Types of measurements with PET

- **Neuronal Metabolism**
  - rCGM or rCBF
  - Oxygen-15 labeled water, or fluorine-18 labeled fluorodeoxyglucose

- **Pharmacology**
  - Most drugs are organic and thus can be labeled with Carbon-11

- **Brain Chemistry**
  - Neurotransmitter synthesis, receptors, transporters, and release (sensitive down to $10^{-12} \text{M}$)

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Most common PET tracers

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half time (min)</th>
<th>Max. path (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-11</td>
<td>20.4</td>
<td>4.1</td>
</tr>
<tr>
<td>N-13</td>
<td>9.98</td>
<td>5.4</td>
</tr>
<tr>
<td>O-15</td>
<td>2.03</td>
<td>8.0</td>
</tr>
<tr>
<td>F-18</td>
<td>109.8</td>
<td>2.4</td>
</tr>
</tbody>
</table>

C-11 decay and image times

Elements for processing PET

- Brain extraction, 3D volumes of interest
- Time-activity curves
- Graphical analysis

Methods for quantitative analysis

- Standardized uptake value - SUV
- Count ratios
- Curve fitting and parameters
- Deconvolution followed by curve fitting
- Gamma-variate function
- Compartmental kinetic models
- „Graphical” methods
- Partial volume effect correction

Elements: Coregistration and fusion

PET-MRI fusion (AIR)

SERT distribution volume (Logan) parametric image fused with MRI

(baboon study shown)

Ways and steps of processing dynamic studies

- Dynamic PET series
- SPECT
- VOI drawing
- Model fitting
- Parametric image
- SPM
- Results
- Blood data
- MRI
**Tracer Modeling**

- The basis for most PET studies – numerical value
- Time activity curves → Parametric Images – 3 methods
  - Kinetic – non linear least squares
  - Graphical – linear
  - Equilibrium – no change over time

**General compartment model and PET image**

**Compartmental Analysis**

**Reference Tissue Method**
- A variant of the equilibrium method
- Uses a region that is devoid of the object of interest

\[ C_p(t) = \frac{dC_b(t)}{dt} = K_1C_b(t) - K_2C_p(t) \]

- \( C_p \rightarrow [\text{Plasma}] \)
- \( C_r \rightarrow [\text{Reference}] \)
- \( C_b \rightarrow [\text{Free}] \)
- \( C_o \rightarrow [\text{Bound}] \)

**Obtaining Binding Potential**

- Measure binding in Rref and binding in ROI, and subtract out Rref to get BP in ROI.

**Correction of the arterial activity curve for metabolites (McN-5652)**

- \( C_o(t) = K_1C_b(t) - K_2C_o(t) \)

- Distribution volume:
  \[ DV = \frac{K_1}{k_2} \]

- \( C_b(t) \): concentration in tissue

- \( C_o(t) \): concentration in plasma

<table>
<thead>
<tr>
<th>Time activity curves</th>
<th>Arterial activity</th>
<th>Corrected input</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 20 40 60 80 100 min</td>
<td>0 20 40 60 80 100 min</td>
<td>0 20 40 60 80 100 min</td>
</tr>
</tbody>
</table>

**Reference Tissue Method**

- Advantages:
  - No arterial cannulation
  - Independent of plasma curve and hence the tracer, so there is no error in measurement of metabolites

- Disadvantages:
  - Reference tissue must be assumed to be void of object of interest and to be modeled by only one compartment
**Serotonin Overview**

- 5-HTTLPR is promoter region of SERT gene
- SS causes less SERT, L_L causes more SERT
- Δ in serotonin in synapse should alter postsynaptic receptor, 5-HT_{2A}

http://www.humanillnesses.com/images/hdc_0000_0001_0_img0054.jpg

**Logan parametric image:**
Distribution of Serotonin transporters on PET

Cooperation: Johns Hopkins Univ., Baltimore


Applications: impact of illnesses and drugs.

**Proposed solution:**
"Perpendicular" fit

\[ \sum_{i=1}^{n} d_i^2 = \text{minimal} \]

Least squares:

Traditional

Perpendicular

**Example#1:** Logan plots of single-voxel regions

"Traditional"  "Rectangular"

**Example#2:** Logan plots of single-voxel regions

"Traditional"  "Rectangular"
**Ichise’s bilinear plot**

\[
\int \frac{C(t) \, dt}{C(t)} = \int \left( \frac{C_{\text{ref}}(t)}{C(t)} \right) \, dt + \left( \frac{ab^t}{a} \right) C_{\text{ref}}(t) + b
\]

with:
- \(C(t)\) : radioactivity concentration in the target region
- \(C_{\text{ref}}(t)\) : radioactivity concentration in the reference region
- \(DVR\) : distribution volume ratio,
  \[\text{DVR} = BP^* + 1 = k_f/k_d + 1\]


**Distribution volume (DV)**

- DV from 3-compartment model
- DV (Akaike-weighted mean of 2 & 3 comp. models)
- simplified (non-lin.) reference area method (SRTM)

**FDG kinetics**

Blood | Free space | Cell
--- | --- | ---
K1 | K2 | K3
FDG | FDG | FDG-6-P

![FDG kinetics diagram](image)

**Patlak image:** K uptake rate constant

**Myocardial perfusion PET with [N-13] ammonia**

- Patlak image: K uptake rate constant
- Area of stenosed artery

Parametric images:
- A: Non-linear fit
- B: Weighted non-linear fit
- C: Patlak analysis
Use of Patlak analysis for hemispherical rCBF

Patlak plot applied to scale a parametric image: Cerebral Blood Flow (HM-PAO)

ROI Analysis

• Cluster Analysis
• SPM utilizes t-test to look for difference between groups in all voxels
• Subjects grouped by genetics (SS or LL)
• No regard to structure or function
• Once difference found, we must determine structures involved

Statistical Parametric Mapping...

SPM key concepts...

• Accurate aorta-brain transit time
• Be transformed to rCBF units utilising hemispherical rCBFs as reference

Statistical Parametric Mapping

• General Linear Model
• Theory of continuous random fields

What lies behind pictures of brain activations?
**SPM: Statistical Parametric Mapping**
- a voxel-based statistical analysis
- for every voxel in the brain:
  - ask how similarly to the task it behaves

Various display methods for statistical maps

**Group analysis: fixed vs. random effects**
- Fixed effects analysis
  - Similar to sample averaging across individuals
  - Results are not generalizable to the population
    (outliers can strongly influence averages)
- Random effects analysis
  - Results are more robust and replicable
  - Generalize to the population
  - Is a more conservative but statistically appropriate approach

**Displaying results**
- The chosen statistical threshold determines what is displayed (and classified) as activated
  - $T = 2.10$, $P < 0.05$ (uncorrected)
  - $T = 3.60$, $P < 0.001$ (uncorrected)
  - $T = 7.15$, $P < 0.05$ (corrected)