUT or BLACK BOX)

SYSTEM MODELS
(STRUCTURAL or WHITE BOX)
Compartmental models: basics

They provide a description of the system internal mechanisms, based on physical principles or structural hypotheses (e.g., mass balance & conservation)

COMPARTMENT: a quantity of “matter” homogeneously “behaving” in the system (e.g., the same substance in different physical spaces OR two different substances in the same physical space)

COMPARTMENTAL MODEL: a set of compartments connected to each other

CONNECTION: substance flow, controlling/regulatory signal (e.g., transport between two sites OR chemical transformation in one site)

2-Tissue Compartment (2TC) model

\[ C_p(t) \xrightarrow{K_1} C_{f+ns}(t) \xrightarrow{k_3} C_s(t) \]
\[ C_p(t) \xleftarrow{k_2} C_{f+ns}(t) \xleftarrow{k_4} C_s(t) \]

**RADIOLIGAND CONCENTRATION IN THE ARTERIAL PLASMA CORRECTED FOR METABOLITES**

**TISSUE CONCENTRATION OF THE SPECIFICALLY BOUND RADIOLIGAND**

**TISSUE CONCENTRATION OF THE FREE + NON-SPECIFICALLY BOUND RADIOLIGAND**
**In vitro - in vivo**

**In vitro**

\[
R + F \rightleftharpoons B
\]

- **RECEPTORS**
- **FREE RADIOLIGAND**
- **BOUND RADIOLIGAND-RECEPTOR COMPLEX**
- **Michaelis-Menten @ equilibrium**
- **Dissociation Constant**
- **Density of Receptors**

**Equation**

\[
B = \frac{B_{\text{max}}F}{K_D + F}
\]

**In vivo**

\[
k_3 \propto k_{\text{on}}
\]

\[
k_4 = k_{\text{off}}
\]

\[
BP = \frac{B_{\text{max}}}{K_D} = B_{\text{max}} \times \frac{1}{K_D} = B_{\text{max}} \times \text{affinity}
\]
Matching data & model

TISSUE ROI TAC

activity/concentration [µCi/cm³]

0 2.5 3

0 23 46 69 92 115

time [min]

$C_f(t)$

$K_1$

$C_{f+ns}(t)$

$k_2$

$k_3$

$C_s(t)$

$k_4$

$k_1$

$k_3$

$k_4$
Fitting functions of cIF & model rate constants
1-Tissue Compartment (1TC) model

\[ C_p(t) \xrightarrow{K_1} C_t(t) \xleftarrow{k_2} \]

RADIOLOGAND CONCENTRATION
IN THE ARTERIAL PLASMA
CORRECTED FOR METABOLITES

TISSUE CONCENTRATION OF THE
FREE + NON-SPECIFICALLY + (SPECIFICALLY)
BOUND RADIOLOGAND

Matching data & model

TISSUE ROI TAC

\[ Ct(t) \]

activity/concentration [µCi/cm³]

0 0.5 1 1.5 2 2.5 3

0 23 46 69 92 115

time [min]

\[ C_{P(t)} \]

activity/concentration [µCi/cm³]

0 0.1 0.2 0.3 0.4 0.5 0.6

0 10 20 30 40 50 60 70 80 90 100 110

time [min]

\[ C_{P(t)} \]

\[ C_{P+ns(t)} \]

\[ C_{s(t)} \]

\[ C_{t(t)} \]

\[ K_1 \]

\[ k_2 \]

\[ k_3 \]

\[ k_4 \]
Kinetic analysis

“GOLD-STANDARD”

MICRO-PARAMETERS ($k_i$)
MACRO-PARAMETRES ($V_T$, $B_P_f$)

IN VIVO
IN VITRO

OPTIMIZATION

NON-LINEARITY

RADIOLIGAND SPECIFIC
2TC irreversible (e.g., $^{[18F]}$FDG)
2TC constrained (e.g., $^{[11C]}$WAY)

NON IDENTIFIABILITY
NON STABILITY

COMPUTATIONAL DEMAND
NOT VOXEL-ANALYSIS FRIENDLY

CONVERGING ISSUES

push towards simpler (but less informative) analysis
Graphical Analysis (GA)

- **PATLAK PLOT**

- **LOGAN PLOT**

"MANIPULATIONS" OF THE MODEL EQUATIONS

"TRANSFORMATIONS" OF THE DATA
**Patlak plot**

\[ K_i = \left[ \frac{ml_{\text{plasma}}}{gr_{\text{tissue}} \cdot \text{min}} \right] \]

**FRACTIONAL IRREVERSIBLE METABOLIC RATE OF THE RADIOLIGAND**

\[ \log(C_{\text{input}}(t))/C_{\text{input}(0)} \text{ vs } \frac{\text{ROI}(t)}{C_{\text{input}(t)}} \]

\([^{18}\text{F}]\text{FDG in the brain}\]

Slope \(=\) how many milliliters of radioligand present in the plasma are metabolized for each gram of tissue every minute
Logan plot

\[ V_T = \left[ \frac{ml_{\text{plasma}}}{gr_{\text{tissue}}} \right] \]

**RADIOLIGAND DISTRIBUTION VOLUME**

\( ( = \text{ratio between the radioligand concentration inside the tissue & in the plasma @ steady state}) \)
<table>
<thead>
<tr>
<th>PROs</th>
<th>CONs</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Small computational time</td>
<td>★ Only 1 macro-parameter estimated (no info on micro-parameters)</td>
</tr>
<tr>
<td>✓ No need for a compartmental model</td>
<td>★ Patlak works only for irreversible radioligand</td>
</tr>
<tr>
<td>defined in details</td>
<td>★ Logan estimates are affected by bias</td>
</tr>
<tr>
<td>✓ Easy implementation</td>
<td>★ The choice of the “linearity time window” can be not trivial &amp; impact the results</td>
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From “bloody” to “bloodless”

INPUT is common to all brain regions/voxels

RADIOLIGAND IN ARTERIAL PLASMA AVAILABLE TO BIND

INPUT is common to all brain regions/voxels
Reference Region Approaches (RRAs)
Ideal Reference Region

\[ C_p(t) \xrightarrow{K_1} C_i(t) \xrightarrow{k_2} C_p(t) \]

- devoid of specific binding
- invariant between groups
- independent of treatment effect
**Full Reference Tissue Model (FRTM)**

FRTM relies on the presence of a region without specific binding that can be used as RR for all the others.

\[ C_{f+ns}(t) \]

\[ C_{RR}(t) \]

\[ C_p(t) \]

\[ C_s(t) \]

Any target region


*J. Cereb. Blood Flow Metab. 16*: 42–52
Simplified Reference Tissue Model (SRTM)

INPUT is COMMON to both target region & RR

\( C_p(t) \)

\( K_1 \)

\( k_2 \)

\( C_p(t) \)

\( K_1' \)

\( k_2' \)

\( C_{RR}(t) \)

\( C_{RR}(t) \)

\( Ci(t) \)

ANY TARGET REGION

SRTM RELIES ON THE PRESENCE OF A REGION WITHOUT SPECIFIC BINDING THAT CAN BE USED AS RR FOR ALL THE OTHERS

The non-displaceable binding potential ($\text{BP}_{\text{ND}}$) is related to the slope.

<table>
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<tr>
<td>✓ Do not require arterial sampling</td>
<td>★ Require RR (devoid of receptors of interest &amp; invariant between groups), not available for many radioligands</td>
</tr>
<tr>
<td>✓ Easy implementation</td>
<td>★ Only the non-displaceable binding potential (BP_{ND}), only linearly related to B_{available} &amp; K_D</td>
</tr>
<tr>
<td>✓ Cheap</td>
<td>★ Different degrees of BP_{ND} BIAS compared to cIF-based analysis*</td>
</tr>
</tbody>
</table>

*Zanderigo et al. Reference region approaches in PET: a comparative study on multiple radioligands. In submission with JCBF&Met (third review)
A custom-built software: BrainFit
Other alternatives

1. **Bolus + infusion** protocols

2. **Pseudo-equilibrium** methods

3. **Auto-radiographic** protocols

4. **Semi-quantitative** analysis (e.g., Standard Uptake Value, SUV – Time To Peak, TTP)
Other alternatives

1. **Bolus + infusion protocols**

*FIG. 4.* Region-of-interest data from basal ganglia (●) and cerebellum (■) following bolus plus infusion administration of \[^{11}\text{C}]\text{raclopride}\) (administered dose, 6.1 mCi). The bolus portion of the dose (\(K_{bol}\)) was equal to the volume administered during 60 min of infusion.

Other alternatives

2. Pseudo-equilibrium methods

FIG. 3. Identification of the point in time at which equilibrium occurs for \(^{11}C\)raclopride binding to D<sub>2</sub>-dopamine receptors in the putamen in a healthy subject. Measured values in the cerebellum were subtracted from measured values in the putamen. The difference was defined as specific binding and fitted to a set of three exponentials. Equilibrium was defined as occurring at the point in time when \(dC_{v}/dt\) for specific binding was 0.

Other alternatives

3. Auto-radiographic protocols

4. Semi-quantitative analysis (e.g., Standard Uptake Value, SUV - Time To Peak, TTP)

THANKS FOR YOUR ATTENTION! :-)