II. Identifiability

Minturn paper - quick review

Why is Minturn's term

\[ K_1 f_1 C_2 (B_{\text{max}} - C_3) \]

Not identifiable?

Recall Minturn

Model arrangement

or in 'modern' nomenclature

\[ F \xrightarrow{k_{\text{on}} (B_{\text{max}} - B)} K_{\text{off}} \]

Write balance in \( B \)

\[ \frac{\text{in - out}}{\text{accumulation}} = m - \text{out} \]

Minturn

\[ \frac{\text{dx}}{\text{dt}} = \Phi_in - \Phi_out \]

\[ \frac{dB}{dt} = k_{\text{on}} (B_{\text{max}} - B) F - k_{\text{off}} B \]

models are Mass Balances

\[ \text{accru} = \text{(probability)} \left( \frac{\text{recept}}{(1 \text{/ pad})} \right) - \text{probability} \times \text{liquid bond} \]

\[ \text{dissoc} \]

\[ \text{probability} \times \text{interact} \]

\[ \text{b molecular} \]

per concentration

\[ \text{p} \]

\[ \text{conc} \]
On page 218, Shimizu says:

If we consider the ideal tracer methodology, the specific activity sufficiently high in certain quantities vanishingly low in

Then

\[ B_{\text{max}} \gg B \]

the bound tracer-receptor complex never walks

so \( (B_{\text{max}} - B) \approx B_{\text{max}} \)
total # kept sites

Mass balance on B compartment reduces to

\[
\frac{dB}{dt} = k_{\text{on}} B_{\text{max}} F - k_{\text{off}} B
\]

So what's problem?

If \( k_{\text{on}} B_{\text{max}} \) always travel together then they might as well be one parameter

"\( k_3 \)" we'll never tell them apart \( \Rightarrow \) we'll never be able to estimate them separately reliably, "NOT IDENTIFIABLE"

Consider

\[
y = mx + b
\]

\[
x = \text{age of child}
\]

\[
y = \text{height}
\]

\[
b = \text{height at birth}
\]

\[
h = m \cdot a + b
\]

but even if we knew that \( m = \text{rate of growth} \)

\[
w = \text{age} + 6
\]

we could not estimate the \( n \) and \( g \).
HAVING SAID THAT

IN the PET (in vivo brain imaging case) we KNOW that $k_3$ must be

$$k_3 = k_{on} \cdot B_{avail}$$

but w/ a single bolus injection & high SA tracer, we cannot estimate $k_{on}$, $B_{max}$ separately from the PET data.

II Predictive value of (compartmental) models

Recall that we KNOW in one case that

$$k_3 = k_{on} \cdot B_{avail}$$

$$= k_{on} (B_{max} - B)$$

a more precisely

$$= k_{on} (B_{max} - B^{DA} - B)$$

but by same reasoning as long as $B^{DA} \neq B^{DA}(t)$

Thus

$$k_3 = k_{on} (B_{max} - B^{DA} - B)$$

$$= k_{on} (B_{max} - B)$$

So, we can't identify $k_{on}$, $B_{max}$, $B^{DA}$

where $B^{DA}$ is steady state level of receptors bound to DA molecules.

But, theoretically, everything change when everything changes, i.e., ...
\[ \frac{dB}{d\tau} = k_{on} (B_{\text{max}} - B) + k_{off} B \]

**Explanation:**

In this context, we might be able to detect the effect of the change in these parameters and in this way, this is what Logan was trying to do in his 1991 paper. First, general word about models for simulations and sensitivity analysis. We may not be able to estimate all parameters from data but we can certainly vary them in a simulation.

Start with the "correct" model. Simulate different data sets by changing values of \( k_{on}, k_{off}, B_{\text{max}}, \) and \( \frac{dB}{d\tau} \) for each parameter case.

- Data set 1
- Data set 2
- Data set 3
- Data set 4

Ask question: When does \( \frac{dB}{d\tau} \) to \( k_{3} \) estimated? We then use this simpler model for process estimation.
Now, what question 6) was Logan trying to answer via simulation?

(Actually, I forgot that I had a nice explanation of Logan in my 1995 HBM paper on)

Logan made model... to study effect of transient changes in endogenous chemical on measured density of D2 receptors.

Logan models (1)

\[ \frac{dF^*}{dt} = k_1 C_p(t) - k_2 F^* - k_{on} (B_{max} - B^* - B)^* + k_{off} B^* \]

\[ \frac{dB^*}{dt} = k_{on} (B_{max} - B^* - B)^* - k_{off} B^* \]

\[ \frac{dB}{dt} = k_{on} (B_{max} - B^* - B)(T - B) - k_{off} B \]

(k_{on} for trace, k_{on} for DA)

Says that total DA must be preserved why - have no idea.
Side question
Why no $C(0, t)$ term for mass balance on $B$ (Bond dopamine)?

$F_B$ is fixed total dopamine
is a way of saying

$F_B$ for $B_{DA}$

really The model Logan should have drawn for terms $3$ is

$$B_{max} = B_{max} - B$$

**Quiz:**

1. Draw a model for NMS$^*$ binding to $D_2$ and $S_2$

2. Draw in the boundaries of $B_{max}$
   Answer: need 2 different $B_{max}$ terms
Quiz Q3

How to change model if NMS is essentially irreversible (recall irrevers. is for the time-duration of the exp.)

A: \[ F^* \rightarrow B^* \]

Quiz Q4 (Morris HBM)

How to modify model to include explicit terms for hot and cold tracers

A: \[ \frac{P}{F} \rightarrow \frac{E}{B} \rightarrow \frac{B^*}{B} \]

"Delirious model"

Why would we need this of

or what is SA in terms of this picture?

\[ SA_p = \frac{P}{F} \quad SA_F = \frac{F}{E} \quad SA_B = \frac{B^*}{B} \]

Don't need if \( SA_p = SA_F = SA_B = \text{const} \)

But what if we introduce changes in SA -- how by injections of high SA and low SA ...

Why do this? ... to separate \( B^* \), \( B^* \) and in doing so, separate \( B_{\text{max}} \).
Final Quiz Q5a

How to model (Full morty)

Hot tracer, cold tracer and analog compete.

\[
\begin{align*}
F^* & \rightarrow F^* \rightarrow B^* \\
F & \rightarrow F \rightarrow B \\
F^{DA} & \rightarrow B^{DA}
\end{align*}
\]

Q5b. How does definition of the \( B^{max} \) differ from other \( B^{max} \)?

A: This is true \( B^{max} \).

\[ \text{total receptors in play} \]

\[ B^{cold} \]

Morris simulations IBM 1995

What were we trying to simulate?

Effect on PET data of small cognition-induced changes in DA (DA(1))
How did we (HBM'98) model DA(t)?

- Realistic - No.

What questions did we ask?

1. For varying duration of activation, was there a 'detectable' change in PET curve (or some measurable parameter)? ... 10 min gives most effect.

   What output parameter?
   A: \( \gamma \) between baseline & activation.

2. What are optimal kinetics of the ligand?

   ... for our particular set up, irreversible.
Let's review the simplest scenario for using the predictive part of a model. Say we know that binding exists.

True topology: \[ P = F = \Box \]

But say (for one or another reason) we can only fit w/ 2p model.

What are consequences to estimation of \( K_1, k_r \)?

\[ K_1, k_2, k_3, k_4 \] -> \[ \Box \Box \Box \Box \] -> Sim'd data

\[ \hat{K}_1, \hat{K}_2 \] -> estimate

So these \( K_1, K_2 \) estimates are "apparent" parameters.
Let's examine the result of Logan.

**Table IV**

<table>
<thead>
<tr>
<th>DA</th>
<th>kd = 5 10 50 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

Degree of underestimation of $K_i$

Where $K_i = \frac{k_1 k_3}{k_2 + k_3}$

"Uptake constant" (for irreversible tracer)

Logan '91 Fig 5

What was the simulated DA(t)?
Koeppe paper cited 486 times according to Google Scholar

(so how come no one cites mine?)

What did Koeppe do

1. What was the goal
   Measure DA release associated with cognitive/activation
   behavior (neglects motor)

2. What did he measure
   BP
   Blank screen vs. BP while video game

3. What was timeline of scan/game

   +10
   Scan
   ( VS ) injectradio
   90
   Blank screen
   -10
   Scan
   0
   Inject radio
   90
4. Findings (a bit scary)
   What was estimated
   
   3 params
   \[ R_1 = \frac{k_i}{k_e} \; ; \; BP = \frac{k_3}{k_4} \]

   Key: estimating a constant BP
   from each scan and then
   a change in BP (DBP) from
   baseline to final
   
   This amounts to the following

   ![Graph](image)

   It is reasonable to approx
   additional DA
   bound to state. Dz
Note: Table 1 Legend!

P₁ and BP both changed \( \downarrow \) (as did ROI size) during video game.

So, how do we know that we are seeing BP change \( \rightarrow \) DA?!

Claim:

\[
\text{Performance on game is not for OR vs performance (not shown).}
\]
last page
actually calculated
\[ \text{DVR} = \frac{K_1 K_2}{K_2 \text{ser} (1 + K_3 \text{ser})} \]

\[ \Delta \text{BP} \downarrow \text{attrib to DA} \]

Threshold drawn,

\[ \Delta \text{BP} \]

Spearman coeff.
because (Issues)

performance is
a non-continuous
scale.

Can do this model on every pixel
\[ \Delta \text{BP images in both conditions} \]
\[ \rightarrow \text{SPM ~ t test at all voxels} \]
problems w/ design.

1. Need movement in baseline condition

2. Is it likely that DA(t) = const for 50 min?

3. Tell us what their null hypothesis blank screen vs blank screen gives.

Blank vs random motion compare to blank vs motivated motion.