An Invitation to Pharmacostatics

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Society for Mathematical Biology

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Salt Lake City, Utah, USA
17-20 July 2017

Pharmacostatics?

Pharmacology:

Studying interactions between biological processes and therapeutic agents

- ✓ Pharmacokinetics (PK):

  How drugs distribute and metabolize in biological systems

- ✓ Pharmacodynamics (PD):

  How biological systems respond to drugs

- ? Pharmacostatics (PS)

Pharmacostatics

Pharmacostatics:

- Pharmacology in discovery-stage drug research
- **Characterization of equilibrium parameters and states of core interactions of physiologic and therapeutic interest**
- *Do “things” stick, how strongly, how much, etc?*

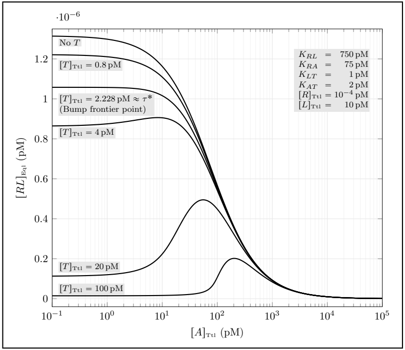
Two Interesting Math Problems in Pharmacostatics

Problem I

$$x_i + \sum_{\alpha \in I} \alpha_i \, a_\alpha \, x^\alpha \;=\; b_i$$

Calculate binding equilibrium

Problem II



Anticipate non-monotone dose-response curves

Background: Chemical Networks of Reversible Binding Reactions

This Presentation

- Background:

  Networks of Reversible Binding Reactions

- Problem I:

  Calculate binding equilibrium

- Problem II:

  Anticipate non-monotone dose-response curves

Networks of Reversible Binding Reactions – Examples

$$R + L \rightleftharpoons RL$$

Reversible binding of a ligand L to a receptor R

$$\begin{array}{cccc} R & + \; L & \rightleftharpoons & RL \\ + & & & \\ A & & & \\ \downharpoonleft\upharpoonright & & & \\ RA & & & \end{array}$$

Reversible orthosteric binding of a ligand L and an antagonist to a receptor R

$$\begin{array}{ccccc} R & + & L & \rightleftharpoons & RL \\ + & & + & & \\ A & + & T & \rightleftharpoons & AT \\ \downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\ RA & & LT & & \end{array}$$

Ligand L and antagonist A competing for the same site on receptor R and likewise on decoy receptor (or trap) T

$$\begin{array}{cccc} R & + \; L & \rightleftharpoons & RL \\ + & & & + \\ A & & & A \\ \downharpoonleft\upharpoonright & & & \downharpoonleft\upharpoonright \\ RA & + \; L & \rightleftharpoons & RLA \end{array}$$

Reversible allosteric binding of a ligand L and modulator A to a receptor R

$$\begin{array}{lcl} R + L & \rightleftharpoons & RL \\ R + A & \rightleftharpoons & RA \\ R + L + A & \rightleftharpoons & RLA \end{array}$$

“Normalized” network for equilibrium calculation

Elementary Species, Composite Species, Composition

$$
\begin{array}{ccc}
R + L & \rightleftharpoons & RL \\
+ & & + \\
A & & A \\
\Downarrow\!\Uparrow & & \Downarrow\!\Uparrow \\
RA + L & \rightleftharpoons & RLA
\end{array}
$$

$$
\begin{array}{lcl}
R + L & \rightleftharpoons & RL \\
R + A & \rightleftharpoons & RA \\
R + L + A & \rightleftharpoons & RLA
\end{array}
$$

Elementary species: R, L, A

Composite species: RL, RA, RLA

Composition: RL: $(1, 1, 0)$

RA: $(1, 0, 1)$

RLA: $(1, 1, 1)$

Elementary Species, Composite Species, Composition

$$\begin{array}{ccccc}
R & + & L & \rightleftharpoons & RL \\
+ & & + & & \\
A & + & T & \rightleftharpoons & AT \\
\downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\
RA & & LT & &
\end{array}$$

Elementary species:	R, L, A, T	
Composite species:	RL, RA, LT, AT	
Composition:	RL:	$(1, 1, 0, 0)$
	RA:	$(1, 0, 1, 0)$
	LT:	$(0, 1, 0, 1)$
	AT:	$(0, 0, 1, 1)$

Networks of Reversible Binding Reactions – Formalism

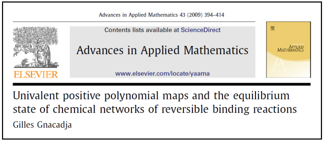
Normal Networks of Reversible Binding Reactions

- Elementary species $X_1, \ldots, X_n$; $n \in \mathbb{Z}_{\geqslant 1}$
- Composite species Y_α of composition α with respect to $(X_1, \ldots, X_n)$; $\alpha \in I$, I nonempty finite $\subseteq \mathbb{Z}^n_{\geqslant 0} \backslash \{0_n, e_{n,1}, \ldots, e_{n,n}\}$
- For each $\alpha = (\alpha_1, \ldots, \alpha_n) \in I$, the binding-dissociation reaction pair $\sum_{i=1}^n \alpha_i X_i \rightleftharpoons Y_\alpha$ and its equilibrium binding constant a_α

Complete Networks of Reversible Binding Reactions

Sensibly support composite species as reactants in binding reactions

- Conservation of composition
- Detailed-balance equilibrium


Advances in Applied Mathematics 43 (2009) 394–414
Contents lists available at ScienceDirect
Advances in Applied Mathematics
www.elsevier.com/locate/yaama
Univalent positive polynomial maps and the equilibrium state of chemical networks of reversible binding reactions
Gilles Gnacadja

Dose-Response Functions

$$
\begin{array}{ccccc}
R & + & L & \rightleftharpoons & RL \\
+ & & + & & \\
A & + & T & \rightleftharpoons & AT \\
\downarrow\!\uparrow & & \downarrow\!\uparrow & & \\
RA & & LT & &
\end{array}
\qquad\qquad
\begin{array}{ccccc}
R & + & L & \rightleftharpoons & RL \\
+ & & & & + \\
A & & & & A \\
\downarrow\!\uparrow & & & & \downarrow\!\uparrow \\
RA & + & L & \rightleftharpoons & RLA
\end{array}
$$

$$[A]_{\text{Total}} \mapsto [RL]_{\text{Equil}} \qquad\qquad [A]_{\text{Total}} \mapsto [RL]_{\text{Equil}} + [RLA]_{\text{Equil}}$$

Dose-response function in general:

$$[X]_{\text{Total}} \mapsto [Y]_{\text{Equil}} \quad \text{or} \quad [X]_{\text{Total}} \mapsto [X']_{\text{Equil\_Total\_Bound}}$$

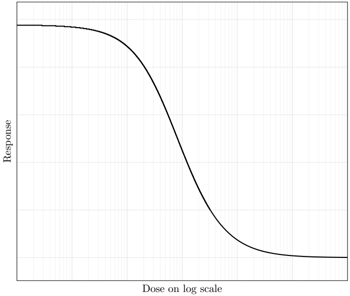
X: An elementary species, the dose species

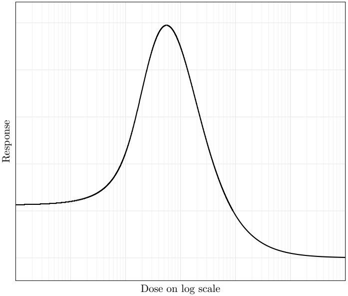
Y: The response species, usually composite

X': An elementary species, usually one whose effect one seeks to antagonize

Monotonicity of Dose-Response Functions

Dose-response functions
usually are monotone
with a sigmoid profile...





...but non-monotone
dose-response functions
do occur

- Rare in published pharmacostatics work
- More awareness in toxicology area

Non-Monotone Response: An Actual Case

Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Journal of Theoretical Biology 244 (2007) 478–488
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

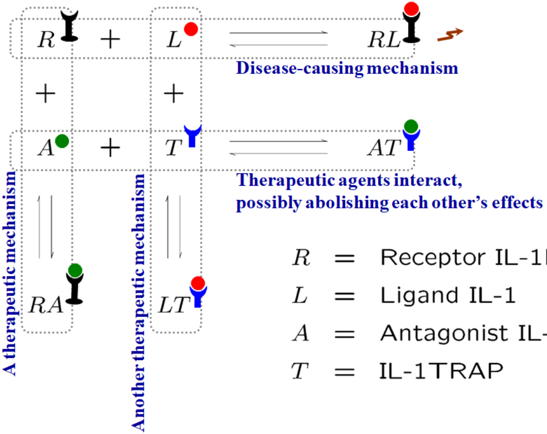
Monotonicity of interleukin-1 receptor–ligand binding with respect to antagonist in the presence of decoy receptor

Gilles Gnacadja , Alex Shoshitaishvili , Michael J. Gresser , Brian Varnum , David Balaban , Mark Durst , Chris Vezina , Yu Li

$$
\begin{array}{ccccc}
R & + & L & \rightleftharpoons & RL \\
+ & & + & & \\
A & + & T & \rightleftharpoons & AT \\
\downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\
RA & & LT & &
\end{array}
$$

$$[A]_{\text{Total}} \mapsto [RL]_{\text{Equil}}$$

Non-Monotone Response: An Actual Case



R	$=$	Receptor IL-1RI
L	$=$	Ligand IL-1
A	$=$	Antagonist IL-1Ra
T	$=$	IL-1TRAP

Non-Monotone Response: An Actual Case

$$
\begin{array}{ccccc}
R & + & L & \rightleftharpoons & RL \\
+ & & + & & \\
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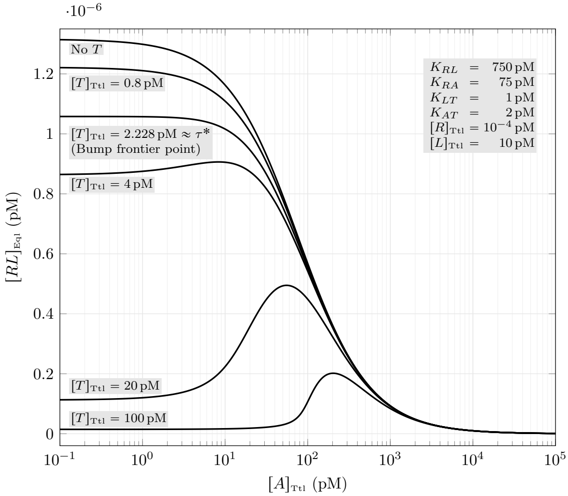

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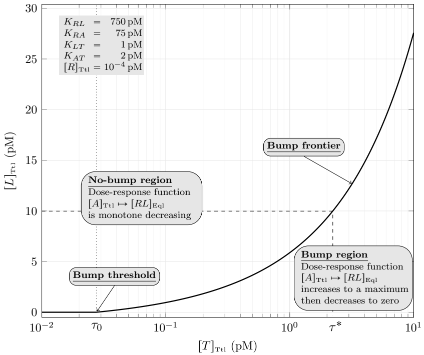
$$\begin{array}{ccccc} R & + & L & \rightleftharpoons & RL \\ + & & + & & \\ A & + & T & \rightleftharpoons & AT \\ \downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\ RA & & LT & & \end{array}$$



The bump frontier:

- A hypersurface in the 7-dimensional space with coordinate system $(K_{RL}, K_{RA}, K_{LT}, K_{AT}, [R]_{\text{Total}}, [L]_{\text{Total}}, [T]_{\text{Total}})$
- Shown here is the 2-dimensional slice resulting from fixing K_{RL}, K_{RA}, K_{LT}, K_{AT}, $[R]_{\text{Total}}$ as specified
- Bump threshold $\tau_0 = K_{LT}K_{AT}/(K_{RA} - K_{AT})$;
  No bump if $[T]_{\text{Total}} \leqslant \tau_0$, regardless how much L there is
- No bump if $K_{RA} \leqslant K_{AT}$

Other Work on Non-Monotone Dose-Response

Applicable to functions of the kind $[X]_{\text{Total}} \mapsto [Y]_{\text{Equil}}$

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ISSN 1751-8849

A technique for determining the signs of sensitivities of steady states in chemical reaction networks

Eduardo D. Sontag

Algebraic-combinatorial technique and algorithm

J. CHEM. SOC. FARADAY TRANS., 1995, **91**(2), 259–267

Response Reactions: A Way to Explain the Unusual Behaviour of Multiple Equilibrium Systems

Ilie Fishtik
István Nagypál and Ivan Gutman

Multivariate analysis and algorithm

Anecdotal reports of investigative molecules having been discarded because of unexplainable dose-response curves

Problem II: Anticipate non-monotone dose-response

Problem II

Characterize the complete networks of reversible binding reactions that are capable of producing non-monotone dose-response functions, and the precise conditions under which non-monotonicity does occur (i.e. something akin to the bump frontier).

Considerations for problem scope reduction

- "Complete networks" is small in the reaction network universe, but still quite large.
- Even in applicable networks, not all species would be worthy dose species.
- Short of a fully characterized bump frontier, a bump threshold would still be of interest.

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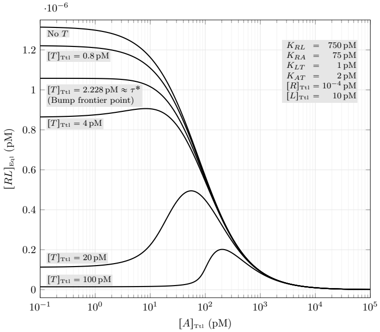
Problem II



Anticipate non-monotone dose-response curves

Background: Chemical Networks of Reversible Binding Reactions