A Convergent and Efficient Algorithm for Calculating Equilibrium for Chemical Networks of Reversible Binding Reactions

Gilles Gnacadja
http://math.GillesGnacadja.info/

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Objective

Solve the equilibrium problem for
complete networks of reversible binding reactions

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

by a *worry-free* algorithm

Objective

Solve the equilibrium problem for
complete networks of reversible binding reactions

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

by a *worry-free* algorithm

Requirements for "worry-free"	Weight
Simplicity (yes, this is subjective...)	10%
Computational performance (much less subjective, but still...)	31%
A priori certainty of convergence	59%

Example: Fixed-point iteration of a contraction map

Complete Networks of Reversible Binding Reactions

Examples from Pharmacology in Math Notation

$$X_1 + X_2 \rightleftharpoons Y_{(1,1)}$$

$$\begin{array}{ccccc} X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0)} \\ + & & & & \\ X_3 & & & & \\ \downharpoonleft\upharpoonright & & & & \\ Y_{(1,0,1)} & & & & \end{array}$$

$$\begin{array}{ccccc} X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0,0)} \\ + & & + & & \\ X_3 & + & X_4 & \rightleftharpoons & Y_{(0,0,1,1)} \\ \downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\ Y_{(1,0,1,0)} & & Y_{(0,1,0,1)} & & \end{array}$$

$$\begin{array}{ccccc} X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0)} \\ + & & & & + \\ X_3 & & & & X_3 \\ \downharpoonleft\upharpoonright & & & & \downharpoonleft\upharpoonright \\ Y_{(1,0,1)} & + & X_2 & \rightleftharpoons & Y_{(1,1,1)} \end{array}$$

$$\begin{array}{lcl} X_1 + X_2 & \rightleftharpoons & Y_{(1,1,0)} \\ X_1 + X_3 & \rightleftharpoons & Y_{(1,0,1)} \\ X_1 + X_2 + X_3 & \rightleftharpoons & Y_{(1,1,1)} \end{array}$$

General Idea

- $X_1, \ldots, X_n$: Elementary species (“atoms”)
- Y_α : Composite species of composition α
- Conservation of composition
- Detailed-balance equilibrium

The Equilibrium Problem – Polynomial Formulation

Example: The Allosteric Ternary Complex Model

$$
\begin{array}{ccccc}
X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0)} \\
+ & & & & + \\
X_3 & & & & X_3 \\
\downharpoonleft\upharpoonright & & & & \downharpoonleft\upharpoonright \\
Y_{(1,0,1)} & + & X_2 & \rightleftharpoons & Y_{(1,1,1)}
\end{array}
$$

$$
\begin{array}{lcl}
X_1 + X_2 & \rightleftharpoons & Y_{(1,1,0)} \\
X_1 + X_3 & \rightleftharpoons & Y_{(1,0,1)} \\
X_1 + X_2 + X_3 & \rightleftharpoons & Y_{(1,1,1)}
\end{array}
$$

$$
\left\{
\begin{array}{lcl}
x_1 + a_{(1,1,0)}\, x_1 x_2 + a_{(1,0,1)}\, x_1 x_3 + a_{(1,1,1)}\, x_1 x_2 x_3 & = & b_1 \\
x_2 + a_{(1,1,0)}\, x_1 x_2 \qquad\qquad\qquad + a_{(1,1,1)}\, x_1 x_2 x_3 & = & b_2 \\
x_3 \qquad\qquad\qquad + a_{(1,0,1)}\, x_1 x_3 + a_{(1,1,1)}\, x_1 x_2 x_3 & = & b_3
\end{array}
\right.
$$

The Equilibrium Problem – Fixed-Point Formulation

Example: The Allosteric Ternary Complex Model

$$
\begin{array}{ccccc}
X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0)} \\
+ & & & & + \\
X_3 & & & & X_3 \\
\downarrow\uparrow & & & & \downarrow\uparrow \\
Y_{(1,0,1)} & + & X_2 & \rightleftharpoons & Y_{(1,1,1)}
\end{array}
$$

$$
\begin{array}{lcl}
X_1 + X_2 & \rightleftharpoons & Y_{(1,1,0)} \\
X_1 + X_3 & \rightleftharpoons & Y_{(1,0,1)} \\
X_1 + X_2 + X_3 & \rightleftharpoons & Y_{(1,1,1)}
\end{array}
$$

$$
\left\{
\begin{array}{lcl}
x_1 & = & \dfrac{b_1}{1 + a_{(1,1,0)}\, x_2 + a_{(1,0,1)}\, x_3 + a_{(1,1,1)}\, x_2\, x_3} \\
x_2 & = & \dfrac{b_2}{1 + a_{(1,1,0)}\, x_1 + a_{(1,1,1)}\, x_1\, x_3} \\
x_3 & = & \dfrac{b_3}{1 + a_{(1,0,1)}\, x_1 + a_{(1,1,1)}\, x_1\, x_2}
\end{array}
\right.
$$

The Equilibrium Problem – Polynomial Formulation

Example: The Receptor-Ligand-Antagonist-Trap Network

$$\begin{array}{ccccc}
X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0,0)} \\
+ & & + & & \\
X_3 & + & X_4 & \rightleftharpoons & Y_{(0,0,1,1)} \\
\downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\
Y_{(1,0,1,0)} & & Y_{(0,1,0,1)} & &
\end{array}$$

$$\left\{\begin{array}{lcl}
x_1 + a_{(1,1,0,0)}\, x_1 x_2 + a_{(1,0,1,0)}\, x_1 x_3 & = & b_1 \\
x_2 + a_{(1,1,0,0)}\, x_1 x_2 + a_{(0,1,0,1)}\, x_2 x_4 & = & b_2 \\
x_3 + a_{(1,0,1,0)}\, x_1 x_3 + a_{(0,0,1,1)}\, x_3 x_4 & = & b_3 \\
x_4 + a_{(0,1,0,1)}\, x_2 x_4 + a_{(0,0,1,1)}\, x_3 x_4 & = & b_4
\end{array}\right.$$

The Equilibrium Problem – Fixed-Point Formulation

Example: The Receptor-Ligand-Antagonist-Trap Network

$$
\begin{array}{ccccc}
 & X_1 & + & X_2 & \rightleftharpoons Y_{(1,1,0,0)} \\
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 & \downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & \\
 & Y_{(1,0,1,0)} & & Y_{(0,1,0,1)} &
\end{array}
$$

$$
\left\{
\begin{array}{rcl}
x_1 & = & \dfrac{b_1}{1 + a_{(1,1,0,0)}\, x_2 + a_{(1,0,1,0)}\, x_3} \\
x_2 & = & \dfrac{b_2}{1 + a_{(1,1,0,0)}\, x_1 + a_{(0,1,0,1)}\, x_4} \\
x_3 & = & \dfrac{b_3}{1 + a_{(1,0,1,0)}\, x_1 + a_{(0,0,1,1)}\, x_4} \\
x_4 & = & \dfrac{b_4}{1 + a_{(0,1,0,1)}\, x_2 + a_{(0,0,1,1)}\, x_3}
\end{array}
\right.
$$

The Equilibrium Problem

Polynomial Formulation

$$f(x) \;=\; b$$

where

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

Fixed-Point Formulation

$$F(b, x) \;=\; x$$

where

$$F_i(b, x) \;=\; \frac{b_i}{1 + \sum_{\alpha \in I,\, \alpha_i \geqslant 1} \alpha_i \, a_\alpha \, x^{\alpha - e_{n,i}}}$$

The Equilibrium Problem – Polynomial Formulation

$$f(x) = b$$

where

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

Theorem

The map $f : \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0}$ is an infinitely smooth diffeomorphism.

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Univalent positive polynomial maps and the equilibrium state of chemical networks of reversible binding reactions

Gilles Gnacadja

The Equilibrium Problem – Fixed-Point Formulation

$$F(b, x) = x$$

where

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

Theorem

With respect to the metric d, the map $F(b, \cdot) : \mathbb{R}^n_{>0} \to \mathbb{R}^n_{>0}$ is k-Lipschitz on $]0, b_1] \times \cdots \times]0, b_n]$.

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

Gilles Gnacadja

The Equilibrium Problem – Fixed-Point Formulation

The metric d and the Lipschitz constant k

$$d(u,v) = \max_{1 \leqslant i \leqslant n} \left| \ln(u_i/v_i) \right|$$

$$k = \max_{1 \leqslant i \leqslant n} k_i$$

$$k_i = \frac{\displaystyle\sum_{\alpha \in I,\, \alpha_i \geqslant 1} \left|\alpha - e_{n,i}\right| \alpha_i \, a_\alpha \, b^{\alpha - e_{n,i}}}{1 + \displaystyle\sum_{\alpha \in I,\, \alpha_i \geqslant 1} \alpha_i \, a_\alpha \, b^{\alpha - e_{n,i}}}$$

The Equilibrium Problem – Fixed-Point Formulation

When do we have a contraction?

- $F(b,\cdot)$ is a contraction if b is small enough.
  Not particularly useful for intended application.

- $F(b,\cdot)$ is a contraction if $(a_\alpha)_{\alpha\in I}$ is small enough.
  Even less useful.

- $F(b,\cdot)$ is a contraction if all composite species are binary.
  Useful but narrowly applicable.

  Example: The Receptor-Ligand-Antagonist-Trap Network

$$
\begin{array}{ccccc}
X_1 & + & X_2 & \rightleftharpoons & Y_{(1,1,0,0)} \\
+ & & + & & \\
X_3 & + & X_4 & \rightleftharpoons & Y_{(0,0,1,1)} \\
\downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright & & \\
Y_{(1,0,1,0)} & & Y_{(0,1,0,1)} & &
\end{array}
$$

The Equilibrium Problem – Fixed-Point Formulation

When can we have a contraction?

- $F(b, \cdot)$ can be "turned into" a contraction if there is only one elementary species.

Not particularly useful for intended application.

Proposition

For a self-map of a convex domain in $\mathbb{R}^n$, a homotopy with the identity map preserves fixed points.
If $n = 1$ and the original map is monotone-decreasing, then the homotopy transform can be chosen to be a contraction.

The Equilibrium Problem – Fixed-Point Formulation

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If $n = 1$ and the original map is monotone-decreasing, then the homotopy transform can be chosen to be a contraction.

Let D be an interval in $\mathbb{R}$, let ψ a differentiable self-map of D, and suppose there exist $m, M \geqslant 0$ such that $-M \leqslant \psi' \leqslant -m$.
For any $\lambda \in [0,1]$, let

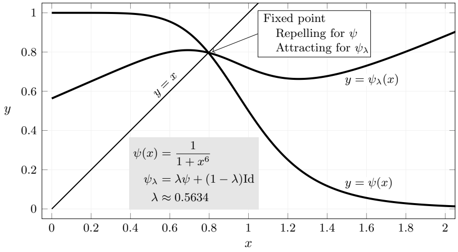
$\psi_\lambda = \lambda\psi + (1-\lambda)\mathrm{Id}_D : x \mapsto \lambda\psi(x) + (1-\lambda)x$ and

$k_\lambda = \max(|1-(1+m)\lambda|, |1-(1+M)\lambda|)$.

The map ψ_λ is k_λ-Lipschitz w.r.t. the ordinary norm.

If (and only if) $0 < \lambda < \dfrac{2}{1+M}$, then $k_\lambda < 1$, and iteration of ψ_λ converges to the (unique) fixed point of ψ.

$$\arg\min_{\lambda\in[0,1]}(k_\lambda) = \lambda_0 = \frac{2}{2+m+M}\,;\ k_{\lambda_0} = \frac{M-m}{2+m+M} < 1.$$



The Equilibrium Problem – Fixed-Point Formulation

PROBLEM

Can we exploit the properties of $F(b, \cdot)$ to transform it so as to solve the fixed point problem $F(b, x) = x$ by a "worry-free" algorithm?

- $F(b, \cdot)$ has a unique fixed point in $[0_n, b] \subset \mathbb{R}^n_{\geqslant 0}$.
- $F(b, \cdot)$ is order-reversing on $\mathbb{R}^n_{\geqslant 0}$.
- We know a Lipschitz constant for $F(b, \cdot)$ on $]0_n, b]$.

The Equilibrium Problem – Fixed-Point Formulation

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- We know a Lipschitz constant for $F(b, \cdot)$ on $]0_n, b]$.

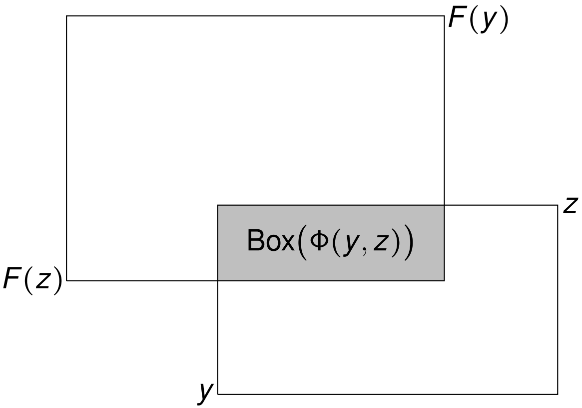
TENTATIVE SOLUTION

Enclosure algorithm

	Requirements for "worry-free"	Weight
✘	Simplicity	10%
✘	Computational performance	31%
✔	A priori certainty of convergence	59%

Enclosure Algorithm – Fixed-Box Iteration

$$\Phi(y,z) \quad := \quad \big(\sup\big(y, F(z)\big), \inf\big(z, F(y)\big)\big)$$



$$\begin{aligned} \mathrm{Fix}(F) \cap \mathrm{Box}(y,z) &= \mathrm{Fix}(F) \cap \mathrm{Box}\big(\Phi(y,z)\big) \\ &= \mathrm{Fix}(F) \cap \mathrm{Box}\big(\Phi^k(y,z)\big)\,, \ \forall\, k \in \mathbb{Z}_{\geqslant 0} \end{aligned}$$

Enclosure Algorithm – Stopping Fixed-Box Iteration

Descending sequence $\left(\mathrm{Box}\left(\Phi^k(y,z)\right)\right)_{k\in\mathbb{Z}_{\geqslant 0}}$ converges to $\mathrm{Box}\left(\Phi^\infty(y,z)\right) := \bigcap_{k\in\mathbb{Z}_{\geqslant 0}} \mathrm{Box}\left(\Phi^k(y,z)\right)$.

- $\mathrm{Box}\left(\Phi^k(y,z)\right) = \varnothing$ for some $k \in \mathbb{Z}_{\geqslant 0}$:

  Discard $\mathrm{Box}(y,z)$

- For some $k \in \mathbb{Z}_{\geqslant 0}$, $\mathrm{Box}\left(\Phi^k(y,z)\right)$ is found to contain a good approximation of the fixed point :

  Done

- Otherwise :

  Subdivide $\mathrm{Box}\left(\Phi^{k_{\max}}(y,z)\right)$ *and repeat*

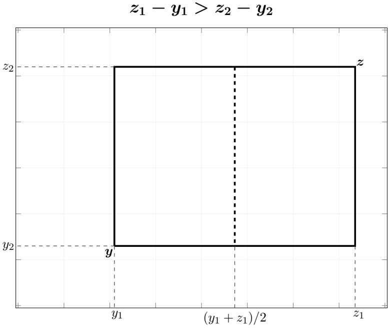
Enclosure Algorithm – Subdivision Strategy

There are numerous box subdivision strategies.

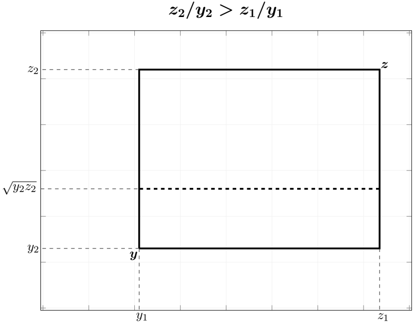
Best (relatively) performance achieved with *geometric long-edge bisection*:

> *Cut box orthogonally to the first multiplicatively-longest edge at the geometric center.*

Arithmetic



Geometric



Enclosure Algorithm – Starting Box

- $F^2(0) \leqslant F^4(0) \leqslant F^6(0) \leqslant \cdots \leqslant F^5(0) \leqslant F^3(0) \leqslant F(0)$
- $\left(F^k(0)\right)_{k \in \mathbb{Z}_{\geqslant 0}}$ converges:

  Done
- $\left(F^k(0)\right)_{k \in \mathbb{Z}_{\geqslant 0}}$ accumulates to a 2-orbit :

  Perform enclosure algorithm starting at
  $\mathrm{Box}\left(F^{2h_{\max}}(0), F^{2h_{\max}-1}(0)\right)$

Evolution of the algorithm on a 4-dimensional example

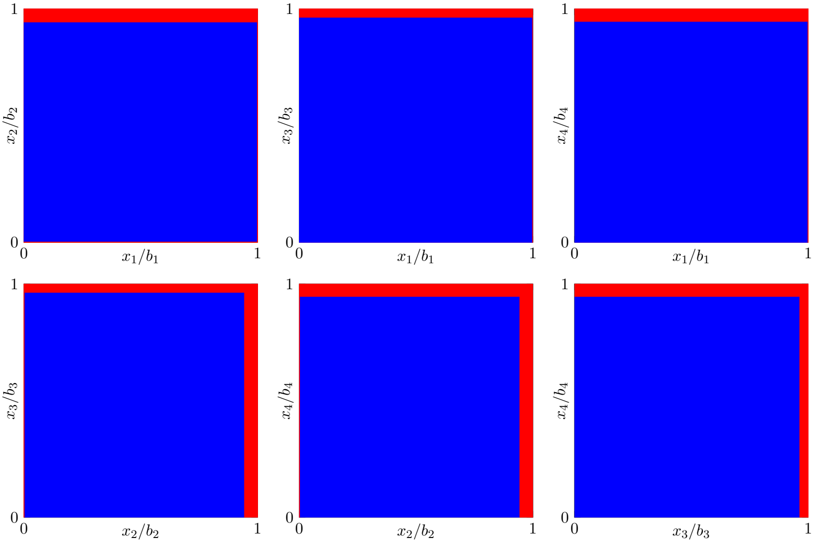
$$
\begin{aligned}
X_1 + X_2 &\rightleftharpoons Y_{(1,1,0,0)} \\
X_1 + X_3 &\rightleftharpoons Y_{(1,0,1,0)} \\
X_2 + X_3 &\rightleftharpoons Y_{(0,1,1,0)} \\
X_3 + X_4 &\rightleftharpoons Y_{(0,0,1,1)} \\
Y_{(1,0,1,0)} + X_4 &\rightleftharpoons Y_{(1,0,1,1)}
\end{aligned}
$$

$$
\left\{
\begin{aligned}
f_1(x) &= x_1 + a_{(1,1,0,0)} x_1 x_2 + a_{(1,0,1,0)} x_1 x_3 + a_{(1,0,1,1)} x_1 x_3 x_4 \\
f_2(x) &= x_2 + a_{(1,1,0,0)} x_1 x_2 + a_{(0,1,1,0)} x_2 x_3 \\
f_3(x) &= x_3 + a_{(0,1,1,0)} x_2 x_3 + a_{(1,0,1,0)} x_1 x_3 + a_{(0,0,1,1)} x_3 x_4 + a_{(1,0,1,1)} x_1 x_3 x_4 \\
f_4(x) &= x_4 + a_{(0,0,1,1)} x_3 x_4 + a_{(1,0,1,1)} x_1 x_3 x_4
\end{aligned}
\right.
$$

$$
\left\{
\begin{aligned}
F_1(b,x) &= \frac{b_1}{1 + a_{(1,1,0,0)} x_2 + a_{(1,0,1,0)} x_3 + a_{(1,0,1,1)} x_3 x_4} \\
F_2(b,x) &= \frac{b_2}{1 + a_{(1,1,0,0)} x_1 + a_{(0,1,1,0)} x_3} \\
F_3(b,x) &= \frac{b_3}{1 + a_{(0,1,1,0)} x_2 + a_{(1,0,1,0)} x_1 + a_{(0,0,1,1)} x_4 + a_{(1,0,1,1)} x_1 x_4} \\
F_4(b,x) &= \frac{b_4}{1 + a_{(0,0,1,1)} x_3 + a_{(1,0,1,1)} x_1 x_3}
\end{aligned}
\right.
$$

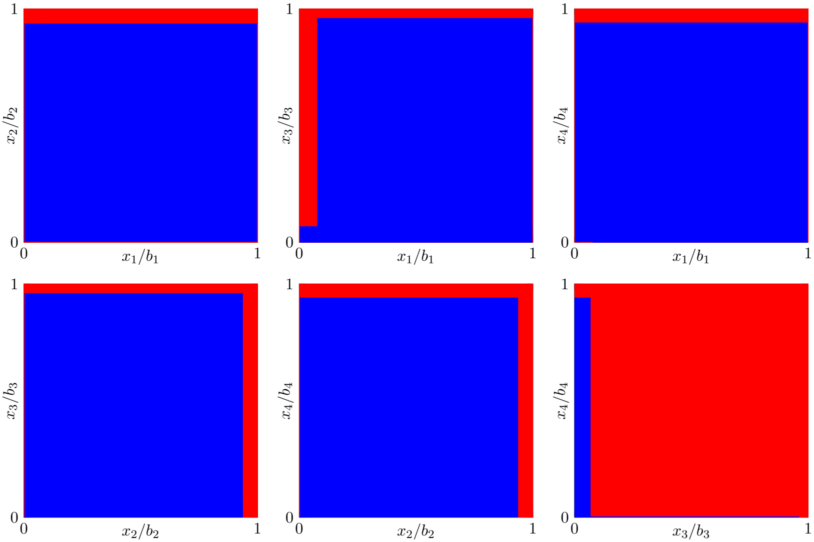
Evolution of the algorithm on a 4-dimensional example

Starting box from stalled fixed-point iteration



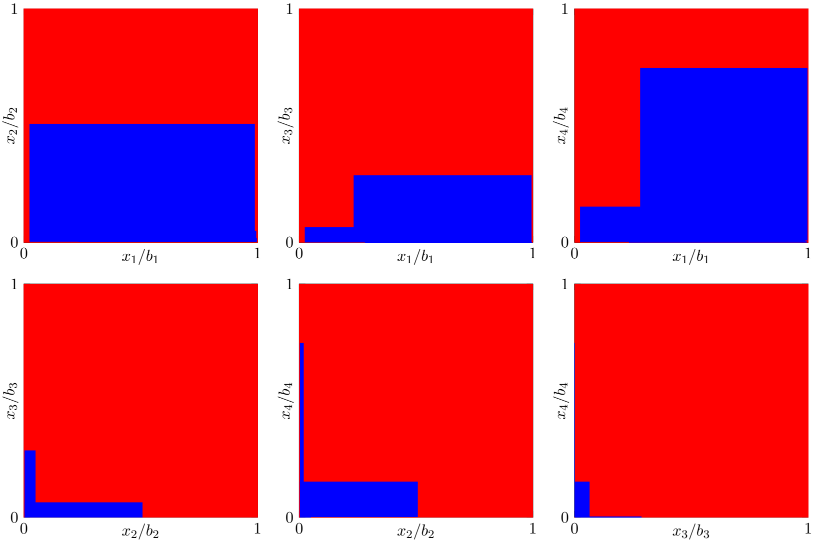
Evolution of the algorithm on a 4-dimensional example

Geometric long-edge bisection – Level 1 of 18 – Boxes examined/admitted/discarded : 2/2/0



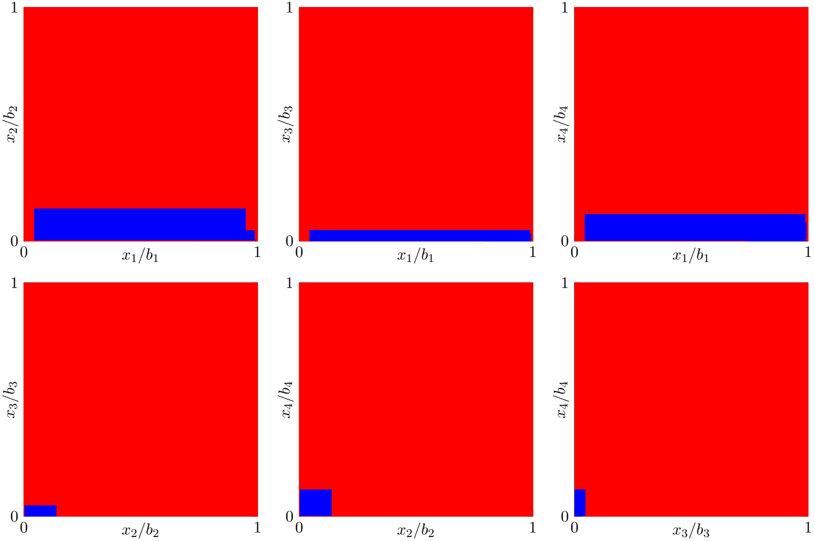
Evolution of the algorithm on a 4-dimensional example

Geometric long-edge bisection – Level 2 of 18 – Boxes examined/admitted/discarded : 4/3/1



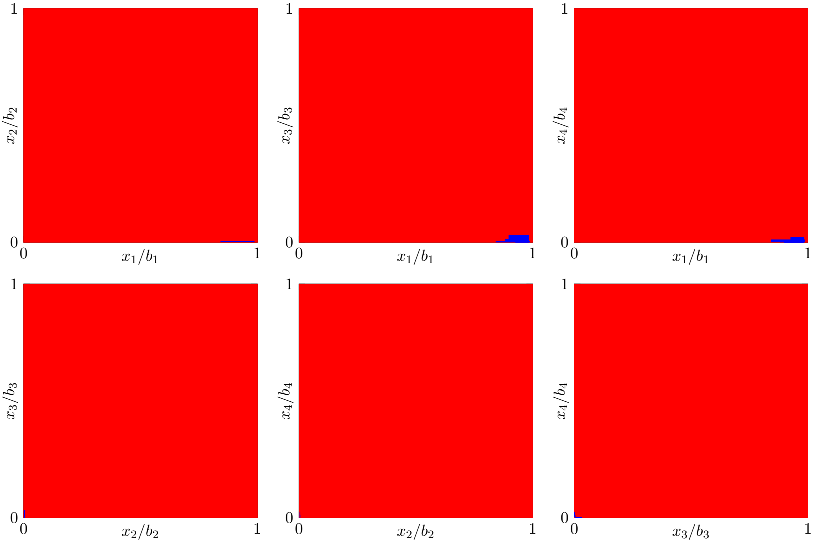
Evolution of the algorithm on a 4-dimensional example

Geometric long-edge bisection – Level 3 of 18 – Boxes examined/admitted/discarded : 6/4/2



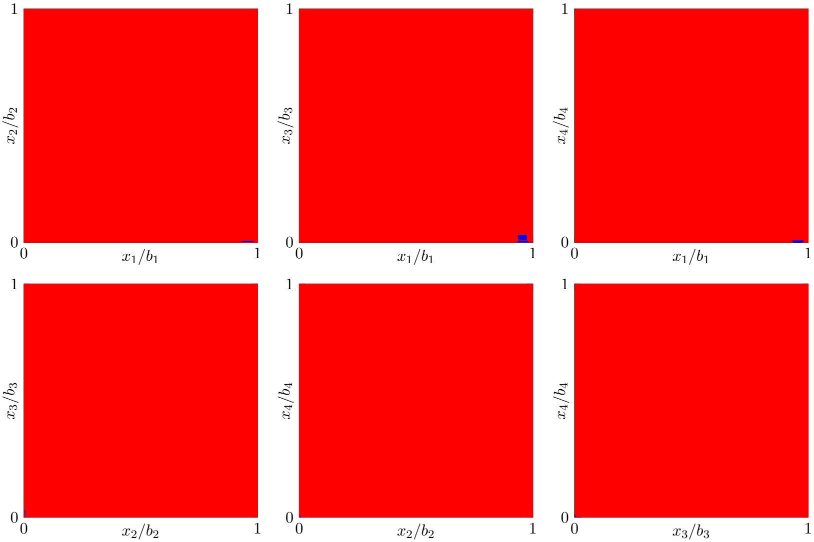
Evolution of the algorithm on a 4-dimensional example

Geometric long-edge bisection – Level 4 of 18 – Boxes examined/admitted/discarded : 8/4/4



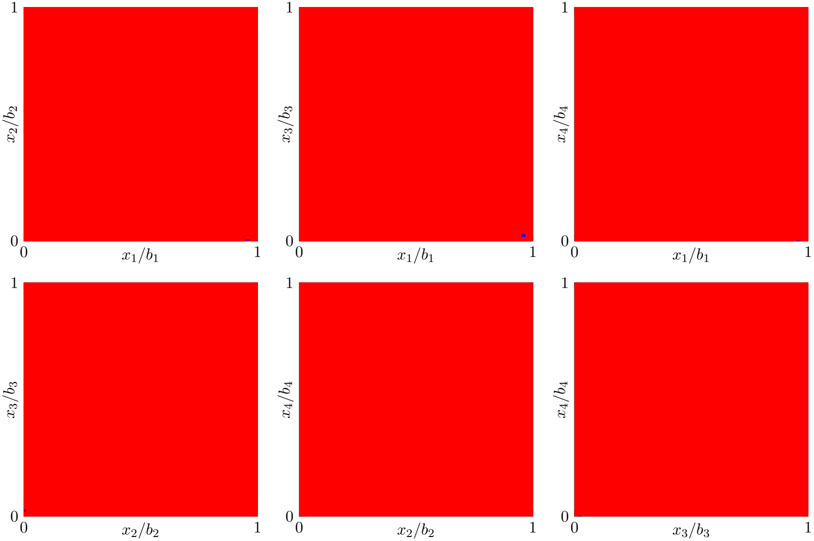
Evolution of the algorithm on a 4-dimensional example

Geometric long-edge bisection – Level 5 of 18 – Boxes examined/admitted/discarded : 8/4/4



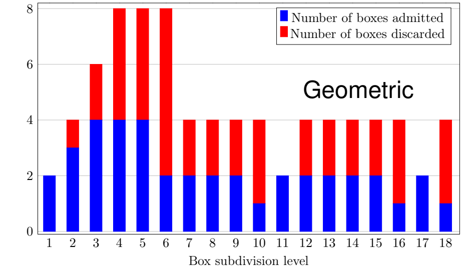
Evolution of the algorithm on a 4-dimensional example

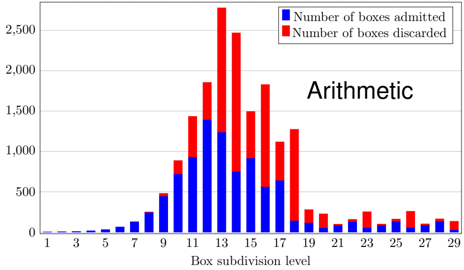
Geometric long-edge bisection – Level 6 of 18 – Boxes examined/admitted/discarded : 8/2/6 **[END]**



Evolution of the algorithm on a 4-dimensional example

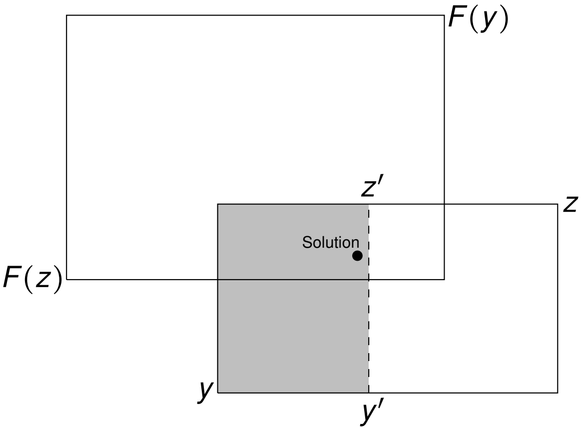
Boxes admitted/discarded : geometric-vs-arithmetic long-edge bisection





Another Approach: Box Squeezing

Fixed-point formulation optional. Surprisingly unimpressive performance.



$$\begin{cases} y \leqslant F(y) \\ F(z) \leqslant z \end{cases} \dashrightarrow\dashrightarrow\dashrightarrow \begin{cases} y' \not\leqslant F(y') \\ F(z') \leqslant z' \end{cases}$$

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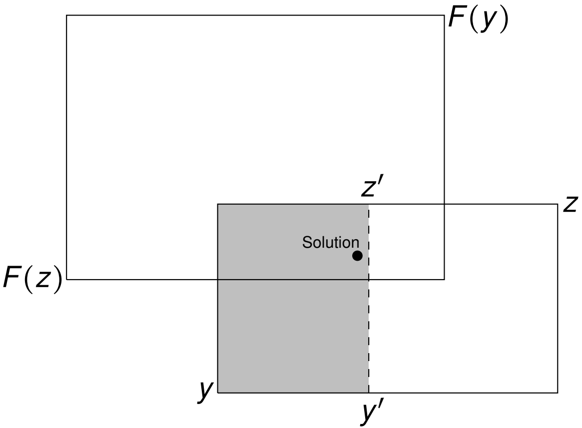

$$\begin{cases} y \leqslant F(y) \\ F(z) \leqslant z \end{cases} \dashrightarrow \begin{cases} y' \nleqslant F(y') \\ F(z') \leqslant z' \end{cases} \qquad \begin{cases} f(y) \leqslant b \\ b \leqslant f(z) \end{cases} \dashrightarrow \begin{cases} f(y') \nleqslant b \\ b \leqslant f(z') \end{cases}$$

Recapitulation

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

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

Key Properties

- $f : \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0}$ is an infinitely smooth diffeomorphism.
- $F(b,\cdot)$ has a unique fixed point in $[0_n, b] \subset \mathbb{R}^n_{\geqslant 0}$.
- $F(b,\cdot)$ is order-reversing on $\mathbb{R}^n_{\geqslant 0}$.
- We know a Lipschitz constant for $F(b,\cdot)$ on $]0_n, b]$.

Problem

Solve $\boldsymbol{F(b,x) = x}$ (or $\boldsymbol{f(x) = b}$) by a worry-free algorithm.

Worry-Free Algorithm

Simplicity	10%
Computational performance	31%
A priori certainty of convergence	59%