Review material over time

1. rethink: better to call the compartments "pools" and the curves "activities in each pool over time"

2. each site has the same (a PSF) ... and is influenced most by events in middle but to some degree by events in the tails. Note in old scanner, the PSF of cross slices was different from the PSF of direct slices

3. In equilibrium binding assay we measure Vmax as total binding area a long time.

\[ \text{Vmax} \]

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

So I was wrong last week to draw a second curve; if we normalize i.e. (concentration of ligand by K_d), then all curves are identical.
Areas of confusion

1. Does the tracer knock off the dopamine. Effectively no — because the total mass of tracer is limited to avoid drug effects.

   (Drug effects could be considered synonymous with "binding-occupying" a "significant"/appreciable percentage of receptors.)

2. Consider Mariot Fisher together.

   1983-1992-ish use PET w/ radiopride a CFT to image dopamine receptors.

   1993 T. Logan "Effects of Endog DA on NMS behavior: sensitivity" check stability of param estimate predict (from simulations) effect of DA on measurements w/ PET.

   Key words: sensitivity predict / effect.
Effects of Endogenous Dopamine on Measures of $[^{18}\text{F}]\text{N-}
\text{Methylspiropiperidol}$ Binding in the Basal Ganglia: Comparison of Simulations and Experimental Results From PET Studies in Baboons

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KEY WORDS Positron emission tomography, Amphetamine, Kinetic modeling, Dopamine, Receptor

ABSTRACT The effect of endogenous dopamine on PET measures of radioligand binding is important to the measurement of receptor density (or availability) and neurotransmitter interactions in vivo. We recently reported that pretreatment with amphetamine, a drug which stimulates dopamine release, significantly reduced NMS binding in the baboon brain as determined by the product $\lambda k_s$ derived from the graphical analysis method for irreversible systems ($\lambda$ is the ratio of the forward to reverse plasma to tissue transport constants and $k_s$ is proportional to receptor density) (Dewey et al.: Synapse 7:324–327, 1991). The purpose of this work is twofold: to evaluate the sensitivity and stability of the analysis method used for the NMS data and from simulation studies which include the competitive effects of dopamine on NMS binding to predict the effect of dopamine on the in vivo PET experiment. Using a measured plasma $[^{18}\text{F}]$-NMS input function from a control study in a baboon, simulation data was numerically generated explicitly allowing competition between NMS and dopamine in the calculation. This data was analyzed using the same techniques as used for the experimental data and the results were compared to in vitro calculations. The following conclusions were reached: 1) The effect of dopamine on specific binding was found to be greater in vivo than in vitro because the in vitro equilibrium experiment is controlled only by the relative $K_D$'s of tracer and dopamine while the in vivo experiment also depends upon the halftime of tracer in tissue which is controlled by the tissue-to-plasma transport constant; 2) Experimental evidence from rodent studies (Seeman et al.: Synapse 3:96–97, 1989) and the agreement between PET studies (Wong et al.: Science 234:1566–1563, 1986a) and postmortem human studies (Seeman et al.: Science 225:728–731, 1984) in schizophrenics suggest that NMS is not likely to be affected by normal levels of endogenous dopamine. From the calculations reported here the effective in vivo $K_D$ of dopamine for the NMS binding site would have to be on the order of or greater than 100 nM, assuming a synaptic dopamine concentration of 20 nM, in order that this concentration of dopamine have little effect on NMS binding.

INTRODUCTION

Two recent PET measurements of the concentration of dopamine D2 receptors in the brains of untreated schizophrenic patients have given conflicting results. Wong et al. (1986a), using the higher affinity radioligand $[^{13}\text{C}]\text{N-}
\text{Methylspiropiperidol}$ (NMS), found an elevated concentration of D2 receptors, in vivo, confirming measurements made in post-mortem brain tissue (See- man et al., 1984, 1987). In contrast Farde et al. (1987, 1990) using the lower affinity ligand, $[^{13}\text{C}]\text{raclopride}$, found no elevation in the concentration of D2 receptors in schizophrenic patients relative to normal subjects. Whether or not receptor density ($B_{\text{max}}$) is elevated in

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How do we predict an effect or measure the sensitivity of a measurement to alteration of a condition?

Simulations!
(right? ... can't perform every possible experiment).

general idea:
outcome measure (typically a param)

\[ \text{inputs} \rightarrow \text{Model of the data} \rightarrow \text{predicted data} \]

\[ \text{Model of system + noise} \]

\[ \text{predicted "realistic" data w/ noise} \]
What is Sensitivity of the PET curve to changes in DA (Morr's paper)

begins

![Diagram of DA and tracer interaction]

effect of DA

a model that describes behavior of tracer, below DA, and their interaction (e.g., how they compete...)

More specific question.

If my endpoint is an estimate of BP binding potential,

Then Sensitivity Analysis will ask: how much does my estimate BP vary if I change various inputs by +/- 10%?

![Diagram of variables and model]

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Optimization is slightly different (sort of related to) sensitivity analysis.

First decide what I want to optimize.

Morin et al. close to optimum.

Max \( X^2 \) between rest & activation curves:

\[
X^2 = \frac{1}{n} \sum (o_i - r_i)^2
\]

\( n \) variable

\( a, b, c, d, y \)

Vary these all mockernically

Model:

Simulated data

\( \chi^2 \)

X2

Length of variable 2

Taller (hand drawn) variable
but why did Maris et al choose $\beta$ an irreversible ligand like CPT ??

Because your result is all about

a. inputs
b. model
c. objective function (what you choose to optimize)

if we want big football players we may optimize calorie intake ...
but that might just give us FAT football players, not good ones.

Maris optimized $X$ but
(a) did not add noise to data
(b) did not explain how to deal w/ different activities injected during rest/activation.

Logan advocated 

[Signature]
What is the Model?

See 9/21/10 notes.

\[
F \Rightarrow F \Rightarrow B
\]

Saturation, bimolecular.

(Measured) input

Production, rate constant

Compartment

Write a mass balance around each compartment.
Koepp → 649 citations
Mois → 43 citations (mostly me)

He did it!

Google scholar 9-18-12

Issues

Why a task w/ so much crap?
Motion
Craving
Performance
Planning

... Just get a damn effect

Control task (blank screen)

Need motor only (un-directed)

Need ...