PK/PD MODELING OF DRUG INTERACTIONS

William J. Jusko, Ph.D.

Outline:

In Vitro Drug Interaction Studies: Loewe Additivity
   Combination Index, Isobolograms, URSA

In Vivo Drug Interactions with Active Metabolites
   Competitive, Noncompetitive Interactions

In Vivo Drug Interactions with Antagonists
   Gaddum Equation

In Vivo Drug Interactions for Indirect Responses
   Diversity of Mechanistic Models

Methods of Assessing Drug Interactions In Vitro

“Null Reference” Models

Loewe Additivity


Bliss Independence


Loewe Additivity

For 50 % inhibition*:

\[ CI = \frac{C_a}{IC_{50a}} + \frac{C_b}{IC_{50b}} \]

CI = Combination Index

where \( C_i \) is the concentration of drug \( i \)

\( IC_{50} \) is the Inhibition Constant

\[ \begin{align*}
CI = 1 & \quad \text{Additivity} \\
CI < 1 & \quad \text{Synergism} \\
CI > 1 & \quad \text{Antagonism}
\end{align*} \]

* Can select any endpoint (eg. 50%)
Perform study:

\[ CI = \frac{C_a}{IC_{50a}} + \frac{C_b}{IC_{50b}} \]

Say: \( IC_{50a} = 10 \) \( IC_{50b} = 40 \)
Say: \( C_a = 3 \) and \( C_b = 10 \) to get 50% Inhibition

\[ CI = \frac{3}{10} + \frac{10}{40} = 0.3 + 0.25 = 0.55 \]

Conclusion: Synergism

Isobologram

“Additivity refers to concentration and is derived from the concept that a drug \( A \) is additive with (any dilution) of itself”


Applications:


Cyclosporine/Prednisolone/Sirolimus Interactions in Three Human Lymphocyte Proliferation Assays

G. Ferron

Results of inhibition studies for three types of cell culture systems (left and center panels) and isobologram for 17 drug combinations yielding the URSA interaction parameter, \( \alpha \).
**Concentration-Effect Surface**

![Concentration-Effect Surface](image)

**Extended Loewe Additivity Method**

\[ \Lambda = \frac{C_1}{IC_{50,1}} \left( \frac{\%S_{max}}{S_{max} - \%S_{max}} \right)^{1/\gamma_1} + \frac{C_2}{IC_{50,2}} \left( \frac{\%S_{max}}{S_{max} - \%S_{max}} \right)^{1/\gamma_2} \]

- Synergism \( \Lambda < 1 \)
- Antagonism \( \Lambda > 1 \)

**Mechanistic Models For Drug Interactions**

These are usually models based on interactions of two drugs with receptors or enzymes.

\[ C_A + R \xrightarrow{k_1} C_AR \quad K_{01} = EC_{50_A} = k_{-1}/k_1 \]

\[ C_B + R \xrightarrow{k_2} C_BR \quad K_{02} = EC_{50_B} = k_{-2}/k_2 \]

\[ R_{TOT} = R + C_AR + C_BR \]

**The Universal Response Surface Approach (URSA)**


\[ 1 = \frac{C_1}{IC_{50,1}} \left( \frac{E - Back_{1}}{S_{max} - E} \right)^{-1/\gamma_1} + \frac{C_2}{IC_{50,2}} \left( \frac{E - Back_{2}}{S_{max} - E} \right)^{-1/\gamma_2} \]

- Case I \( \alpha = 0 \) Additivity
- Case II \( \alpha = \) positive Synergism
- Case III \( \alpha = \) negative Antagonism

E = Effect in % of \( S_{max} \), \( S_{max} = 100 \% \) (response at zero drug conc.),
Back = background (response at infinite drug conc.),
\( I_{max} = S_{max} - Back \), \( \gamma = \) Hill coefficient, \( \alpha = \) interaction parameter.

Problem: Unclosed form equation. Need iterative solution (Bisection Method)

**Mechanistic Models For Drug Interactions**

These are usually models based on interactions of two drugs with receptors or enzymes.

\[ C_A + R \xrightarrow{k_1} C_AR \quad K_{01} = EC_{50_A} = k_{-1}/k_1 \]

\[ C_B + R \xrightarrow{k_2} C_BR \quad K_{02} = EC_{50_B} = k_{-2}/k_2 \]

\[ R_{TOT} = R + C_AR + C_BR \]

**Mechanistic Models For Drug Interactions**

These are usually models based on interactions of two drugs with receptors or enzymes.

\[ C_A + R \xrightarrow{k_1} C_AR \quad K_{01} = EC_{50_A} = k_{-1}/k_1 \]

\[ C_B + R \xrightarrow{k_2} C_BR \quad K_{02} = EC_{50_B} = k_{-2}/k_2 \]

\[ R_{TOT} = R + C_AR + C_BR \]

**Mechanistic Models For Drug Interactions**

These are usually models based on interactions of two drugs with receptors or enzymes.

\[ C_A + R \xrightarrow{k_1} C_AR \quad K_{01} = EC_{50_A} = k_{-1}/k_1 \]

\[ C_B + R \xrightarrow{k_2} C_BR \quad K_{02} = EC_{50_B} = k_{-2}/k_2 \]

\[ R_{TOT} = R + C_AR + C_BR \]
Competitive Interaction Between Two Drugs Acting at the Same Receptor


\[ E_{A+B} = \frac{E_{max_A} \cdot \frac{C_A}{EC_{50_A}} + E_{max_B} \cdot \frac{C_B}{EC_{50_B}}}{C_A + EC_{50_A} + C_B \cdot \xi} \]

If \( \frac{EC_{50_A}}{EC_{50_B}} = \xi \) (Xi)

\[ E_{A+B} = \frac{E_{max_A} C_A + E_{max_B} C_B \cdot \xi}{C_A + EC_{50_A} + C_B \cdot \xi} \]

- Involves parametric modeling.
- Allows mechanistic interpretation.

Interactions: Competitive Inhibition

\[ E = 100 \left[ 1 - \frac{I_{max_A} \left( \frac{A \cdot (\psi \cdot IC_{50_A})}{IC_{50_A}} \right)^{\gamma_A} + I_{max_B} \left( \frac{B \cdot (\psi \cdot IC_{50_B})}{IC_{50_B}} \right)^{\gamma_B}}{A \left( \frac{\psi \cdot IC_{50_A}}{IC_{50_A}} \right)^{\gamma_A} + B \left( \frac{\psi \cdot IC_{50_B}}{IC_{50_B}} \right)^{\gamma_B} + 1} \right] \]

- \( \psi = 1 \) Simple additive effect
- \( \psi < 1 \) Synergy
- \( \psi > 1 \) Antagonism


Noncompetitive Interaction

\[ E_{max_A} \cdot \frac{C_A}{EC_{50_A}} + E_{max_B} \cdot \frac{C_B}{EC_{50_B}} + \left( E_{max_A} + E_{max_B} - E_{max_A} \cdot E_{max_B} \right) \cdot \frac{(C_A \cdot C_B)}{EC_{50_A} \cdot EC_{50_B}} \]

\[ \frac{C_A}{EC_{50_A}} + \frac{C_B}{EC_{50_B}} + \left( \frac{C_A}{EC_{50_A}} \cdot \frac{C_B}{EC_{50_B}} \right) + 1 \]

Noncompetitive antagonism occurs when the agonist and antagonist can be bound, at the same time, to different regions of the receptor macromolecule.

Also called allotropic or allosteric antagonism.


Interactions: Noncompetitive Inhibition


Concentration Ratio = 0.29

Results:

<table>
<thead>
<tr>
<th>Pred</th>
<th>IC_{50}</th>
<th>( \gamma )</th>
<th>( \psi )</th>
<th>Interaction Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>4.43</td>
<td>1.57</td>
<td>0.72</td>
<td>Competitive (Synergy)</td>
</tr>
<tr>
<td>0.90</td>
<td>16.65</td>
<td>1.33</td>
<td>1.08</td>
<td>Non-Competitive (no interaction)</td>
</tr>
</tbody>
</table>

WinNonlin Example: Noncompetitive Inhibition

COMMANDS
NFUNCTIONS 1
NPARAMETERS 8
NPAMES 'R0', 'ImaxA', 'IC50A', 'ImaxB', 'IC50B', 'Psi', 'Ga', 'Gb'
END
remark - define temporary variables
TEMPORARY
Ca=dta(1)
Cb=dta(2)
END remark - define algebraic functions
FUNCTION 1
F = 100 * (1 –(((ImaxA*(Ca/(psi*IC50A)**Ga))+(ImaxB*(Cb/(psi*IC50B)**Gb)+(ImaxA+ImaxB-ImaxA*ImaxB)*(Ca/(psi*IC50A)**Ga)* (Cb/(psi*IC50B))**Gb))/(1+((Ca/(psi*IC50A))**Ga)+(Cb/(psi*IC50B))**Gb)+(Ca/(psi*IC50A)**Ga)*(Cb/(psi*IC50B))**Gb)))
END

Results: \( I_{max} \quad IC_{50} \)

Drug A  1.00   46.8 \( \psi = 0.66 \) Synergy
Drug B  1.00   1330

Does not require bisection method.

Modeling Combination Therapy

Colon carcinoma (HCT116) xenografts

\[ \text{growth: } f(t) = \frac{a \cdot x_1}{b + x_1} \]

Does not require bisection method.

Active Metabolites: Metoprolol and Alpha-hydroxymetoprolol Concentrations and Reduction in Essential Tremor.


Pharmacokinetic-Pharmacodynamic Modeling of the Central Nervous System Effects of Midazolam (○) and Its Main Metabolite α - Hydroxymidazolam (□) in Healthy Volunteers

Relationships Between Midazolam (●) and α-Hydroxymidazolam (■) Concentrations and Peak Saccadic Velocity Derived After IV Administration of Both Compounds.

<table>
<thead>
<tr>
<th>Pharmacodynamic parameters</th>
<th>Midazolam</th>
<th>Mean (± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{ox}$ (min$^{-1}$)</td>
<td>0.15 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>$E_0$ (deg/sec)</td>
<td>432 ± 28</td>
<td></td>
</tr>
<tr>
<td>$E_{max}$ (deg/sec)</td>
<td>-197 ± 34</td>
<td></td>
</tr>
<tr>
<td>$EC_{50}$ (ng/mL)</td>
<td>40 ± 7</td>
<td></td>
</tr>
<tr>
<td>$N$</td>
<td>4.5 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

α-Hydroxymidazolam

<table>
<thead>
<tr>
<th>Pharmacodynamic parameters</th>
<th>α-Hydroxymidazolam</th>
<th>Mean (± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{ox}$ (min$^{-1}$)</td>
<td>0.15 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>$E_0$ (deg/sec)</td>
<td>439 ± 29</td>
<td></td>
</tr>
<tr>
<td>$E_{max}$ (deg/sec)</td>
<td>-171 ± 30</td>
<td></td>
</tr>
<tr>
<td>$EC_{50}$ (ng/mL)</td>
<td>49 ± 10</td>
<td></td>
</tr>
<tr>
<td>$N$</td>
<td>4.7 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

The model based on competitive and additive interaction of the two compounds (solid line) produced imperfect prediction of actual data.

Drug Antagonism

Assume $E_{maxB} = 0$ for the Gaddum Equation:

$$ E_{A+B} = \frac{E_{maxA} \cdot C_A}{C_A + EC_{50A} + \frac{EC_{50A}}{EC_{50B}} \cdot C_B} $$

- This equation is identical to the well known equation for competitive inhibition used in enzymology.
- Combination of an active (A) and an inactive compound (B), where the inactive compound has affinity to the specific receptor of the active moiety thus behaving as a competitive antagonist.


Profiles of Midazolam (●), α-Hydroxymidazolam (■) After Oral Administration of Midazolam

InVivo Characterization of the Pharmacodynamic Interaction of a Benzodiazepine Agonist and Antagonist: Midazolam and Flumazenil

Averaged pharmacokinetic and pharmacodynamic parameter estimates (mean ± S.E.) of flumazenil and midazolam used to predict the time course of EEG effect after concomitant administration of both drugs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Midazolam</th>
<th>Flumazenil</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK A₁ (mg/l)</td>
<td>3.96 ± 0.18</td>
<td>5.19 ± 0.41</td>
</tr>
<tr>
<td>α₁ (/min)</td>
<td>0.517 ± 0.034</td>
<td>0.534 ± 0.074</td>
</tr>
<tr>
<td>A₂ (mg/l)</td>
<td>6.97 ± 0.38</td>
<td>4.56 ± 0.43</td>
</tr>
<tr>
<td>α₂ (/min)</td>
<td>0.0235 ± 0.0008</td>
<td>0.0549 ± 0.026</td>
</tr>
<tr>
<td>PD Eₘₐₓ (μV/sec)</td>
<td>75 ± 2</td>
<td>0</td>
</tr>
<tr>
<td>EC₅₀ (ng/ml)</td>
<td>30 ± 3</td>
<td>26</td>
</tr>
<tr>
<td>N</td>
<td>1.07 ± 0.06</td>
<td>1.6</td>
</tr>
</tbody>
</table>

ASA/IBU Pharmacodynamic Interaction Model of COX1 Inhibition

\[
\begin{align*}
\frac{dE}{dt} &= k_{in} - k_{out} \cdot E - K \cdot C_{asa} \cdot E - k_{on} \cdot C_{ibu} \cdot E + k_{off} \cdot EI \\
R &= (E + EI) \cdot (1 - \beta \cdot C_{ibu})
\end{align*}
\]

Basic Models

- IC₅₀ Inhibition
- SC₅₀ Stimulation

Drug Interactions: Indirect Responses

- Competitive
- Noncompetitive Same
- Noncompetitive Different
Drug Interaction: IDR Models

Case e: Noncompetitive Inhibition on $k_{in}$

$$\frac{R_{ss}}{R_0} = \left(1 - \frac{I_{maxA} \cdot C_{ssA}}{IC_{50A} + C_{ssA}}\right) \cdot \left(1 - \frac{I_{maxB} \cdot C_{ssB}}{IC_{50B} + C_{ssB}}\right)$$

Fitted Parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>$I_{max}$</th>
<th>CV%</th>
<th>IC50</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Vinorelbine</td>
<td>0.920</td>
<td>1.31</td>
<td>19.9</td>
<td>14.4</td>
</tr>
<tr>
<td>B: Paclitaxel</td>
<td>0.878</td>
<td>0.915</td>
<td>5.35</td>
<td>11.07</td>
</tr>
</tbody>
</table>

Data from:

Exploring drug interactions for indirect response models with agents acting separately at the production and dissipation sites

Simulated profiles for drugs with $C_p = 200 \cdot \exp(-0.3t)$,
Drug A: $I_{max} = 1$, $IC_{50} = 15$, and Drug B: $S_{max} = 2$, $SC_{50} = 15$.

“Synergy” Cases m & n: Noncompetitive Interaction Acting on Different Processes

Synergy Results from Multiplicative Effect
(Cases: m, n):

For m:
$$\frac{dR}{dt} = k_{in} \cdot S(t) - k_{out} \cdot R$$

For n:
$$\frac{dR}{dt} = k_{in} - k_{out} \cdot I(t) \cdot R$$

Cases: m, n

<table>
<thead>
<tr>
<th>$I_{max_A}$</th>
<th>$S_{max_A}$</th>
<th>$I_{max_B}$</th>
<th>$S_{max_B}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.990</td>
<td>2.000</td>
<td>0.850</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Ice Jam Develops in Cazenovia Creek

February 18, 2011
Traditional empirical methods (isobolograms) are nonmechanistic, but allow simple evaluation of synergism or antagonism in static (in vitro) systems.

Competitive and noncompetitive interaction equations are useful for assessing various types of simple interactions and insertion of $\psi$ is an easy empirical adjustment.

Traditional equations for two agents can be inserted into indirect response models and allow discernment of “synergy” on a mechanistic basis.