Calculating Detailed-Balanced Equilibrium by Fixed-Point Iterations and Cell Exclusion

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AMGEN
Thousand Oaks, California, USA

Society for Industrial and Applied Mathematics

Conference on Applied Algebraic Geometry, 2013

Colorado State University, Fort Collins, Colorado, USA
1-4 August 2013

Algebraic Aspects of Biochemical Reaction Networks

Calculating Detailed-Balanced Equilibrium

Calculating Detailed-Balanced Equilibrium

Pharmacology

Pharmacology: Study interactions between biological processes and therapeutic agents

- **Pharmacokinetics (PK)**: *what the body does to the drug*
- **Pharmacodynamics (PD)**: *what the drug does to the body*
- ***"Pharmacostatics"*** at beginning of research pipeline: Study binding equilibrium *in vitro* of interactions between
  - receptors (biochemical recognition units)
  - ligands (pathogenic and therapeutic molecules)
  - other molecules

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Pharmacology and Mathematics

- **Pharmacokinetics and Pharmacodynamics**:

  Dynamical systems, etc

- **"Pharmacostatics"**:

  Polynomial systems of a particular kind, etc

Calculating Detailed-Balanced Equilibrium

Current Practices – Illustrated with Trivial Receptor-Ligand Interaction

Chemistry

$$R + L \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftharpoons}} RL$$

Equilibrium state
Implicit equations
(Polynomial system)

$$[R]_{\text{Equil}} + [RL]_{\text{Equil}} = [R]_{\text{Total}}$$
$$[L]_{\text{Equil}} + [RL]_{\text{Equil}} = [L]_{\text{Total}}$$
$$[RL]_{\text{Equil}} = [R]_{\text{Equil}}[L]_{\text{Equil}}/K_{\text{d}}$$

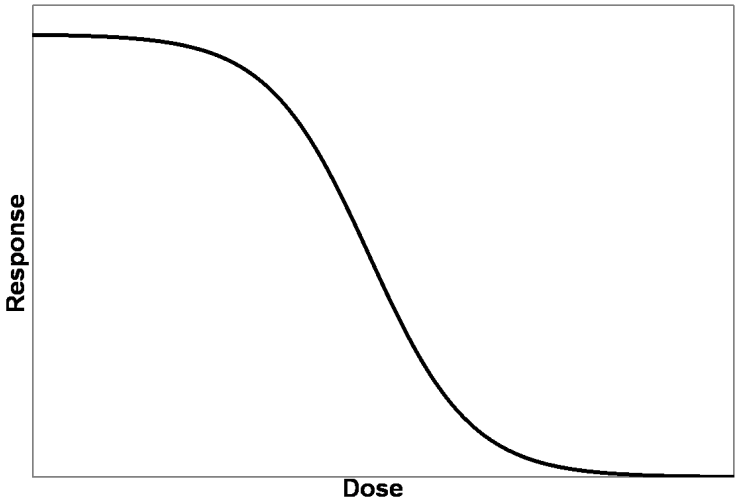
Equilibrium state
Explicit formula
(Forcibly derived)

$$[R]_{\text{Total}} \ll [L]_{\text{Total}}$$
$$[L]_{\text{Equil}} = [L]_{\text{Total}} \quad \text{(“No Ligand Depletion”)}$$
$$\frac{[RL]_{\text{Equil}}}{[R]_{\text{Total}}} = \frac{[L]_{\text{Total}}}{K_{\text{d}} + [L]_{\text{Total}}}$$

Issues with Forcibly Derived Formulas

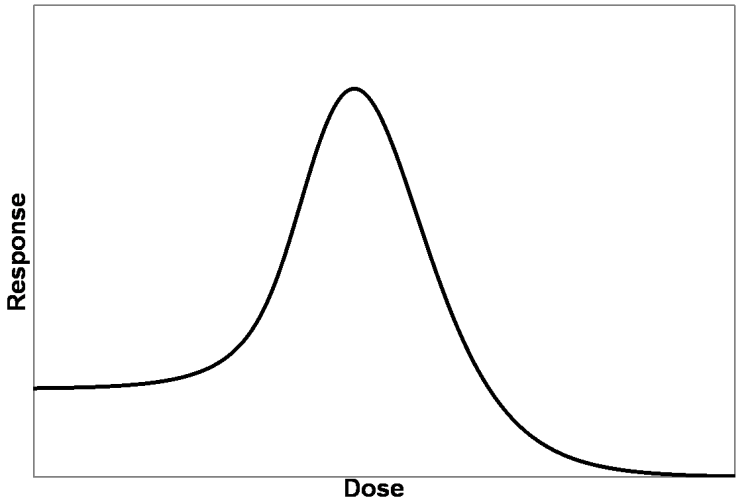
- $[R]_{\text{Total}} \ll [L]_{\text{Total}}$ is not mathematically sound.
  Operational wisdom: $[R]_{\text{Total}} < [L]_{\text{Total}}/10$.
- Not always applicable experimentally,
  e.g. in miniaturized assays.
- Need not be applicable *in vivo*.
- New formula derivation needed for every new interaction.
- Only possible with *"receptor-centric"* systems.
  (There is one receptor and all complex molecules contain it.)

One More Issue with Forcibly Derived Formulas



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.



Excuses for Forcibly Derived Formulas

- Somewhat admissible:

  These formulas are simple and always give an answer. They are (often, not always) directionally correct.

- Not admissible:

  We have many sources of error, so why fix this one?

Calculating Detailed-Balanced Equilibrium

"No Ligand Depletion" Assumption Discarded for Competitive Antagonism

Miniaturized Receptor Binding Assays: Complications Arising from Ligand Depletion
Clare M. Scaramellini Carter, Juliet R. Leighton-Davies and Steven J. Charlton
J Biomol Screen 2007; 12; 255 originally published online Jan 26, 2007

$$R + L \rightleftharpoons RL$$
$$+$$
$$A$$
$$\Downarrow\Uparrow$$
$$RA$$

"No Ligand Depletion" Assumption Partially Discarded for Allosteric Modulation

0022-3565/08/3253-927–934$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

JPET 325:927–934, 2008

The Impact of Orthosteric Radioligand Depletion on the Quantification of Allosteric Modulator Interactions

Vimesh A. Avlani, David J. McLoughlin, Patrick M. Sexton, and Arthur Christopoulos

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

with

$$[A]_{\text{Equil}} = [A]_{\text{Total}}$$

More Shots at the "No Ligand Depletion" Assumption

Biochimica et Biophysica Acta, 632 (1980) 464—469
© Elsevier/North-Holland Biomedical Press

COMPETITIVE BINDING STUDIES WITH MULTIPLE SITES
EFFECTS ARISING FROM DEPLETION OF THE FREE RADIOLIGAND

J.W. WELLS, N.J.M. BIRDSALL, A.S.V. BURGEN and E.C. HULME

0026-895X/87/060603-07$02.00/0
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MOLECULAR PHARMACOLOGY, 31:603–609

Ligand Dissociation Constants From Competition Binding Assays: Errors Associated with Ligand Depletion

AVRAM GOLDSTEIN and RONALD W. BARRETT

Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 6654–6658, October 1987
Biochemistry

An accurate method for determination of receptor–ligand and enzyme–inhibitor dissociation constants from displacement curves

AMNON HOROVITZ AND ALEXANDER LEVITZKI

ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS
Vol. 284, No. 1, January, pp. 26–29, 1991

A Simple Method for Calculating the Dissociation Constant of a Receptor (or Enzyme)·Unlabeled Ligand Complex from Radioligand Displacement Measurements

Robert L. Martin, Franco Renosto, and Irwin H. Segel

0026-895X/95/061197-07$3.00/0
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MOLECULAR PHARMACOLOGY, 47:1197–1203 (1995).

Interpretation of Binding Curves Obtained with High Receptor Concentrations: Practical Aid for Computer Analysis

STÉPHANE SWILLENS

Miniaturized Receptor Binding Assays: Complications Arising from Ligand Depletion
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0026-895X/08/7303-718–726$20.00
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Mol Pharmacol 73:718–726, 2008

Cell-Based and Biochemical Structure-Activity Analyses of Analogs of the Microtubule Stabilizer Dictyostatin

Brianne S. Raccor, Andreas Vogt, Rachel P. Sikorski, Charitha Madiraju, Raghavan Balachandran, Kia Montgomery, Youseung Shin, Yoshikazu Fukui, Won-Hyuk Jung, Dennis P. Curran, and Billy W. Day

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Journal of Neuroscience Methods 188 (2010) 32–38

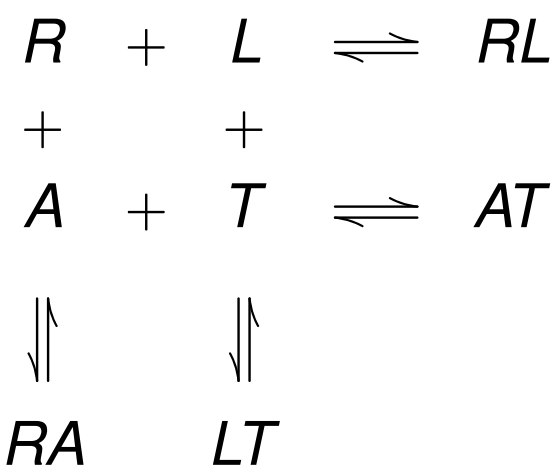
Concentration of receptor and ligand revisited in a modified receptor binding protocol for high-affinity radioligands: [^{3}H]Spiperone binding to D_2 and D_3 dopamine receptors

Juan Zhen, Tamara Antonio, Aloke K. Dutta, Maarten E.A. Reith

Calculating Detailed-Balanced Equilibrium

The Receptor-Ligand-Antagonist-Trap System

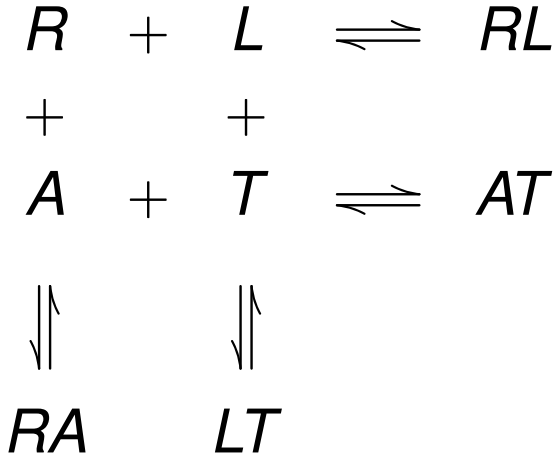
Polynomial System for Equilibrium State



$$
\begin{aligned}
[R] + K_{RL}[R][L] + K_{RA}[R][A] &= [R]_{\text{Total}} \\
[L] + K_{RL}[R][L] + K_{LT}[L][T] &= [L]_{\text{Total}} \\
[T] + K_{AT}[A][T] + K_{LT}[L][T] &= [T]_{\text{Total}} \\
[A] + K_{AT}[A][T] + K_{RA}[R][A] &= [A]_{\text{Total}}
\end{aligned}
$$

The Receptor-Ligand-Antagonist-Trap System

Polynomial System for Equilibrium State, Reformulated as a Fixed-Point Equation



$$[R] = \frac{[R]_{\text{Total}}}{1 + K_{RL}[L] + K_{RA}[A]}$$

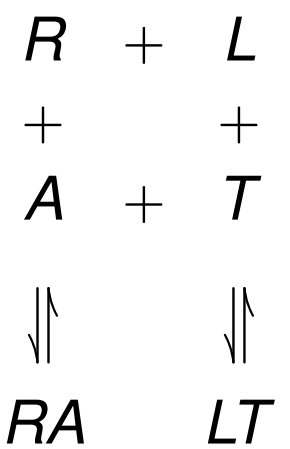
$$[L] = \frac{[L]_{\text{Total}}}{1 + K_{RL}[R] + K_{LT}[T]}$$

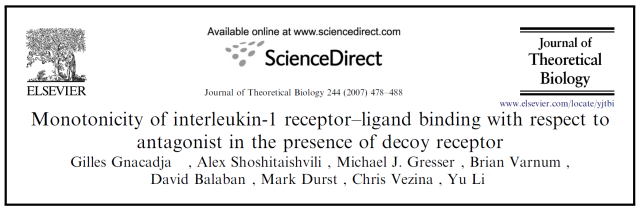
$$[T] = \frac{[T]_{\text{Total}}}{1 + K_{AT}[A] + K_{LT}[L]}$$

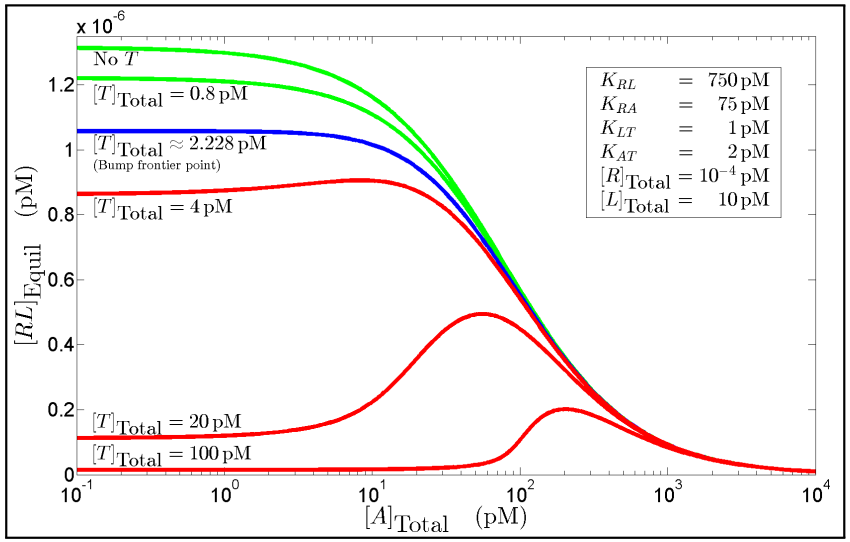
$$[A] = \frac{[A]_{\text{Total}}}{1 + K_{AT}[T] + K_{RA}[R]}$$

The Receptor-Ligand-Antagonist-Trap System

Polynomial System for Equilibrium State, Solved by Fixed-Point Iterations




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



- Fixed-point iterations converge, always and quickly. (Contraction w.r.t. Thompson metric; not L^1, L^2, L^∞, etc.)
- Experimentally observed motonicity features simulated and explained.
- Forcibly derived explicit formulas only produce always-increasing and always-decreasing curves.

Calculating Detailed-Balanced Equilibrium

The Reaction Networks

Complete Networks of Reversible Binding Reactions

- Reversible binding reaction

  $$\textit{(many species)} \rightleftharpoons \textit{(one species)}$$

- Notion of composition of species
  - Elementary and composite species
  - Conservation of composition
  - No isomers among elementary species

- Coherence among equilibrium binding constants
  - Detailed-balanced equilibria

The Polynomial System for Detailed Balance

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

$$i = 1, \ldots, n$$

Unknown $\quad x = (x_1, \ldots, x_n) \in \mathbb{R}^n_{\geqslant 0}$

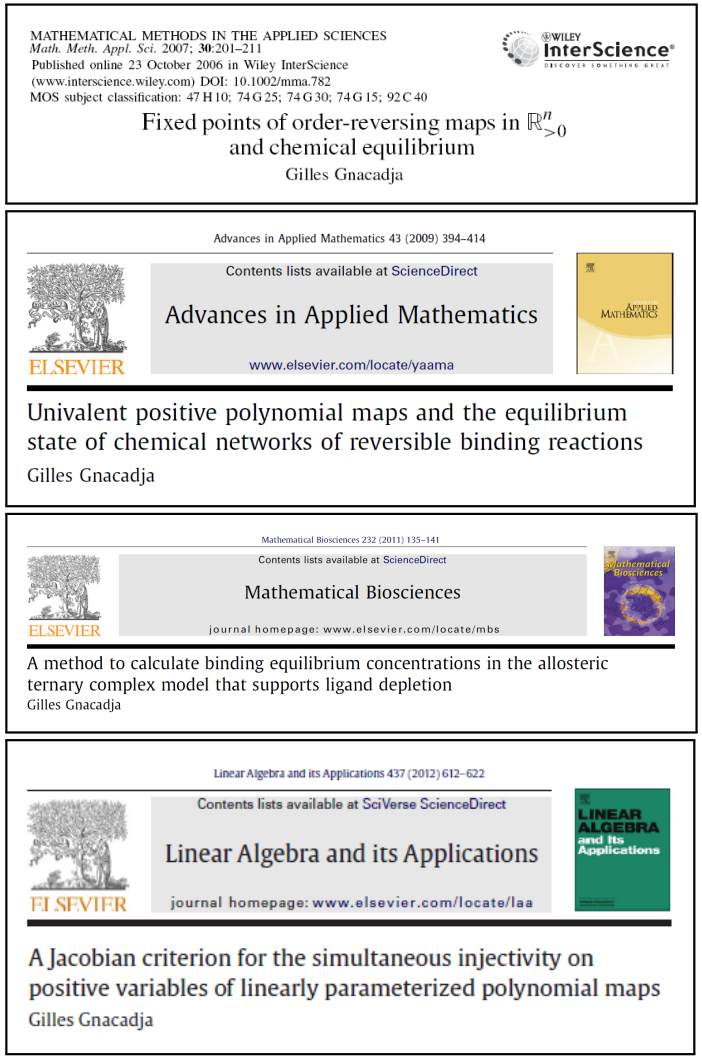
Given

$b_i \geqslant 0 \ , \ \forall \ i = 1, \ldots, n$

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

$a_\alpha \geqslant 0 \ , \ \forall \ \alpha = (\alpha_1, \ldots, \alpha_n) \in I$

$x^\alpha := x_1^{\alpha_1} \cdots x_n^{\alpha_n}$


MATHEMATICAL METHODS IN THE APPLIED SCIENCES
Math. Meth. Appl. Sci. 2007; **30**:201–211
Published online 23 October 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/mma.782
MOS subject classification: 47 H 10; 74 G 25; 74 G 30; 74 G 15; 92 C 40

Fixed points of order-reversing maps in $\mathbb{R}^n_{>0}$ and chemical equilibrium

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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

Mathematical Biosciences 232 (2011) 135–141

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A method to calculate binding equilibrium concentrations in the allosteric ternary complex model that supports ligand depletion

Gilles Gnacadja

Linear Algebra and its Applications 437 (2012) 612–622

Contents lists available at SciVerse ScienceDirect

Linear Algebra and its Applications

journal homepage: www.elsevier.com/locate/laa

A Jacobian criterion for the simultaneous injectivity on positive variables of linearly parameterized polynomial maps

Gilles Gnacadja

Equivalent Fixed-Point Formulation

$$x_i = \frac{b_i}{1 + \sum_{\alpha \in I,\, \alpha_i > 0} \alpha_i \, a_\alpha \, x^{\alpha - e_{n,i}}} \qquad i = 1, \ldots, n$$

$$x = f(a, b, x)$$

$$f(a, b, \cdot) : \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0} \text{ is smooth and order-reversing}$$

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$f(a, b, \cdot) : \mathbb{R}^n_{\geqslant 0} \longrightarrow \mathbb{R}^n_{\geqslant 0}$ is smooth and order-reversing

Solution Exists, is Unique, and is Infinitely Smooth

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

Existence — Brouwer Fixed Point Theorem

Uniqueness — Gale-Nikaidô Global Injectivity Theorem

GALE, D. and H. NIKAIDÔ
Math. Annalen 159, 81—93 (1965)

The Jacobian Matrix and Global Univalence of Mappings

By

DAVID GALE and HUKUKANE NIKAIDÔ in Providence and Osaka

Smoothness — Inverse Function Theorem

Goal

- Calculate binding equilibrium concentrations ...
- by *actually* solving the polynomial system of conservation and equilibrium conditions ...
- with the benefits of forcibly derived closed-form formulas, i.e. **get an answer always and quickly**.

Calculating Detailed-Balanced Equilibrium

Solving by Fixed-Point Iterations

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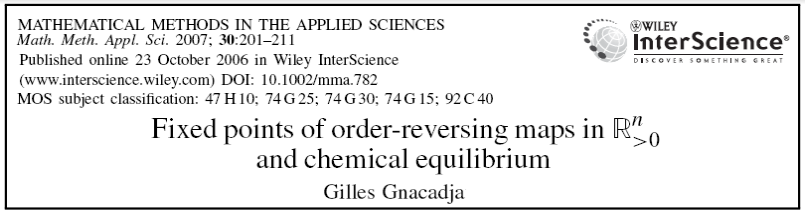
Fixed points of order-reversing maps in $\mathbb{R}^n_{>0}$ and chemical equilibrium

Gilles Gnacadja

1. Fixed point iterations always converge if all complex molecules are (homo- or hetero-) dimers.
   - The map iterated is a contraction w.r.t. the Thompson metric (not L^1, L^2, L^∞, etc) and is order-reversing.
   - Iterates provide a descending sequence of boxes that converges to the solution point.
2. With k-mers with $k \geqslant 3$, the descending sequence of boxes converges, either to the solution point, or to a non-point box that contains it. ("Coupled fixed points")

First part partially rediscovered: M. G. A. van Dorp, F. Berger, E. Carlon
Computing Equilibrium Concentrations for Large Heterodimerization Networks
Physical Review E, Volume 84, Issue 3, September 2011

Solving by Fixed-Point Iterations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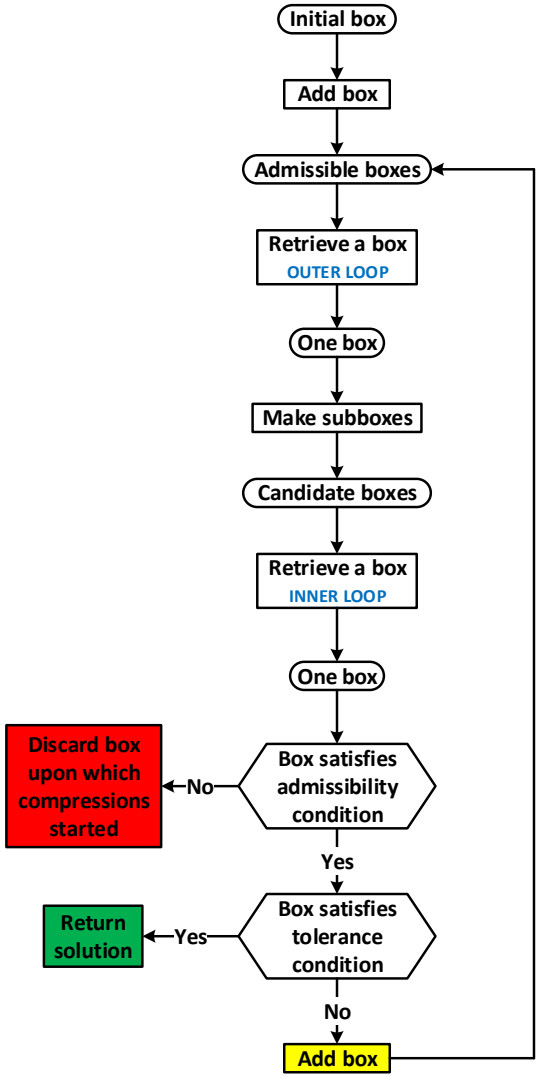
Calculating Detailed-Balanced Equilibrium

Solving by Cell Exclusion

If the descending sequence of boxes converges to a non-point box, divide the box and try the same on each subbox.
Do this again, and again...

Cell Exclusion Algorithm



Cell exclusion algorithm:

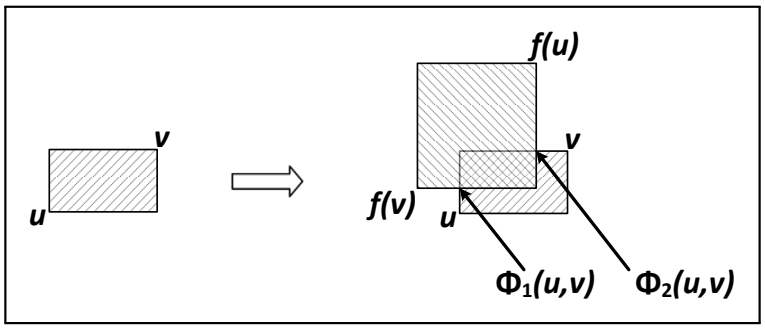
- A test to tell whether a cell contains an approximated solution
  - **NO** Cell is discarded
  - **YES** Solution is found
  - **MAYBE** Cell is admissible
  - Usually based on Lipschitz condition
- A method to subdivide admissible cells

Mathematically guaranteed to converge

How fast? ...

Cell Discarding for Fixed Point of Order-Reversing f

Box compression by intersection with image box



Brouwer Fixed Point Theorem:

$$\mathrm{Fix}(f) \cap \mathrm{Box}(u,v) = \mathrm{Fix}(f) \cap \mathrm{Box}\big(\Phi(u,v)\big)$$

$$\mathrm{Fix}(f) \cap \mathrm{Box}(u,v) = \mathrm{Fix}(f) \cap \bigcap_{r=0}^{\infty} \mathrm{Box}\big(\Phi^r(u,v)\big)$$

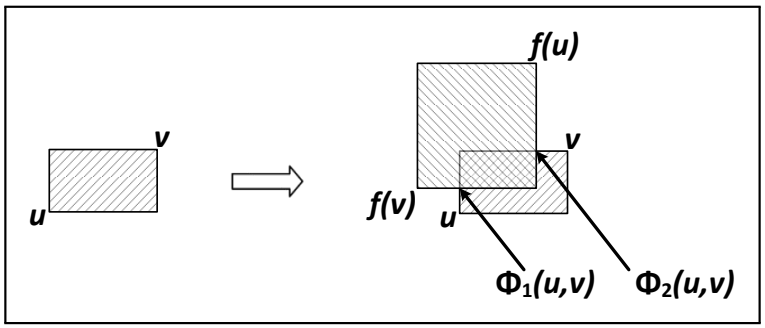
$$\mathrm{Fix}(f) \cap \mathrm{Box}(u,v) \neq \varnothing \Leftrightarrow \bigcap_{r=0}^{\infty} \mathrm{Box}\big(\Phi^r(u,v)\big) \neq \varnothing$$

Cell Discarding Condition:

For some r, $\mathrm{Box}\big(\Phi^r(u,v)\big) = \varnothing$, i.e. $(\Phi^r)_1(u,v) \not\leqslant (\Phi^r)_2(u,v)$.

Cell Discarding for Fixed Point of Order-Reversing f

Box compression by intersection with image box



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Cell Discarding for Fixed Point of Order-Reversing f

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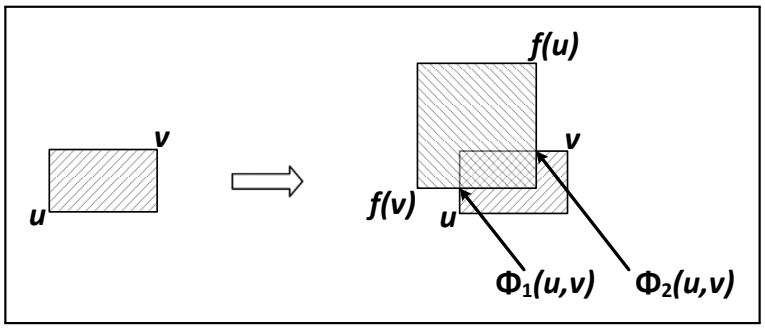

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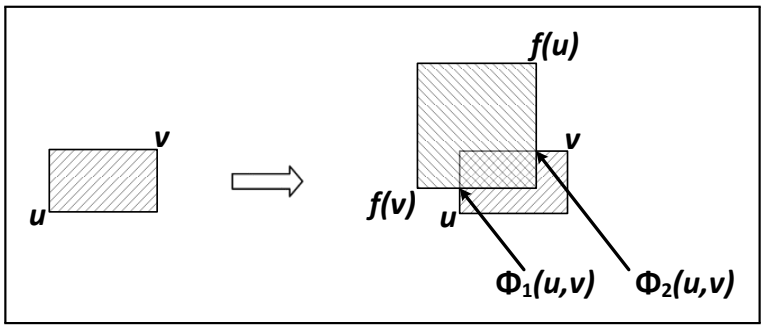

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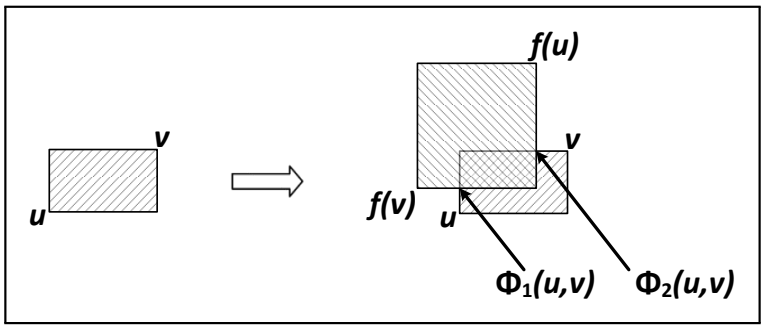
Cell Discarding Condition:

For some r, $\mathrm{Box}\big(\Phi^r(u,v)\big) = \varnothing$, i.e. $(\Phi^r)_1(u,v) \not\leqslant (\Phi^r)_2(u,v)$.

Cell Discarding for Fixed Point of Order-Reversing f

Box compression by intersection with image box



Brouwer Fixed Point Theorem:

$$\mathrm{Fix}(f) \cap \mathrm{Box}(u,v) \;=\; \mathrm{Fix}(f) \cap \mathrm{Box}\big(\Phi(u,v)\big)$$

$$\mathrm{Fix}(f) \cap \mathrm{Box}(u,v) \;=\; \mathrm{Fix}(f) \cap \bigcap_{r=0}^{\infty} \mathrm{Box}\big(\Phi^r(u,v)\big)$$

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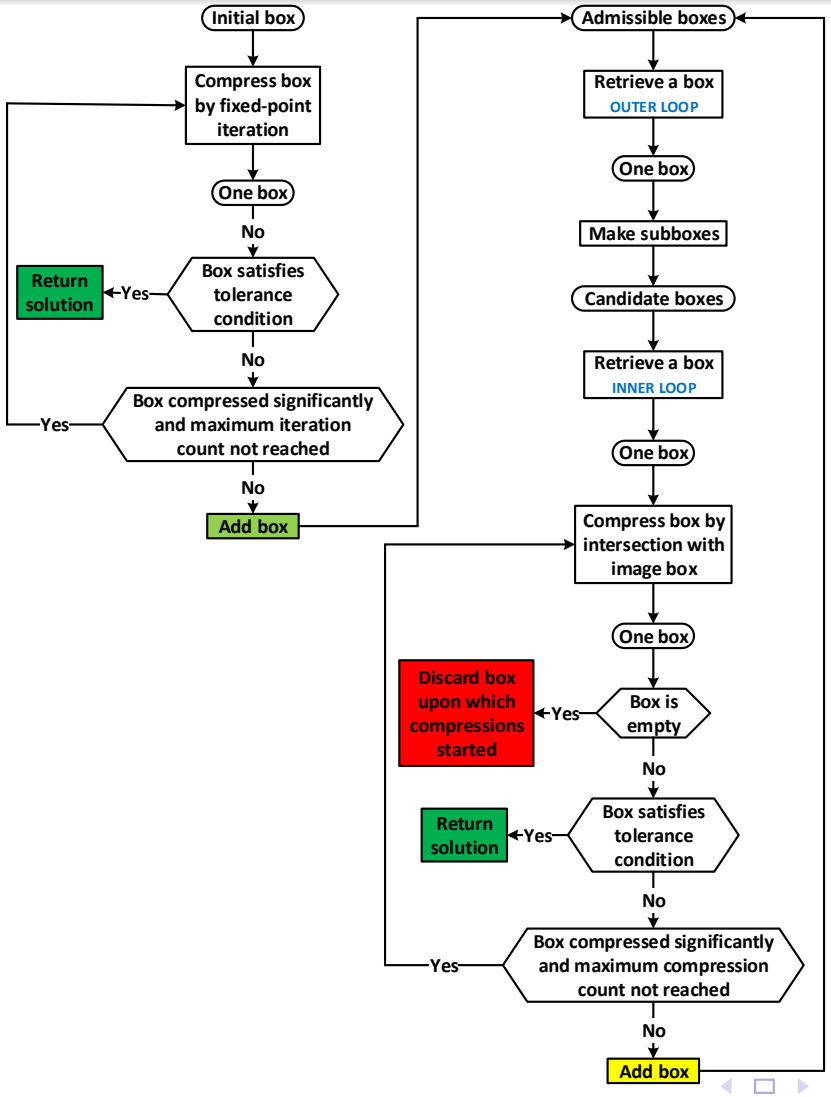
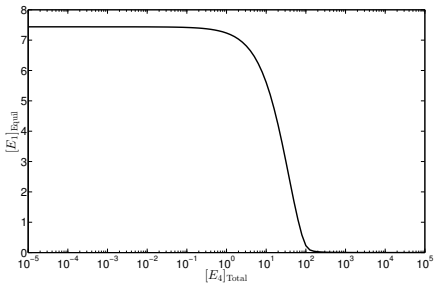
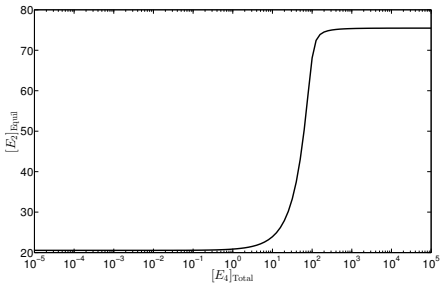
Cell Excl. Algo. for Fixed Pt. of Order-Reversing Map

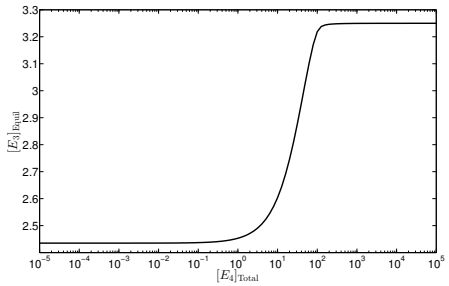


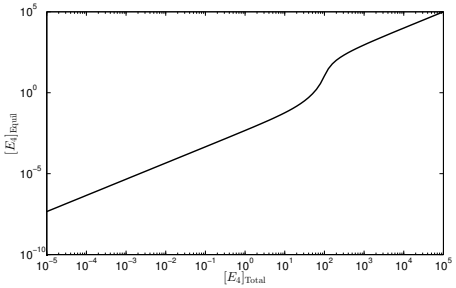
Example (selected to discuss issues)

Four elementary species

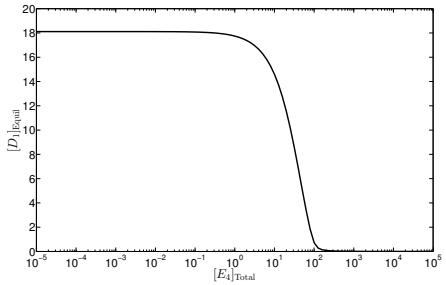


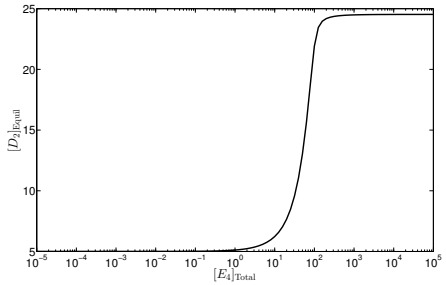


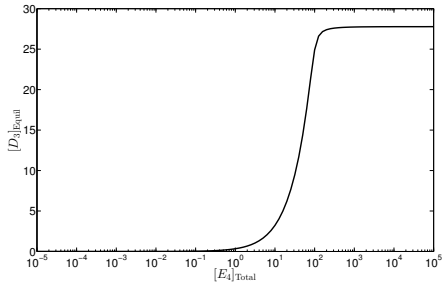




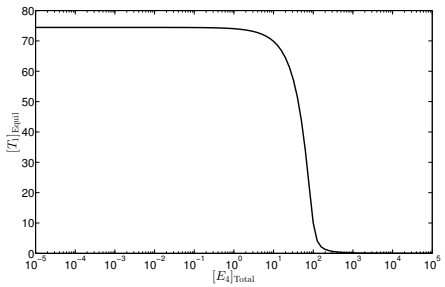
Three dimers

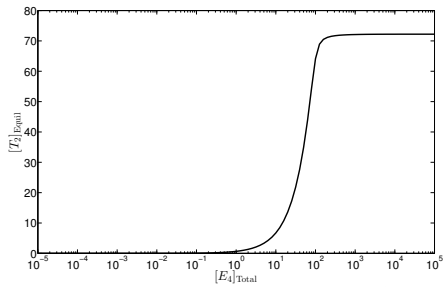




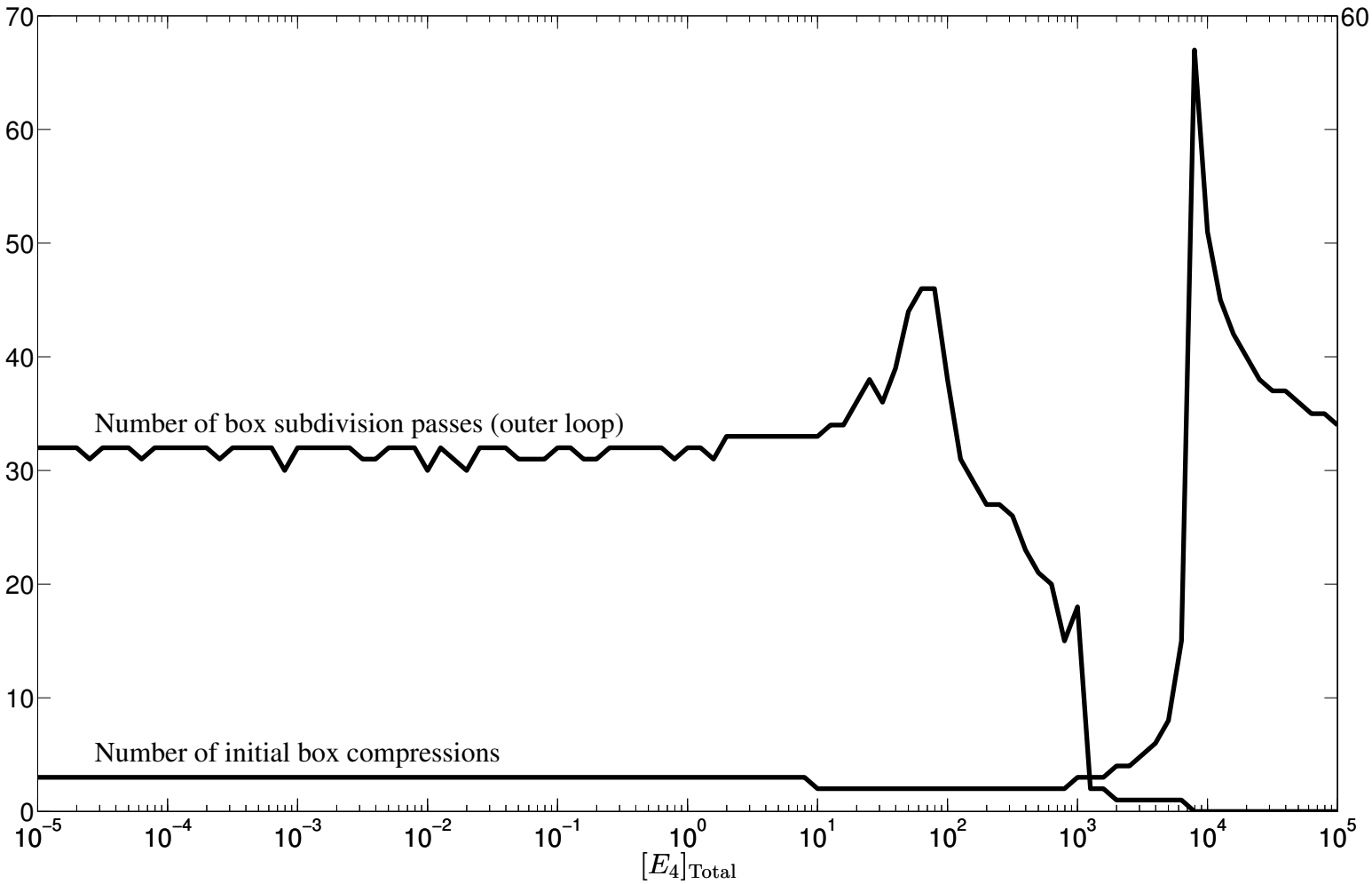


Two trimers

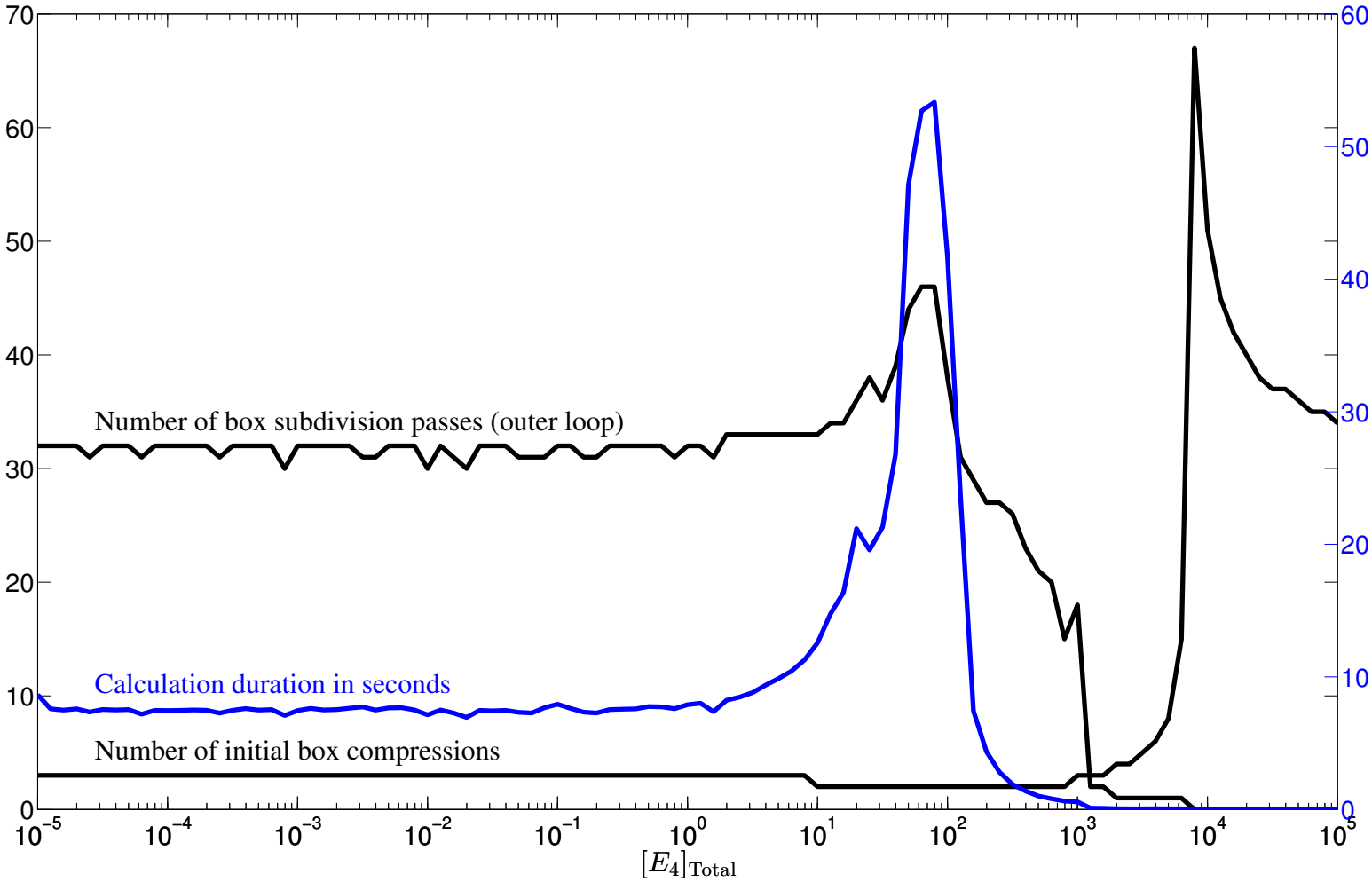




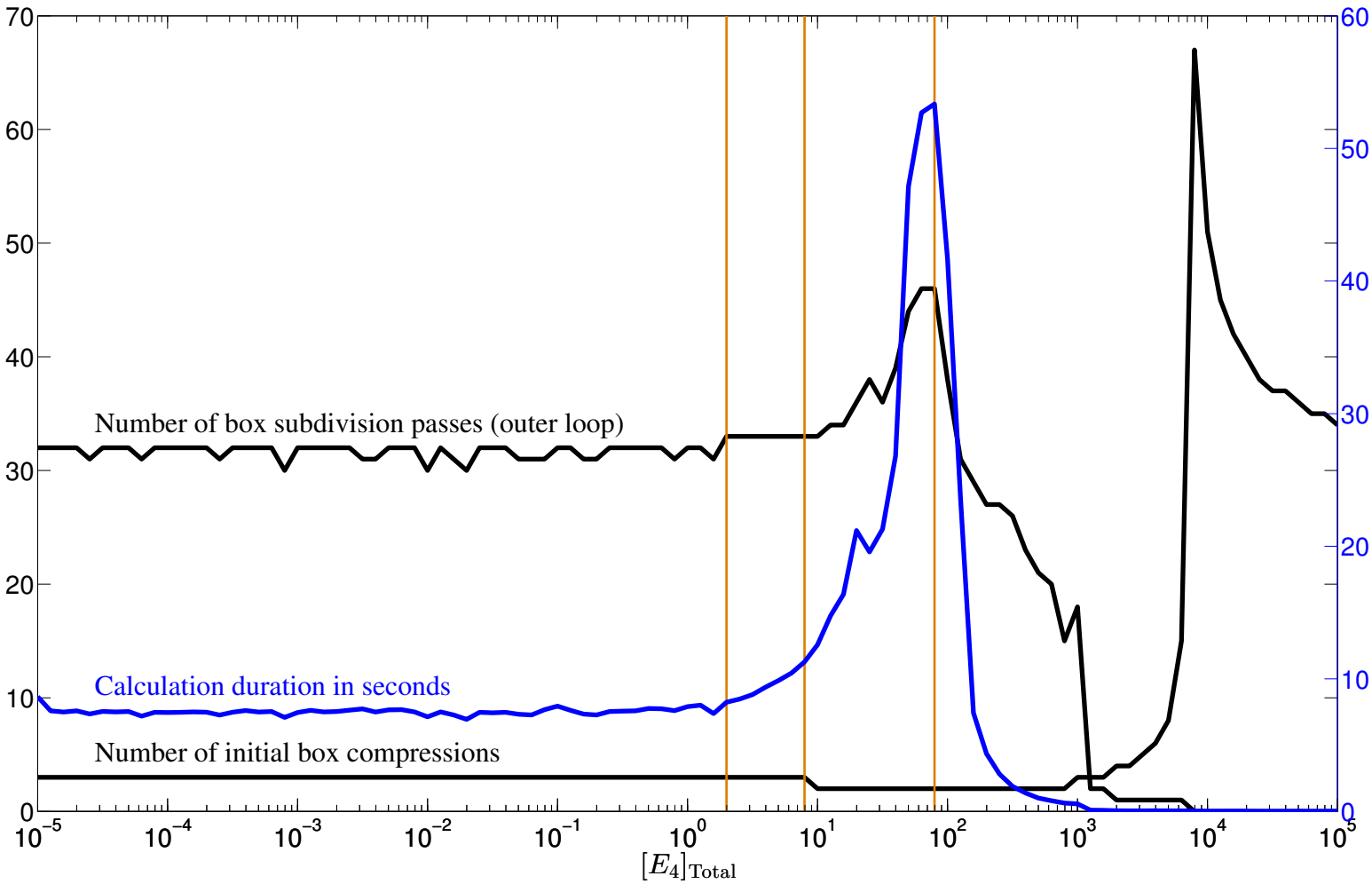
Performance - Counting passes ...



Performance - Counting passes and time



Performance - Three selected points for closer look



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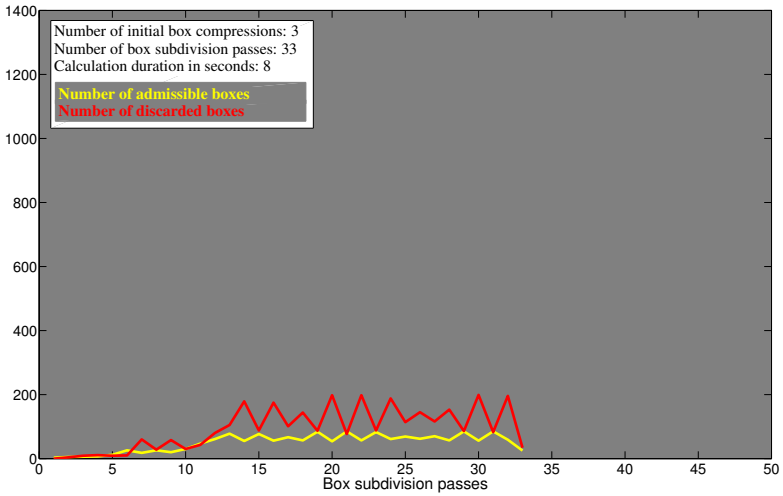

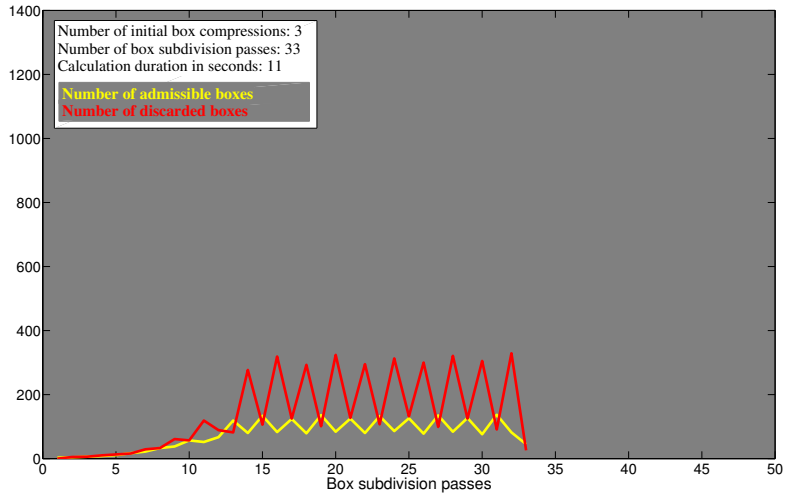

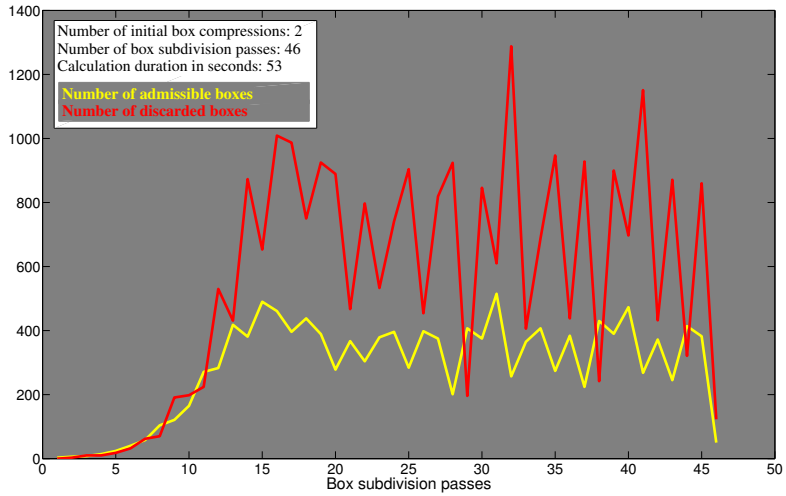

Summary

- Calculating binding equilibrium in “pharmacostatics” is about solving certain nice polynomial systems.
- Customary practice is to derive simple formulas at all cost.
  - Reduced accuracy
  - Only monotone response curves
- Algorithms exist to actually solve the polynomial systems with *a priori* assurance of success.
  - Exploit fixed-point formulation
  - Fixed-point iterations
  - Cell exclusion algorithm, strengthened by cell compression
  - Work in progress: stronger cell discarding conditions
- **Enable scientists to study pharmacostatics of biochemical mechanisms that would otherwise be fudged or discarded.**

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