Chemical Reaction Networks in Pharmacology and Related Mathematical Problems

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Workshop on Mathematical Problems Arising from Biochemical Reaction Networks

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Outline

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Pharmacology

Pharmacology: Study interactions between biological processes and therapeutic agents.

- Pharmacokinetics: *"what the body does to the drug"*. Absorption, Distribution, Metabolism, Excretion (ADME).
- Pharmacodynamics: *"what the drug does to the body"*. Drug response.

Usually studied for specific physiological systems or processes.

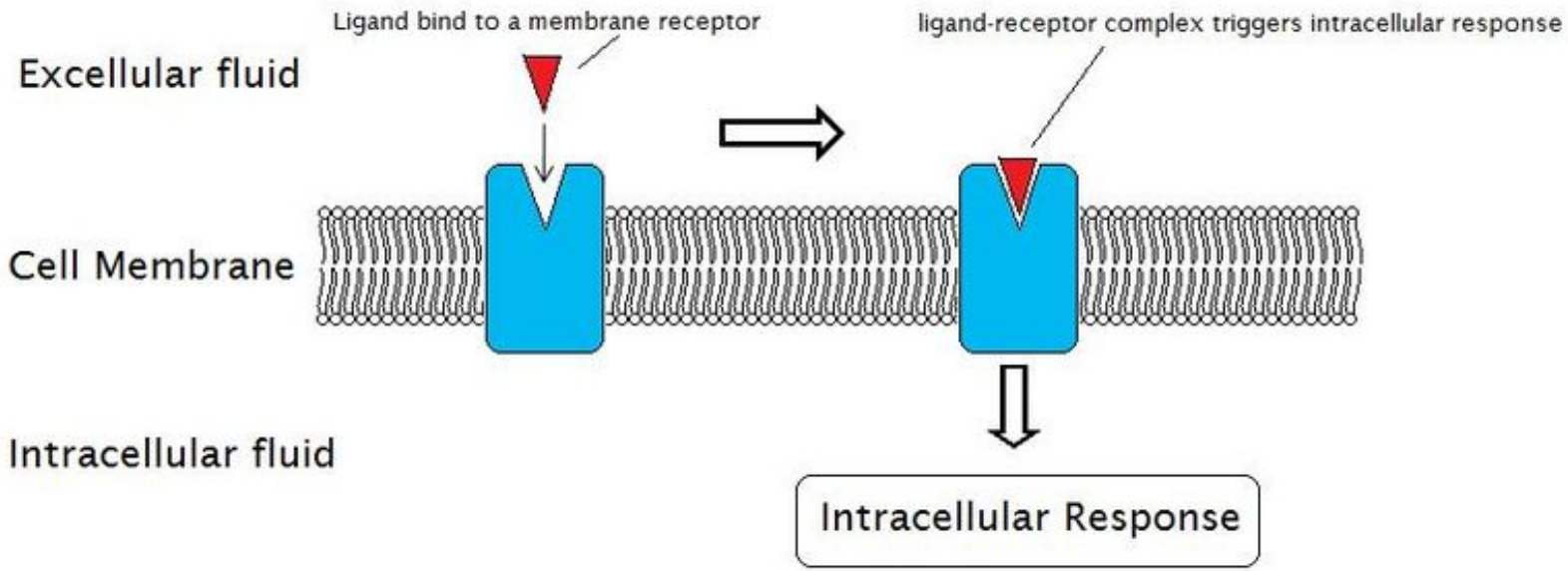
Common foundation: Receptor Pharmacology.

Receptor

Receptor: Biochemical recognition unit.

Cell membrane receptor

- Outside cell: Binding with ligands.
- Inside cell: Transmit, modify or stop signal.



http://en.wikipedia.org/wiki/File:The_External_Reactions_and_the_Internal_Reactions.jpg

Receptor Pharmacology

- "Pharmacostatics" at beginning of research pipeline:
  Study binding equilibrium *in vitro* of interactions between
  - receptors,
  - ligands (pathogenic and therapeutic agents),
  - other actors.
- Mathematical needs: Equilibria of reaction networks.
  - Most needed: "Worry-free" computational algorithms.
    (worry-free > working)
  - Mathematical prerequisites – Properties of equilibrium:
    - Existence;
    - Uniqueness or quantified multiplicity;
    - Asymptotic stability and basins of attraction.
  - Prerequisites to prerequisites:
    Classes of networks to pose and address these questions.

Outline

Competitive Antagonism

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

(Orthosteric binding: binding on same site)

Allosteric Modulation

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

(Allosteric binding: binding on another site)

Competitive Antagonism with Trap (Shed/Decoy) Receptor

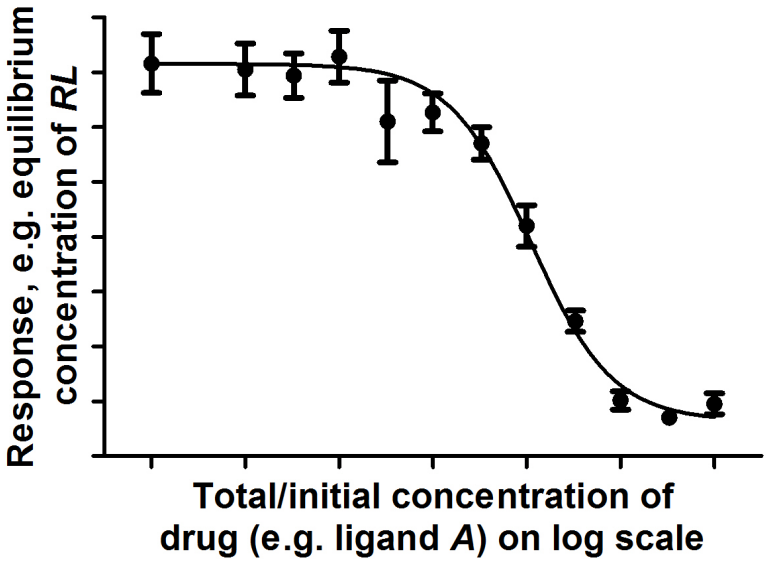
$$\begin{array}{ccccc} R & + & L & \rightleftharpoons & RL \\ + & & + & & \\ A & + & T & \rightleftharpoons & AT \\ \downdownarrows & & \downdownarrows & & \\ RA & & LT & & \end{array}$$

Extensions and Variations

Receptor isomerization	$R \rightleftharpoons R^* \rightleftharpoons \cdots$
Receptor dimerization	$R + R \rightleftharpoons RR$
Ligand dimerization	RLL, $RLLAA$
Intracellular actors	transducing proteins, arresting proteins, etc
Enzymes as receptors	("reversible" but not weakly reversible)

Outline

Parameter Inference and Simulation



Fit dose-response curves to find binding parameters when applicable network is known.

Perform exploratory simulations when applicable network is not known.

Closed-Form Formulas at All Cost

Simple, closed-form formulas for equilibrium concentrations, usually

$$\texttt{EquilConctr} = \texttt{rationalFnctn}(\texttt{BindingParams}, \texttt{TotalConctrs})$$

$$\Uparrow$$

$$\forall\, \texttt{Ligand}\,,\ [\texttt{Ligand}]_{\text{Equil}} = [\texttt{Ligand}]_{\text{Total}}$$

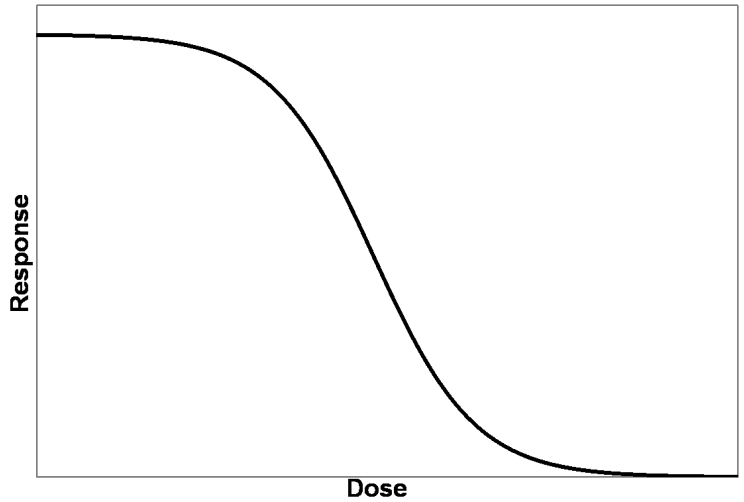
$$\Uparrow$$

$$\forall\, \texttt{Ligand}\,,\ [\texttt{Receptor}]_{\text{Total}} \ll [\texttt{Ligand}]_{\text{Total}}$$

Issues:

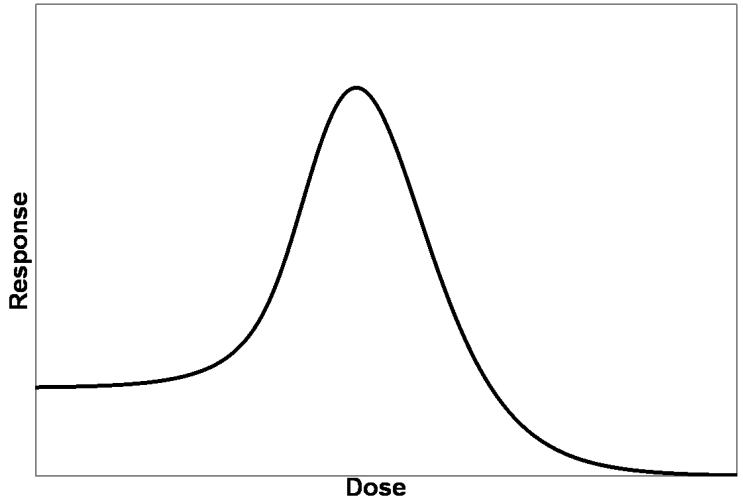
- Not mathematically sound.
  Operational wisdom: $[\texttt{Receptor}]_{\text{Total}} < [\texttt{Ligand}]_{\text{Total}}/10$.
- May be unjustified experimentally, e.g. in miniaturized assays.
- Need not apply *in vivo*.
- New formula derivation needed for every new network.
- Only possible with "receptor-centric" networks.

Expectation of Monotonicity in Dose-Response Curves



This shape is expected and is what forcibly derived closed-form formulas give.

Non-monotone responses do occur and cannot be simulated with forcibly derived closed-form formulas.



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An Attempt at a Relevant Class of Networks

GG: Advances in Applied Mathematics 43 (2009)

Complete networks of reversible binding reactions

- $(\texttt{many species}) \rightleftharpoons (\texttt{one species})$
- Conservation from building blocks and their stoichiometry
- Parameterized for detailed-balanced equilibrium

Properties of equilibrium:

- Unique w.r.t. total concentrations of building blocks
- Globally asymptotically stable

Limitations:

- Enzymes as receptors are not covered
- Multi-state receptors probably covered with mild extensions

An Attempt at a Larger Relevant Class of Networks

GG: Journal of Mathematical Chemistry 49 (2011) – part 2 of 3
GG: Linear Algebra and its Applications 437 (2012)

Explicitly-reversibly constructive networks

- $(\texttt{many species}) \to (\texttt{one species})$ (binding/association)
  $(\texttt{one species}) \to (\texttt{many species})$ (unbinding/dissociation)
  $(\texttt{one species}) \to (\texttt{one species})$ (isomerization)
- Each elementary species is in the source of a binding reaction and in the target of an unbinding reaction (w/ isomerization). Each composite species is the target of a binding reaction and the source of an unbinding reaction (w/ isomerization).
- Conservation from building blocks and their stoichiometry

Limitations:

- Class is quite large. Must be subdivided for useful discussions.
- Reactions $(\texttt{many species}) \to (\texttt{many species})$ not covered. (Do they really exist?)

Outline

Complete Networks of Reversible Binding Reactions

GG: Mathematical Methods in the Applied Sciences 30 (2007)
GG: Advances in Applied Mathematics 43 (2009)
GG: Mathematical Biosciences 232 (2011)

Problem Statement

(skipping straight to the math)

A worry-free algorithm for finding the unique nonnegative solution $x = (x_1, \ldots, x_n)$ of the polynomial system

$$x_i + \sum_{\alpha \in I} \alpha_i \, a_\alpha \, x^\alpha = b_i \ , \ i = 1, \ldots, n$$

where I finite $\subset \mathbb{Z}^n_{\geqslant 0} \backslash \{0_n, e_{n,1}, \ldots, e_{n,n}\}$, $a_\alpha \geqslant 0$, $b_i \geqslant 0$.

Example of Worry-Free: Iteration of a Contraction

Polynomial Equation Reformulated as a Fixed-Point Equation

$$x_i = \frac{b_i}{1 + \sum_{\alpha \in I, \alpha_i \geqslant 1} \alpha_i \, a_\alpha \, x^{\alpha - e_{n,i}}}$$

Iterations converge if

$$\forall \, \alpha \in I, \alpha_1 + \cdots + \alpha_n = 2 \, .$$

Chemistry interpretation: Every reaction is a reversible (homo- or hetero-) dimerization of building blocks. This is quite restrictive!

GG: Mathematical Methods in the Applied Sciences 30 (2007)
Partially rediscovered: *M. G. A. van Dorp, F. Berger, E. Carlon: Physical Review E 84 (2011)*

If not, restrictions on binding parameters and total concentrations.

Can Worry-Free be Extended to Cover more Networks?

- **Conjecture:** There exists a fixed-point preserving operator that transforms the map in the fixed-point equation into a contraction (w.r.t. some metric).
- **Intuition:**
  - Map is monotone-decreasing w.r.t. product order.
    Works in dim 1 (one building block) thanks to total order.
    Works if all composite species are multimers (no coupling).
    Perhaps some kind of nonlinear diagonalization?
  - For networks of reversible dimerizations (not just of building blocks), perhaps some kind of iterations of iterations?
- Cell discarding algorithm with discarding by cell compression. Has worked well on selected examples, especially with parallel computing. Need stronger cell discarding conditions.
- Other ideas?

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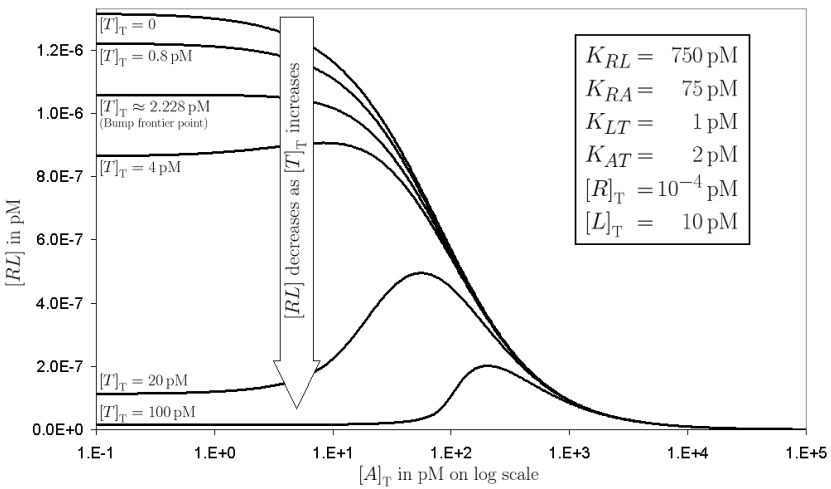
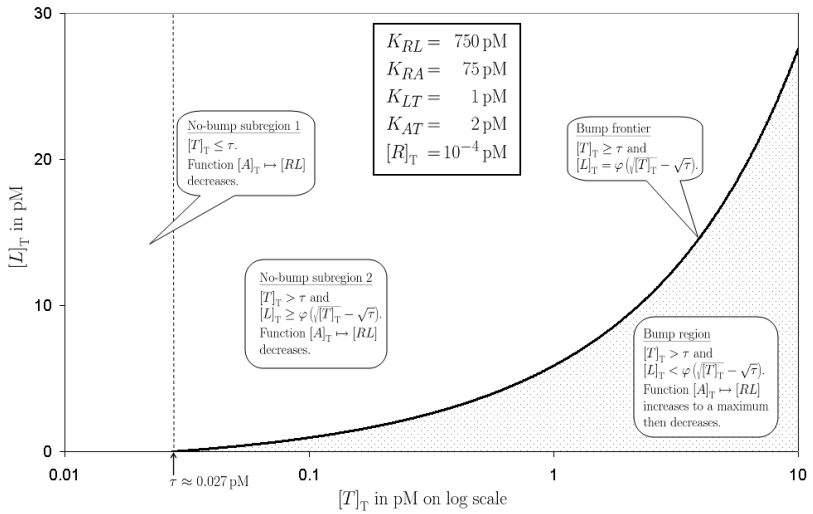
Monotonicity of Dose-Response Curves

GG et al.: Journal of Theoretical Biology 244 (2007)

$$\begin{array}{ccc} R + L & \rightleftharpoons & RL \\ + \quad + & & \\ A + T & \rightleftharpoons & AT \\ \Downarrow \quad \Downarrow & & \\ RA \quad LT & & \end{array}$$





Monotonicity of Dose-Response Curves

Published result found by hard labor – manual and very specific.

Problems:

- Systematic approaches to investigate monotonicity of dose-response curves.
- Classes of networks capable of exhibiting non-monotone dose-response curves, and partitioning of parameter space according the monotonicity.
- Classes of networks incapable of exhibiting non-monotone dose-response curves.

Outline

Recapitulation – Three Interconnected Streams of Problems

- Algorithms for guaranteed and easy computation of equilibrium, with or without fixed-point formulation.
- Reaction networks with non-monotone dose-response curves and related partitioning of parameter space.
- Classes of networks relevant to pharmacology and appropriate for these questions and their prerequisites.