Enclosure Algorithm for the Fixed Points of Order-Reversing Maps

Application to Polynomial Systems for Chemical Equilibrium

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Pharmacology, the study of interactions between biological processes and therapeutic agents, is traditionally seen as consisting of two subdisciplines: pharmacokinetics, which is about the distribution and transformation of drugs in organisms; and pharmacodynamics, which is about the organisms' response to drugs. In discovery-stage pharmacology however, one primary concern is what we call pharmacostatic, the characterization of the equilibrium parameters and states of core interactions of physiologic and therapeutic interest. For a class of such interactions, which includes the reversible binding of endogenous and exogenous ligands to receptors, the equilibrium states are the solutions of polynomial systems of a particular kind. The universal practice in pharmacostatic is to seek closed-form expressions of these solutions based on simplifying assumptions. We present an algorithmic method to solve these systems with theoretically assured convergence and experimentally observed good performance. The impetus are that such a system has a unique nonnegative solution and possesses a canonical reformulation as the fixed-point equation of an order-reversing map. The method is an enclosure algorithm and it uses a box subdivision strategy and an admissibility condition that exploit the specific features of this class of maps.

Keywords
Fixed Point; Fixed Box ; Order-Reversing Map; Polynomial System; Enclosure Algorithm; Interval Analysis Method; Chemical Equilibrium; Pharmacostatic.

Mathematics Subject Classification (2010)
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1 Introduction

We present a fixed-point equation solving method motivated by the need to compute the equilibrium states of certain reaction networks, without simplifying assumptions on the relative concentrations of participating species, and with a priori assurance of success. These reaction networks are those we called Complete Networks of Reversible Binding Reactions in [6]. They are ubiquitous in pharmacology, particularly in discovery-stage biopharmaceutical research, either directly or after judicious transformation, to model core biochemical interactions of interest. Examples may be found in the pharmacology

literature, e.g. [9] and [3]. They appear in other uses of chemistry as well, and the realization that their equilibrium states naturally arise as solutions of fixed-point equations can be traced back to [10] and [14].

The equilibrium equation is of the form

$$f(x) \quad = \quad b, \tag{1.1}$$

with $b \in \mathbb{R}^n_{\geqslant 0}$ and $f = (f_1, \ldots, f_n)$ a self-map of $\mathbb{R}^n_{\geqslant 0}$ given by

$$f_i(x) \quad = \quad x_i + \sum_{\alpha \in I} \alpha_i \, a_\alpha \, x^\alpha, \tag{1.2}$$

where I is a finite subset of $\mathbb{Z}^n_{\geqslant 0}$ and $a_\alpha \in \mathbb{R}_{\geqslant 0}$ for each $\alpha \in I$. We showed in [6] that f is an infinitely smooth self-diffeomorphism of $\mathbb{R}^n_{\geqslant 0}$. In particular, Equation (1.1) has a unique nonnegative solution.

With $e_{n,i}$ denoting the vector in $\mathbb{R}^n$ that has 1 in position i and 0 elsewhere, let the self-map $F = (F_1, \ldots, F_n)$ of $\mathbb{R}^n_{\geqslant 0}$ be given by

$$F_i(x) \quad = \quad \frac{b_i}{1 + \sum\limits_{\alpha \in I,\, \alpha_i \geqslant 1} \alpha_i \, a_\alpha \, x^{\alpha - e_{n,i}}}. \tag{1.3}$$

Then Equation (1.1) is equivalent to the fixed-point problem

$$F(x) \quad = \quad x. \tag{1.4}$$

We showed in [5] that in some cases, the map F is a contraction, and thus the unique solution can be found by fixed-point iteration. This does occur in applications; see for instance our work [7], and also [2] where Theorem 5.4 of [5] was partially rediscovered and applied. More often however, fixed-point iteration converges to a 2-orbit, or what some call a pair of coupled fixed points (though they are coupled in some way, but not fixed). In this paper we present a much needed method that is unrestrictedly applicable.

The method employs ideas from Enclosure Algorithms and Interval Methods, namely box subdivision, contraction, and discarding. We briefly survey these concepts in Section 2. Then in Section 3, we discuss aspects of fixed points pertaining to order-reversing maps; the maps F we will work with need not be as specific as in Equation (1.3). We present our fixed-point enclosure method in Section 4 and continue on in Section 5 with a discussion of its special features. We illustrate the method with an example of chemical equilibrium calculation in Section 6. Additional illustrations of the progression of the method in this example are provided in a supplemental document. The calculations were conducted in the MATLAB® computing environment, and the source code is available at [4].

2 A Digest on Enclosure Algorithms and Interval Methods

The space $\mathbb{R}^n$ is equipped with the componentwise order, whereby for $y = (y_1, \ldots, y_n)$ and $z = (z_1, \ldots, z_n)$ in $\mathbb{R}^n$, we have $y \leqslant z$ if and only if $y_i \leqslant z_i$ for all $i = 1, \ldots, n$.

A box in $\mathbb{R}^n$ (also called cell or interval or rectangle in the literature) is any set

$$\texttt{Box}(y, z) \quad := \quad \big\{ x \in \mathbb{R}^n : y \leqslant x \leqslant z \big\}. \tag{2.1}$$

Let D be a box in $\mathbb{R}^n$, and let S be a subset of D, which would usually be the solution set of an equation or an optimization problem. The goal of enclosure algorithms and interval methods is to enclose S inside a descending sequence of unions of boxes. In more specific terms, a procedure of this kind produces a sequence of finite sets $\mathscr{B}_\ell$ of boxes, indexed by levels $\ell \in \mathbb{Z}_{\geqslant 0}$, with the following properties.

- At level $\ell = 0$, $\mathscr{B}_0 = \{D\}$.
- Let $\ell \geqslant 1$.
  - The interiors of any two distinct boxes from $\mathscr{B}_\ell$ are disjoint.
  - Each box from $\mathscr{B}_\ell$ is properly contained in some (unique) box from $\mathscr{B}_{\ell-1}$.
- With $\overline{\mathscr{B}}_\ell$ denoting the union of the boxes at level ℓ, the sequence $\left(\overline{\mathscr{B}}_\ell\right)_{\ell \geqslant 0}$, an inclusion-descending sequence of sets, converges to S.

Boxes at a level ℓ are deemed admissible, i.e. possibly having a nonempty intersection with S. Then each box $B \in \mathscr{B}_\ell$ is subdivided into subboxes according to a *subdivision strategy*, and each subbox is subjected to an *admissibility test*. If the test fails, the subbox is discarded. If the test succeeds, the resulting box is put in the collection $\mathscr{B}_{\ell+1}$. This resulting box is the subbox that was successfully tested, or can be a proper subset thereof if a *box contraction* mechanism is part of the admissibility test. In each admissible box, a distinguished point, usually the center, is tested against preset approximate solution criteria. If only one solution is sought, and in particular if it is know that there is a unique solution (i.e. the set S is a singleton), then the success of this test terminates the algorithm. If not, with the success of this test, the collection of approximate solutions is augmented, and the algorithm terminates when there are no more admissible boxes.

The literature on enclosure algorithms includes [16], [15], and [1]. There is abundant published material on interval methods. Here we mention [8] as a good introductory textbook and the papers [12, 11, 13] on interval methods applied to fixed-point problems. Interval methods emphasize the use of *interval arithmetic* to control the size of boxes. Enclosure algorithms are guaranteed to converge. However their performance hinges chiefly on the stringency of the admissibility test, and also on the subdivision strategy. In section 4, we specify these features for a class of functions relevant to our targeted application, but first we discuss these functions in the next section.

3 Fixed Points of Order-Reversing Maps

Let F be a map $\mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{>0}$ that is order-reversing, i.e. $y \leqslant z \Rightarrow F(z) \leqslant F(y)$.
Let $\texttt{Fix}(F)$ be the set of fixed points of F. Note that, because $F\left(\mathbb{R}^n_{\geqslant 0}\right) \subseteq \texttt{Box}(0, F(0))$, Brouwer's Fixed-Point Theorem implies that F does have fixed points if it is continuous.

The sequence $\left(F^{2k}(0)\right)_{k \geqslant 0}$ increases and converges to its supremum y_0.
The sequence $\left(F^{2k+1}(0)\right)_{k \geqslant 0}$ decreases and converges to its infimum z_0.
We have

$$\texttt{Fix}(F) \;\subseteq\; \texttt{Box}(y_0, z_0) \;\subseteq\; \texttt{Box}\left(F^{2k}(0), F^{2k+1}(0)\right) \quad , \quad \forall\, k \in \mathbb{Z}_{\geqslant 0}. \tag{3.1}$$

If $y_0 = z_0$ and $\texttt{Fix}(F) \neq \varnothing$, then F has a unique fixed point and the two sequences provide an enclosure for approximating it. Usually however, $y_0 \neq z_0$ whether or not $\texttt{Fix}(F)$

is a singleton. Further progress in such cases is enabled by the following generalization of Property (3.1), which holds for all $y, z \in \mathbb{R}^n_{\geqslant 0}$.

$$\texttt{Fix}(F) \cap \texttt{Box}(y, z) \quad \subseteq \quad \texttt{Box}\big(F(z), F(y)\big). \tag{3.2}$$

Let Φ be the map $\mathbb{R}^n_{\geqslant 0} \times \mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{\geqslant 0} \times \mathbb{R}^n_{\geqslant 0}$ given by

$$\Phi(y, z) \quad = \quad \big(\texttt{max}(y, F(z)), \texttt{min}(z, F(y))\big), \tag{3.3}$$

where `min` and `max` are the componentwise minimum and maximum maps. We have

$$\texttt{Box}(\Phi(y, z)) \quad \subseteq \quad \texttt{Box}(y, z), \tag{3.4}$$

and Property (3.2) is equivalent to

$$\texttt{Fix}(F) \cap \texttt{Box}(y, z) \quad = \quad \texttt{Fix}(F) \cap \texttt{Box}(\Phi(y, z)). \tag{3.5}$$

Properties (3.4) and (3.5) are instrumental in the method we present in Section 4. Next in this section we articulate the approximations we seek to achieve.

Given $\varepsilon \in [0, 1[$, we call ε-approximate fixed point of F, any point $x \in \mathbb{R}^n_{\geqslant 0}$ that satisfies

$$(1 - \varepsilon) \cdot F(x) \quad \leqslant \quad x \quad \leqslant \quad (1 + \varepsilon) \cdot F(x). \tag{3.6}$$

Note that the 0-approximate fixed points are precisely the fixed points. The rationale for Condition (3.6) comes from our intended application. Indeed, our actual objective is to solve the equation

$$f(x) \quad = \quad b, \tag{3.7}$$

where f, a self-map of $\mathbb{R}^n_{\geqslant 0}$, and $b \in \mathbb{R}^n_{>0}$, are related to F by

$$f(x) \odot F(x) \;=\; b \odot x \quad , \quad \forall\, x \in \mathbb{R}^n_{\geqslant 0}; \tag{3.8}$$

the symbol $\odot$ denotes the componentwise multiplication. We accept as ε-approximate solution of Equation (3.7) any $x \in \mathbb{R}^n_{\geqslant 0}$ that satisfies

$$(1 - \varepsilon) \cdot b \quad \leqslant \quad f(x) \quad \leqslant \quad (1 + \varepsilon) \cdot b. \tag{3.9}$$

Conditions (3.9) and (3.6) are equivalent. Condition (3.9) is not adequate if $b = 0$ in Equation (3.7), which would be the most common way equations are presented. It is however well suited in many applications. It says that $f(x)$ approximates b with componentwise relative error of at most ε. This is not sensitive to scaling. In Equation (1.1) for example, f has a specific meaning and b is a vector of (positive) concentrations, and what Condition (3.9) expresses is independent of the choice of concentration unit.

4 Enclosure Algorithm

Let F be a continuous order-reversing map $\mathbb{R}^n_{\geqslant 0} \to \mathbb{R}^n_{>0}$. As noted at the beginning of Section 3, $\texttt{Fix}(F) \neq \varnothing$. We first seek to approximate a fixed point by fixed-point iteration, and when that fails we employ box subdivision and contraction. Fixed-point iteration and box contraction both produce descending sequences of boxes. We use the same stopping criterion for both. This criterion is described next.

4.1 Stopping Criterion for Descending Sequences of Boxes

A descending sequence of boxes is allowed to continue only if the newest subbox features a significant reduction of the linear length of at least one edge. For more specificity, let $\rho \in \mathbb{R}$ with $0 < \rho < 1$, and let $y, z, y', z' \in \mathbb{R}^n_{\geqslant 0}$ with $y \leqslant y' \leqslant z' \leqslant z$. Suppose that $\texttt{Box}(y', z')$ is the subbox of $\texttt{Box}(y, z)$ produced in a descending sequence. The sequence continues after $\texttt{Box}(y', z')$ if and only if $z'_i - y'_i < \rho \cdot (z_i - y_i)$ for some $i = 1, \ldots, n$. Equivalently, the sequence stops at $\texttt{Box}(y', z')$ if $\rho \cdot (z - y) \leqslant z' - y'$.

4.2 Priming Stage: Fixed-Point Iteration

We calculate the iterates $F^{2k}(0)$ and $F^{2k+1}(0)$. At any stage $k \in \mathbb{Z}_{\geqslant 1}$, we assess whether the geometric center x of $\texttt{Box}\left(F^{2k}(0), F^{2k+1}(0)\right)$ is an ε-approximate fixed point, i.e. satisfies Condition (3.6). If this is the case, then calculations are complete. If not, then we assess the stopping criterion of Section 4.1. It it is satisfied, then this iteration is complete and $D := \texttt{Box}\left(F^{2k}(0), F^{2k+1}(0)\right)$ is the box upon which the subdivision and contraction of subboxes will begin.

4.3 Box Subdivision

We call our box subdivision strategy the *geometric long-edge bisection*. We cut a box into two subboxes with an affine hyperplane orthogonally crossing at its center the first edge of maximal length; the edge's length is measured multiplicatively and the edge's center is determined geometrically. For specificities, let $y, z \in \mathbb{R}^n_{>0}$ with $y \leqslant z$, and let $k \in \{1, \ldots, n\}$ characterized by

$$\begin{cases} z_i/y_i < z_k/y_k & \text{for } i = 1, \ldots, k-1, \\ z_i/y_i \leqslant z_k/y_k & \text{for } i = k+1, \ldots, n. \end{cases}$$

The let $w := \sqrt{y_k z_k}$. We cut $\texttt{Box}(y, z)$ into $\texttt{Box}(y, \tilde{z})$ and $\texttt{Box}(\tilde{y}, z)$, where

$$\tilde{z} := (z_1, \ldots, z_{k-1}, w, z_{k+1}, \ldots, z_n) \quad \text{and} \quad \tilde{y} := (y_1, \ldots, y_{k-1}, w, y_{k+1}, \ldots, y_n).$$

The ordinary variant of this strategy is the *arithmetic long-edge bisection*, in which k is characterized by

$$\begin{cases} z_i - y_i < z_k - y_k & \text{for } i = 1, \ldots, k-1, \\ z_i - y_i \leqslant z_k - y_k & \text{for } i = k+1, \ldots, n \end{cases}$$

and $w := (y_k + z_k)/2$. We discuss this choice and more in Section 5.

4.4 Fixed-Box Iteration and Admissibility Condition

We call *fixed-box iteration* the box contraction process to highlight the similarities with fixed-point iteration. We use the map Φ introduced in Section 3. Let $y, z \in \mathbb{R}^n_{>0}$ with $y \leqslant z$. Consider the iterates $\Phi^k(y, z) \in \mathbb{R}^n_{>0} \times \mathbb{R}^n_{>0}$ for $k \in \mathbb{Z}_{\geqslant 0}$ and the resulting descending sequence of boxes $\texttt{Box}\left(\Phi^k(y, z)\right)$. We have

$$\texttt{Fix}(F) \cap \texttt{Box}(y, z) = \texttt{Fix}(F) \cap \texttt{Box}\left(\Phi^k(y, z)\right) \quad , \quad \forall\, k \in \mathbb{Z}_{\geqslant 0}.$$

If for some $k \in \mathbb{Z}_{\geqslant 1}$, the pair $\Phi^k(y, z)$ is not ordered, then $\texttt{Box}\left(\Phi^k(y, z)\right) = \varnothing$, and consequently $\texttt{Fix}(F) \cap \texttt{Box}(y, z) = \varnothing$; $\texttt{Box}(y, z)$ contains no fixed points.

If instead the pair $\Phi^k(y,z)$ is ordered for all $k \in \mathbb{Z}_{\geqslant 1}$, then the descending sequence converges to a nonempty box $\texttt{Box}(\bar{y},\bar{z})$, and

$$\texttt{Fix}(F) \cap \texttt{Box}(y,z) = \texttt{Fix}(F) \cap \texttt{Box}(\bar{y},\bar{z}).$$

The box $\texttt{Box}(\bar{y},\bar{z})$ is a fixed box of F in the sense that $F(\bar{y}) = \bar{z}$ and $F(\bar{z}) = \bar{y}$; the descending sequence starting at $\texttt{Box}(\bar{y},\bar{z})$ is constant. Also, $\texttt{Box}(\bar{y},\bar{z})$ is F-invariant, so $\texttt{Fix}(F) \cap \texttt{Box}(\bar{y},\bar{z}) \neq \varnothing$.

We adapt here the approach described in Section 4.2 to turn fixed-box iteration into a finite process. At any stage $k \in \mathbb{Z}_{\geqslant 1}$, we assess whether the pair is $\Phi^k(y,z)$ is ordered. If it is not, then $\texttt{Box}(y,z)$ contains no fixed points and is discarded, and fixed-box iteration is complete. If the pair is ordered, then we assess the stopping criterion of Section 4.1. It it is satisfied, then fixed-box iteration is complete and the outcome is the box $E := \texttt{Box}\left(\Phi^k(y,z)\right)$; the box E is admissible in the sense that it is not ruled out that it could contained a fixed point.

If fixed-box iteration does terminate with an admissible box E, we assess whether the geometric center x of E is an ε-approximate fixed point, i.e. satisfies Condition (3.6). If this is the case, then calculations are complete. If not, then the box E is added to the collection of admissible boxes for the next level of box subdivision.

5 Discussion

Many features of the algorithm in Section 4 obviously require judgment. Regarding the parameter ρ for the stopping criterion (Section 4.1), in the example of Section 6, we used $\rho = 0.9$ for the priming stage of fixed-point iteration and $\rho = 0.8$ for fixed-box iterations. We want to give a chance to the priming stage to converge, but we do not want to linger there if it is unlikely to converge or will converge slowly. We are more demanding on fixed-box iteration because it can be that a box presents a case of slow conclusive admissibility test but its two subboxes are a lot faster to assess. On another hand, eliminating fixed-box iteration altogether (by basing admissibility assessment on a single box contraction) did penalize performance in experiments.

Perhaps the most intriguing feature is the use of the geometric long-edge bisection (Section 4.3) as the box subdivision strategy. In our applications of interest, the performance impact of this decision was immense by all measures: the number of subdivision levels, the number of admissible boxes at each level, and the computing time. In the example of Section 6, the change from the arithmetic variant to the geometric one reduced computing time by a factor of more than 90. We were inspired to try this approach by our work in [5], which is the main precursor to this paper. To put it briefly, the idea is that (multivariate non-affine) polynomial maps do not have global Lipschitz constants on $\mathbb{R}^n_{>0}$ with respect to the ordinary ℓ^p metrics ($p \in [1,\infty]$); but with respect to the logarithmic metric, the total degree of a multivariate positive-coefficient polynomial is its Lipschitz constant on $\mathbb{R}^n_{>0}$. Because using the logarithmic metric proved to be a fruitful approach in a previous related instance, we thought of doing so again here, seemingly with tangible benefits. The geometric center is the center according to the logarithmic metric, and our intuition is that this approach distributes the variation of F more evenly over subboxes.

6 Application to Chemical Equilibrium

For the convenience of exposition, we alter some notations used in Equation (1.2) by encoding the set I as a matrix. Let α be a $q \times n$ matrix of nonnegative integers and $a = (a_j)_{1 \leqslant j \leqslant q} \in \mathbb{R}^q_{\geqslant 0}$. For each $j = 1, \ldots, q$, let $\alpha_j = (\alpha_{ji})_{1 \leqslant i \leqslant n}$ be the row of α of index j. The map $f = (f_1, \ldots, f_n)$ is now given as follows.

$$f_i(x) \quad = \quad x_i + \sum_{j=1}^{q} \alpha_{ji}\, a_j\, x^{\alpha_j}$$

We note that, with $x^\alpha := (x^{\alpha_j})_{1 \leqslant j \leqslant q}$, and again $\odot$ denoting the componentwise multiplication, we have

$$f(x) \quad = \quad x + (a \odot x^\alpha) \cdot \alpha,$$

a remark that facilitates vectorized computer implementation.

Now consider the reaction network constituted as follows (see [6] for terminology).

- Elementary species X_i, for $i = 1, \ldots, n$
- Composite species Y_j of composition $\alpha_j = (\alpha_{j1}, \ldots, \alpha_{jn})$ with respect to the n-tuple $(X_1, \ldots, X_n)$ of elementary species, for $j = 1, \ldots, q$
- Reversible binding reaction $\alpha_{j1}X_1 + \cdots + \alpha_{jn}X_n \rightleftharpoons Y_j$ with equilibrium binding constant a_j, for $j = 1, \ldots, q$

This network is usually the normalization of a complete network, where typically no more than two species bind at once, a model that is much more chemically realistic. Let x_i and y_j denote the concentrations of X_i and Y_j. The total concentration of X_i is

$$b_i \quad := \quad x_i + \sum_{j=1}^{q} \alpha_{ji}\, y_j.$$

It adds up the concentration of the free form of X_i and of the bound forms $Y_1, \ldots, Y_q$ of X_i with the applicable multiplicities $\alpha_{j1}, \ldots, \alpha_{jq}$. The map f describes the equilibrium states of the reaction network in the sense that, given a vector $b = (b_1, \ldots, b_n)$ of total concentrations, the equation $f(x) = b$ has as its unique nonnegative solution the vector of the equilibrium concentrations of elementary species (and for the composite species we have $y_j = a_j x^{\alpha_j}$ for $j = 1, \ldots, q$).

For an example we choose the composition matrix α, the vector a of equilibrium binding constants, and the vector b of total concentrations, as follows.

$$\alpha = \begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 \end{pmatrix} \qquad a^{\mathrm{T}} = \begin{pmatrix} 0.1 \\ 0.0059 \\ 0.0031 \\ 62.5 \\ 0.5 \end{pmatrix} \qquad b^{\mathrm{T}} = \begin{pmatrix} 2500 \\ 10 \\ 100 \\ 80 \end{pmatrix}$$

The (normalized) reaction network and the maps f and F are as follows.

$$\begin{aligned} X_1 + X_2 &\rightleftharpoons Y_1 \\ X_2 + X_3 &\rightleftharpoons Y_2 \\ X_1 + X_3 &\rightleftharpoons Y_3 \\ X_3 + X_4 &\rightleftharpoons Y_4 \\ X_1 + X_3 + X_4 &\rightleftharpoons Y_5 \end{aligned}$$

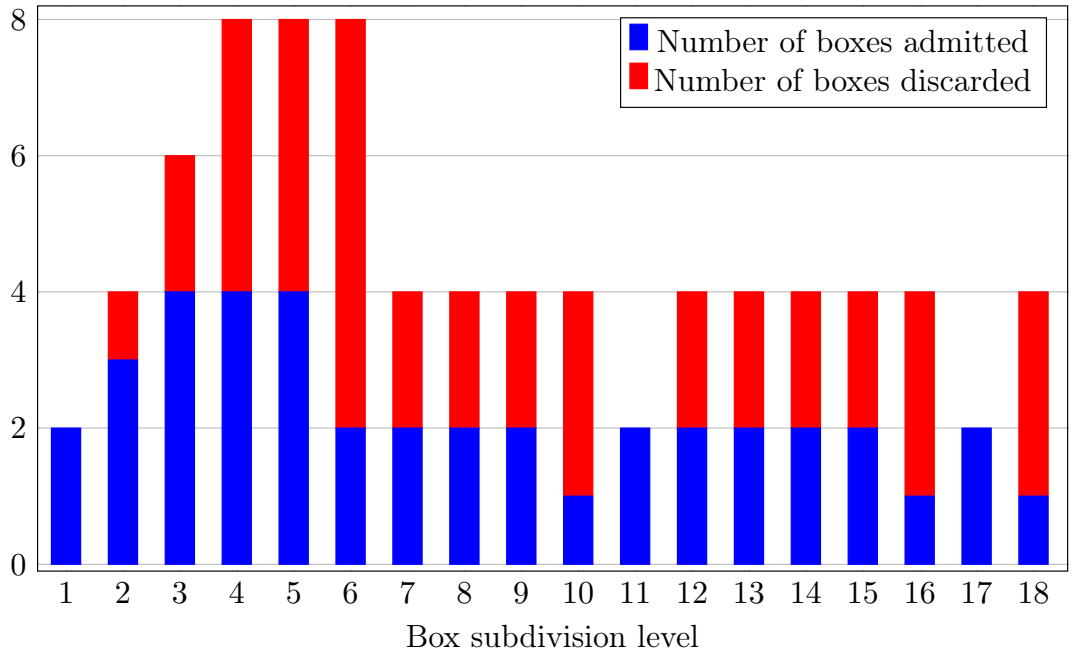

Figure 6.1: This bar chart shows the number of boxes that were admitted and discarded at each subdivision level in the calculation of Section 6. The total height of each bar is the number of boxes that were examined. Observe that at levels 10 and 16, only one box was admitted, yet the algorithm did not stop because the (geometric) center of the box was not an ε-approximate fixed point.

$$\begin{cases} f_1(x) &= x_1 + a_1x_1x_2 + a_3x_1x_3 + a_5x_1x_3x_4 \\ f_2(x) &= x_2 + a_1x_1x_2 + a_2x_2x_3 \\ f_3(x) &= x_3 + a_2x_2x_3 + a_3x_1x_3 + a_4x_3x_4 + a_5x_1x_3x_4 \\ f_4(x) &= x_4 + a_4x_3x_4 + a_5x_1x_3x_4 \end{cases}$$

$$\begin{cases} F_1(x) &= \dfrac{b_1}{1 + a_1x_2 + a_3x_3 + a_5x_3x_4} \\ F_2(x) &= \dfrac{b_2}{1 + a_1x_1 + a_2x_3} \\ F_3(x) &= \dfrac{b_3}{1 + a_2x_2 + a_3x_1 + a_4x_4 + a_5x_1x_4} \\ F_4(x) &= \dfrac{b_4}{1 + a_4x_3 + a_5x_1x_3} \end{cases}$$

Following are the calculation configuration parameters.

Terminating priming fixed-point iteration (Sections 4.2 and 4.1) ..... $\rho = 0.9$
Terminating fixed-box iteration (Sections 4.4 and 4.1) ..... $\rho = 0.8$
Tolerance for approximate fixed point (Condition (3.6)) ..... $\varepsilon = 10^{-6}$

Priming fixed-point iteration terminated after one pass, but we do know that, if left to run, it would stall at a fixed box. The enclosure algorithm ran through 18 levels of box subdivision and yielded the ε-approximate solution

$$x^* = (\,2396.4\,,0.0416\,,2.3916\,,0.0265\,).$$

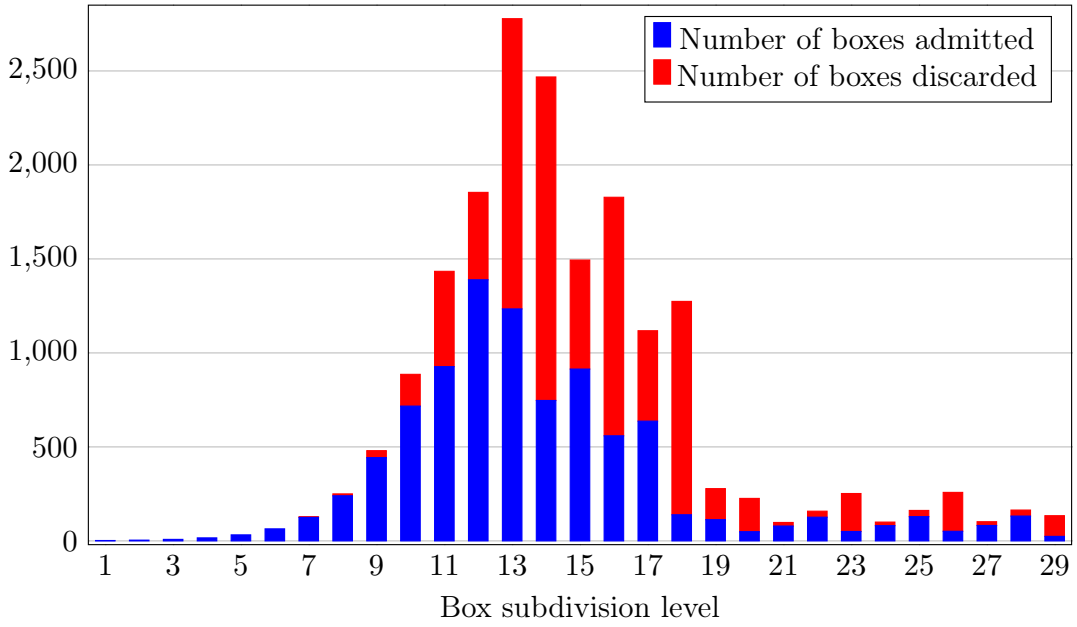

Figure 6.2: This bar chart shows the same data depicted on Figure 6.1 when arithmetic long-edge bisection is used in lieu of geometric long-edge bisection. Performance is significantly worse. It is only at subdivision level 7 that box discarding begins, with just 3 out of $128 = 2^7$ boxes. We also observe that the largest proportion (89%) of discarded boxes occurs at level 18, which perhaps coincidentally is the level at which calculations with geometric long-edge bisection ended on Figure 6.1. At final level 29, 24 boxes were admitted, which means that in 23 of these, the (arithmetic) center was not an ε-approximate fixed point.

Figure 6.1 displays, for each level, the numbers of admitted and discarded boxes. Figure 6.2 presents the same data when the arithmetic variant of the long-edge bisection strategy is used. The difference is plainly remarkable. And with full realization that numerous factors affect computing time, we mention that these two specific calculations ran in 238 milliseconds and 22.34 seconds, respectively.

Box discarding begins at level 2 on Figure 6.1, but only at level 7 on Figure 6.2. We note however that the admissible region does shrink even when no boxes are discarded outright. This is because, due to fixed-box iteration, a box that is admitted is a (usually proper) subset of the box that was examined. We show the progression of the admissible and discarded regions for both calculations in the supplemental document accompanying this article. The MATLAB® source code is available at [4].

7 Conclusion

Computing the equilibrium parameters and states of reaction networks is an important and recurrent mathematical model problem in discovery-stage pharmacology. One is interested in either simulating dose-response curves or determining binding affinities, or both. Either way such calculations are performed in large numbers and it is crucial to have methods that feature no convergence issues and rapid performance. Scientists traditionally achieve these by resorting to a catalog of special-purpose closed-form formulas that are based on more-or-less applicable assumptions. The method presented here offers these two benefits without that penalty. Of course it does require a more sophisticated computer implementation. An obvious follow-up would be a systematic investigation of the remarkable performance of the method when the geometric variant

of long-edge bisection is used. Ideally this would include an understanding of the complexity of the algorithm, with results more concrete than inequalities parameterized by unknown constants and applicable only asymptotically.

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