Fixed-point methods for computing the equilibrium composition of complex biochemical mixtures

Petr KUZMIČ
BioKin Consulting, P.O. Box 8336, Madison, WI 53708, U.S.A.

The fixed-point algebraic method [Storer and Cornish-Bowden (1976) Biochem. J. **159**, 1–5] for computing the concentrations at equilibrium of complex biochemical mixtures fails for many binding stoichiometries, especially those that include molecular self-association. A typical example is the monomer–dimer–tetramer equilibrium. This paper reports two main results. First, the above algorithm is analysed theoretically to predict for which binding stoichiometries it succeeds and for which it will fail. Secondly, an alternative algorithm is described for self-associating biochemical systems. Illustrative examples are based on the dimeric proteinase from HIV.

INTRODUCTION

Storer and Cornish-Bowden [1] proposed a method (further referred to as the SCB algorithm) for computing the composition at equilibrium of complex biochemical mixtures. An initial guess of equilibrium concentrations is refined in a succession of repeated steps, each of which takes as input the result of the previous step. The authors claim that the method is suitable for any number of components that can associate 'with any stoichiometry'.

In fact, the algorithm fails for many stoichiometries, especially those that involve higher-order molecular complexes. At certain total concentrations, and at certain values of association constants, the computation enters an infinite loop (see example below). The SCB algorithm has been incorporated into a purportedly general method for the analysis of kinetic data [2,3]. Our research was undertaken when the latter method failed on the complex equilibria involved in the inhibition of HIV proteinase.

This report contains two main results. First, the SCB algorithm is analysed theoretically to predict for which biochemical reaction mechanisms it can succeed in principle. The theoretical analysis is based on the mean-value theorem of differential calculus. Secondly, an alternative method is described for those mechanisms or stoichiometries where the algorithm fails, for example, the monomer–dimer–tetramer problem or the inhibition of dissociating enzymes.

PRINCIPLES

In this section the SCB algorithm [1] is cast is theoretical terms, explaining its failure or success for particular binding stoichiometries.

Fixed-point algebraic methods

A fixed-point method for solving algebraic equations is defined in the following way. A given equation $f(x) = 0$ is rearranged algebraically into the form $x = g(x)$. The two equations have an identical solution s at which the function g has the same value as its argument (hence 'fixed-point'). Starting from an initial estimate of the solution, x_0, presumably an improved estimate is computed according to the formula $x_1 = g(x_0), x_2 = g(x_1), \ldots, x_{m+1} = g(x_m)$. The recursion is ended when x_{m+1} and x_m become sufficiently close for some m values.

Dimensionality

The SCB algorithm in its original form [1] is an example of a multidimensional fixed-point algebraic method. Convergence properties of such *ad hoc* methods cannot be investigated. Therefore, in this paper we restrict our attention to those biochemical equilibria that can be reduced to a single algebraic equation, representing the mass-balance law for a single molecular species. Many important biochemical binding mechanisms involving several component species can be reduced to this simpler case (see Example 3 below).

Divergence and oscillations

The convergence of any given fixed-point formula is not guaranteed. In fact, x_{m+1} is closer to the correct solution s in comparison with x_m if and only if the derivative $\mathrm{d}g/\mathrm{d}x$ evaluated at x_m is smaller than unity in its absolute value. The proof is given in the Appendix. When $|\mathrm{d}g/\mathrm{d}x|$ evaluated at the solution is greater than unity, the fixed-point formula will not converge. If $|\mathrm{d}g/\mathrm{d}x| < 1$ at x_0 (convergence) but $|\mathrm{d}g/\mathrm{d}x| > 1$ at the solution (divergence), the algorithm must pass a point where $|\mathrm{d}g/\mathrm{d}x|$ evaluated at x_m is exactly equal to unity. At that point the algorithm enters undamped oscillations, thus producing an infinite series of alternating concentrations neither of which represent the conditions at equilibrium.

Forced convergence

When a biochemical mechanism involves molecular complexes containing several identical subunits of a given component, the convergence of the fixed-point can be enforced by rearranging the mass-balance equations $x = g(x)$ into the form $x = h(x) = [x + g(x)]/2$. Now the absolute value of first derivative $|\mathrm{d}h/\mathrm{d}x|$ is smaller than unity near equilibrium. Overall, convergence can be enforced by using mass-balance equations of for type $x = h(x) = [(n-1)\,x + g(x)]/n$, where x is the concentration of the component molecular species at equilibrium and $n \geqslant 2$.

IMPLEMENTATION

All computations reported in this paper were performed by using the program SigmaPlot (Jandel Scientific) for scientific graphics and data analysis. For example, the composition of a monomer–dimer–tetramer mixture according to the fixed-point formula (13) was computed by using the following

SigmaPlot script: 'total = 2.0|k1 = 1.0|k2 = 1.0|iterations = 100|CELL(1,1) = total|FOR i = 2 TO iterations DO|CELL(1,i) = 0.5*CELL(1,i−1)*{1+total/[CELL(1,i−1)+2*k1*CELL(1,i−1)²+4*k1*k2*CELL(1,i−1)⁴]}|END FOR'. The vertical bar stands for a line break. Key words from the SigmaPlot transform language are shown in uppercase. The above script puts into the first 100 cells of the worksheet successive estimates of the equilibrium concentrations c_M. Similar scripts were created by using the Excel spreadsheet program (Microsoft Corporation).

EXAMPLES

This section describes three example problems of increasing complexity. All three examples are based on the proteinase from HIV, which exists as a monomer, dimer or tetramer [4]. Substrate–analogue inhibitors bind to the catalytically active dimer [4]. In the text below, the total or analytical concentration of the molecular species X is denoted by the 'tilde' accent ($\tilde{c}_x$); the concentration at equilibrium is denoted by the 'circumflex' accent ($\hat{c}_x$).

Example 1: monomer–dimer equilibrium

The monomer–dimer equilibrium can be solved directly, thus in principle an iterative method is not needed. However, the problem is useful for explaining the theory of convergence for fixed-point algebraic methods. According to the SCB method [1], the mass balance equation (1) for the monomer–dimer equilibrium $2M \overset{K}{\rightleftharpoons} M_2$ is rearranged into the form (2). The derivative is shown in eqn. (3). A solution is found iteratively as is shown in eqn. (4). In this simple special case, the concentration at equilibrium can also be obtained analytically [eqn. (5)].

$$f(c_M) \equiv c_M + 2K c_M^2 - \tilde{c}_M = 0 \tag{1}$$

$$c_M = g(c_M) \equiv c_M \frac{\tilde{c}_M}{c_M + 2K c_M^2} \tag{2}$$

$$\frac{dg}{dc_M} = -\tilde{c}_M \frac{2K}{(1+2K c_M)^2} \tag{3}$$

$$c_{i+1} = c_i \frac{\tilde{c}_M}{c_i + 2K c_i^2};\ i = 0, 1, \ldots, m;\ c_0 = \tilde{c}_M \tag{4}$$

$$\hat{c}_M = \frac{\sqrt{(8K\tilde{c}_M + 1)} - 1}{4K} \tag{5}$$

Any fixed-point algebraic method is convergent if the derivative is smaller than unity near the correct solution $\hat{c}_M$ (see the Appendix). This condition holds at all total concentrations of the monomer M, as can be seen from eqn. (6). Indeed, the right-hand side is always smaller than unity because $2/\sqrt{(8K\tilde{c}_M + 1)}$ must be greater than zero.

$$\left|\frac{dg}{dc_M}\right|_{c_M = \hat{c}_M} = \tilde{c}_M \frac{2K}{(1+2K\hat{c}_M)^2} = \tilde{c}_M \frac{2K}{[1+\sqrt{(8K c_M + 1)}/2]^2} = \frac{1}{[1+2/\sqrt{(8K\tilde{c}_M + 1)}]^2} < 1 \tag{6}$$

The above inequality proves that the SCB method will always converge for the monomer–dimer problem. It can even be predicted how many iterations will be taken, because the rate of convergence is measured by the absolute magnitude of $|dg/dc|$ evaluated near the solution. Values of $|dg/dc|$ approaching unity mean slow convergence. Thus, if the total concentration $\tilde{c}_M$ is very much larger than the equilibrium constant, the product $K\tilde{c}_M$ tends to infinity, $2/\sqrt{(8K\tilde{c}_M + 1)}$ tends to zero, and consequently $|dg/dc|$ approaches unity. Under these circumstances the SCB iterative method is predicted to be slow.

For example, at the total concentrations of the monomer equal to $\tilde{c}_M = 1/K$, $10/K$, $100/K$, $1000/K$, the derivative evaluated at equilibrium is $|dg/dc| = 0.3600$, 0.6694, 0.8724, 0.9567 respectively. The latter value means that the SCB algorithm will gain one significant digit in accuracy in approx. 52 iterations, because $0.9567^{52} \approx 0.1$. Thus if the concentrations at equilibrium were required with six-digit accuracy, more than 300 iterations would be needed. This prediction has been verified empirically (results not shown).

Example 2: momoner–dimer–tetramer equilibrium

It is shown below that the monomer–dimer–tetramer equilibrium cannot be solved by the SCB method [1]. The reason is explained theoretically, and an alternative method is proposed. The mass-balance equation (7) for the monomer–dimer–tetramer equilibrium $4M \overset{K_1}{\rightleftharpoons} 2D \overset{K_2}{\rightleftharpoons} T$ is rearranged into the form (8). The derivative is shown in eqn. (9). According to the SCB method [1], it is desired to find the solution iteratively as is shown in eqn. (10).

$$f(c_M) \equiv c_M + 2K_1 c_M^2 + 4K_1 K_2 c_M^4 - \tilde{c}_M = 0 \tag{7}$$

$$c_M = g(c_M) \equiv c_M \frac{\tilde{c}_M}{c_M + 2K_1 c_M^2 + 4K_1 K_2 c_M^4} \tag{8}$$

$$\frac{dg}{dc_M} = -\tilde{c}_M \frac{2K_1 + 12K_1 K_2 c_M^2}{(1 + 2K_1 c_M + 4K_1 K_2 c_M^3)^2} \tag{9}$$

$$c_{i+1} = c_i \frac{\tilde{c}_M}{c_i + 2K_1 c_i^2 + 4K_1 K_2 c_i^4};\ i = 0, 1, \ldots, m;\ c_0 = \tilde{c}_M \tag{10}$$

The key question is whether the derivative is greater or smaller than unity when evaluated at the correct solution $\hat{c}_M$. Although the analytical solution of a polynomial equation up to fourth degree always exists (Galois theorem), the analytical solution of the quartic equation (7) is quite complicated. Therefore we shall employ a graphical method to investigate the convergence properties of the fixed-point method.

The graphs in Figure 1 display the function g in the upper panel, and its derivative dg/dc in the lower panel. It is assumed that $K_1 = K_2 = 1$ in arbitrary units. The total concentration of the monomer is $\tilde{c}_M = 1$ (Figure 1A) or $\tilde{c}_M = 2$ (Figure 1B) in the same units.

By definition of the fixed-point method, the concentration of the monomer M at equilibrium is where the plot of function g intersects with a straight line with unit slope and zero intercept. Thus, at the total concentration $\tilde{c}_M = 1$, the equilibrium concentration is approximately $\hat{c}_M = 0.45$. The lower panel of Figure 1(A) shows that the derivative evaluated at this concentration is smaller than unity, $|dg/dc| = 0.87$. Therefore the SCB algorithm should converge, but not very rapidly. It can be predicted that the algorithm needs approx. 48 iterations to converge within three significant digits ($0.87^{48} = 0.001$).

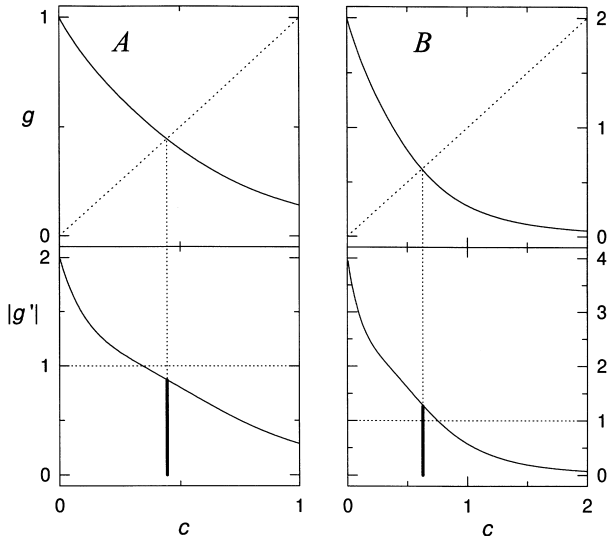

Figure 1 Convergence properties of the SCB algorithm [1] for the monomer–dimer–tetramer equilibrium $4M \overset{K_1}{\rightleftharpoons} 2D \overset{K_2}{\rightleftharpoons} T$

(**A**) total concentration $\tilde{c}_M = 1$ in arbitrary units; (**B**) total concentration $\tilde{c}_M = 2$. The equilibrium constants are $K_1 = K_2 = 1$. Upper panel, plot of function g defined by eqn. (8); lower panel, plot of the derivative $|dg/dc|$ defined by eqn. (9).

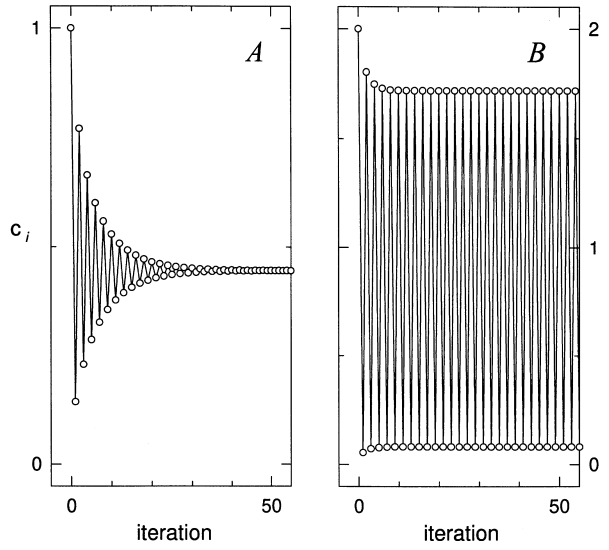

Figure 2 Sequence of iterations in the SCB algorithm [1] applied to the monomer–dimer–tetramer equilibrium $4M \overset{K_1}{\rightleftharpoons} 2D \overset{K_2}{\rightleftharpoons} T$

The iteration formula is defined by eqn. (10). (**A**) Total concentration $\tilde{c}_M = 1$ in arbitrary units; (**B**) total concentration $\tilde{c}_M = 2$. The equilibrium constants are $K_1 = K_2 = 1$.

On the other hand, at the total concentration $\tilde{c}_M = 2$, the equilibrium concentration is approximately $\hat{c}_M = 0.63$ (see the upper panel of Figure 1B). At this concentration the derivative is greater than unity, $|dg/dc| = 1.27$ (see the lower panel of Figure 1B). Therefore, according to the convergence theorem proved in the Appendix, the SCB method cannot converge. However, the derivative is smaller than unity in the first step, where c_M is estimated as $\tilde{c}_M$. Therefore, the very first iteration should be in the correct direction, toward lower values of c_M. Combining these two facts (the derivative is smaller than one in the first step, but larger than one near the solution), it can be predicted that the SCB algorithm must pass a point where $|dg/dc| = 1$. The value of $|dg/dc|$ exactly equal to unity represents neither convergence nor divergence, but instead infinite oscillations between two incorrect values.

Figure 2 compares the above predictions with facts. At $\tilde{c}_M = 1$ the SCB algorithm converged in approx. 50 iterations, while at $\tilde{c}_M = 2$ the algorithm fell into infinite oscillations after initially taking several convergent steps. Clearly, the SCB method [1] and methods derived from it [2,3] cannot be used to calculate the composition at equilibrium for self-associating biochemical systems.

The failure of the SCB method is remedied in the following way. Any fixed-point formula $x = g(x)$ can be modified by adding x to both sides and subsequently dividing both sides by two, which gives $x = h(x) = [x + g(x)]/2$. For the monomer–dimer–tetramer mixture, we obtain eqn. (11) and the corresponding derivative (12).

$$c_M = h(c_M) \equiv \frac{1}{2}\left[c_M + c_M \frac{\tilde{c}_M}{c_M + 2K_1 c_M^2 + 4K_1 K_2 c_M^4}\right] \tag{11}$$

$$\frac{dh}{dc_M} = \frac{1}{2} - \tilde{c}_M \frac{K_1 + 6K_1 K_2 c_M^2}{(1 + 2K_1 c_M + 4K_1 K_2 c_M^3)^2} \tag{12}$$

$$c_{i+1} = \frac{1}{2}\left[c_i + c_i \frac{\tilde{c}_M}{c_i + 2K_1 c_i^2 + 4K_1 K_2 c_i^4}\right] \tag{13}$$

When h and $|dh/dc|$ are plotted at different total concentrations of the monomer, the derivative $|dh/dc|$ is always smaller than unity when evaluated at the equilibrium concentration $\hat{c}_M$. For example at $\tilde{c}_M = 2$, the derivative at equilibrium ($\hat{c}_M = 0.63$) is $|dh/dc| = 0.13$ (see the lower panel in Figure 3A). Therefore near the solution the fixed-point equation (13) should gain approximately three significant digits in accuracy within three iterations ($0.13^3 < 0.001$). This prediction is confirmed in Figure 3(B).

Example 3: inhibition of dissociative enzymes

Inhibition of the HIV protease involves two component molecular species (the enzyme monomer M and the inhibitor I). It is cast here as a single-component problem, for which successful convergence can be mathematically guaranteed. The reaction mechanism consists of two steps, namely the monomer–dimer equilibrium $2M \overset{K_1}{\rightleftharpoons} M_2$ and the binding of an inhibitor to the enzyme dimer, $M_2 + I \overset{K_2}{\rightleftharpoons} M_2 I$. According to the SCB method, the mass-balance equations (14) and (15) are rearranged as is shown in (16) and (17).

$$f_M(c_M) \equiv c_M + 2K_1 c_M^2 + 2K_1 K_2 c_M^2 c_I - \tilde{c}_M = 0 \tag{14}$$

$$f_I(c_I) \equiv c_I + K_1 K_2 c_M^2 c_I - \tilde{c}_I = 0 \tag{15}$$

$$c_M = g_M(c_M) \equiv c_M \frac{\tilde{c}_M}{c_M + 2K_1 c_M^2 + 2K_1 K_2 c_M^2 c_I} \tag{16}$$

$$c_I = g_I(c_I) \equiv c_I \frac{\tilde{c}_I}{c_I + K_1 K_2 c_M^2 c_I} \tag{17}$$

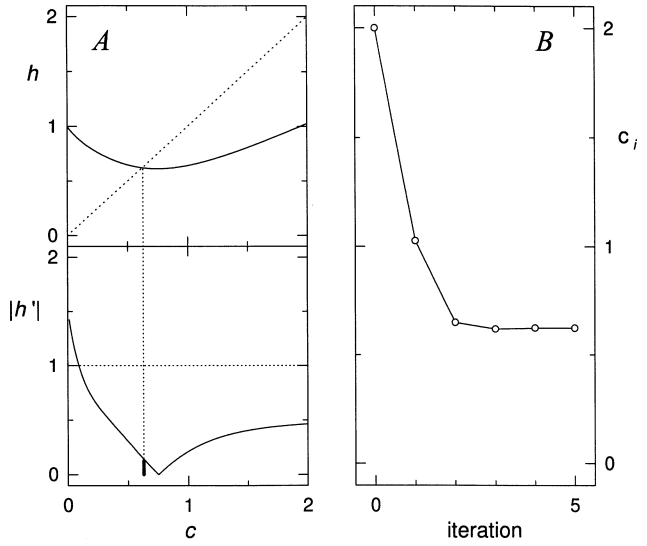

Figure 3 Convergence properties of a modified fixed-point algorithm [eqns. (11)–(13)] applied to the monomer–dimer–tetramer equilibrium $4M \underset{K_1}{\rightleftharpoons} 2D \underset{K_2}{\rightleftharpoons} T$ (A) and sequence of iterations defined by eqn. (13) (B)

(**A**) Upper panel, plot of function h defined by eqn. (11); lower panel, plot of the derivative $|dh/dc|$ defined by eqn. (12). (**B**) Total concentration $\tilde{c}_M = 2$, equilibrium constants $K_1 = K_2 = 1$ (compare with Figure 2B).

Convergence of any fixed-point algebraic method can be investigated only if it is cast as a single equation. Therefore the inhibitor mass balance was eliminated by substituting for c_I from eqn. (18) into the enzyme mass balance (14). Applying the graphical technique described above for the monomer–dimer–tetramer problem revealed that the resulting fixed-point formula had poor convergence properties. At some concentrations of the inhibitor and the enzyme, the concentration at equilibrium could not be computed because the algorithm oscillated indefinitely between two incorrect concentrations (results not shown). On the other hand, the recurrent formula based on function h defined in eqn. (19) converged safely in all tests.

$$c_I = \frac{\tilde{c}_I}{1 + K_1 K_2 c_M^2} \tag{18}$$

$$c_M = h(c_M) \equiv \frac{1}{2}\left[c_M + c_M \frac{\tilde{c}_M}{c_M + 2K_1 c_M^2 + 2K_1 K_2 c_M^2 \tilde{c}_I/(1 + K_1 K_2 c_M^2)} \right] \tag{19}$$

DISCUSSION

Often the biochemist is faced with the following question. Given the total or analytical concentrations of several interacting components, and given also the equilibrium constants for the formation of all molecular complexes, what are the concentrations of components and complexes at equilibrium? Except for the most simple equilibria, an answer can be obtained only by using a computer. Starting from a suitable initial estimate of the concentrations at equilibrium, the machine gradually refines the answer until, after enough cycles, it is obtained with the desired accuracy.

Sometimes the method of computation is designed so poorly that the correct answer is never obtained. For example, a succession of intermediate results can get progressively farther from the correct solution (divergence) instead of closer to it (convergence). In this paper we have encountered another kind of pathological computation: the machine produced an alternating series of two different and incorrect answers. These oscillations were observed when the SCB algorithm [1] was applied to the monomer–dimer–tetramer equilibrium, or to the inhibition of dissociative enzymes.

Despite failures for certain stoichiometries, the family of fixed-point algebraic methods [1,5] is attractively simple. Composition of complex biochemical mixtures at equilibrium can be computed even by using the most simple programmable calculator, or a desktop computer with a conventional spreadsheet program. Simple recurrent formulae have been used successfully to analyse mixtures of tightly bound inhibitors [6], or multiple equilibria arising in receptor–ligand displacement assays [7]. Therefore it was decided to subject the fixed-point algebraic methods to theoretical scrutiny, explain the occasional failures and, if possible, rectify them.

Theoretical analysis of the fixed-point method, based on the mean-value theorem of differential calculus (see the Appendix), can be undertaken in principle only for a function of one variable. Nothing can be said about the convergence of *ad hoc* multidimensional methods. Therefore the equilibrium problem should be cast as a single mass-balance equation whenever possible. In Example 3 above it has been shown that mixtures containing several components can be analysed in this way. For multidimensional equilibrium problems, which cannot be cast in terms of a single-component species, the present method in principle cannot offer any advantage.

The success or failure of a fixed-point formula $x = g(x)$ to solve iteratively the original algebraic equation $f(x) = 0$ (here a mass-balance equation) depends on the absolute magnitude of the derivative $|dg(x)/dx|$ near the correct solution. Unfortunately the original Storer and Cornish-Bowden method [1] often leads to derivatives greater than unity, especially when certain molecular complexes contain more than one subunit of the same component. In such cases, most typically for the simple monomer–dimer–tetramer equilibrium, oscillations may occur. The failure is remedied by transforming the equation $x = g(x)$ into the equivalent form $x = h(x) = [x + g(x)]/2$. The derivative $|dh(x)/dx|$ then becomes smaller than unity at the correct solution, so that the modified fixed-point method converges even for the monomer–dimer–tetramer equilibrium or for the inhibition of dissociating enzymes.

Thus, every iterative formula $x = g(x)$ proposed for the computation of multiple simultaneous biochemical equilibria should be scrutinized as follows. Evaluate the derivative $dg(x)/dx$ over the entire range of possible solutions, namely, with x spanning the interval between zero and the total or analytical concentration. If it appears that the derivative is greater than one in absolute magnitude over a significant portion of this interval, rearrange the fixed-point formula into a different form. The goal is to decrease the derivative below one over the widest possible domain of x.

In summary, fixed-point iterative methods for the computation of multiple biochemical equilibria are useful if they are applied discriminately. Trying to build around any particular fixed-point method a general-purpose system for the analysis of biochemical data [8] is ill-advised. A truly universal equilibrium algorithm must be employed for that purpose [9]. In addition, it must be kept in mind that the safer variant of the fixed-point method described here, preventing oscillations, might require more iterations in those special cases where oscillations are not a threat.

Fixed-point methods, far from being universally applicable to 'any stoichiometry', can be applied only to particular problems such as simultaneous acidobasic equilibria [5], complex mixtures of ATP and metal ions [1], or oligomerization equilibria examined here. By using a diagnostic method described in this paper, the convergence properties of a fixed-point algorithm can be investigated to see if it is applicable to the given type of simultaneous biochemical equilibria.

I thank Lorna M. Banks-Aaronson for useful discussions and continuing support.

REFERENCES

1 Storer, A. C. and Cornish-Bowden, A. (1976) Biochem. J. **159**, 1–5
2 Barshop, B. A., Wrenn, R. W. and Frieden, C. (1983) Anal. Biochem. **130**, 134–145
3 Zimmerle, C. T. and Frieden, C. (1989) Biochem. J. **258**, 381–387
4 Holzman, T. F., Kohlbrenner, W. E., Weig, D., Rittenhouse, J., Kempf, D. and Erickson, J. (1991) J. Biol. Chem. **266**, 19217–19220
5 Perrin, D. D. and Sayce, I. G. (1967) Talanta **14**, 833–842
6 Kuzmič, P., Ng, K.-Y. and Heath, T. D. (1992) Anal. Biochem. **200**, 68–73
7 Kuzmič, P., Moss, M. L., Kofron, J. L. and Rich, D. H. (1992) Anal. Biochem. **205**, 65–69
8 Frieden, C. (1994) Methods Enzymol. **240**, 311–322
9 Kuzmič, P. (1996) Anal. Biochem. **237**, 260–273

APPENDIX

Theorem 1: mean-value theorem

Let $f(x)$ be continuous and have continuous first derivatives in the internal $(x, x+\delta x)$. Then $f(x+\delta x)-f(x) = \delta x|\mathrm{d}f/\mathrm{d}x|_{x=\hat{x}}$, the partial derivative being evaluated at a suitable point $\hat{x}$ within the interval $(x, x+\delta x)$.

Theorem 2: convergence of a fixed-point method

Let s be a solution of the equation $x = g(x)$, and suppose that the function g has continuous first derivatives $\mathrm{d}g/\mathrm{d}x$ everywhere in some interval J containing s. Then if the first derivatives satisfy $|\mathrm{d}g(x)/\mathrm{d}x| \leqslant \alpha < 1$ everywhere in J, the iteration process defined by $x_{n+1} = g(x_n)$ converges for any x_0 from the interval J.

Proof

By the mean-value theorem of differential calculus there is an $\hat{x}$ between x and s such that $g(x)-g(s) = \mathrm{d}g/\mathrm{d}x|_{\hat{x}\in(s,x)}\,(x-s)$ for all x in J. Because $g(s) = s$ and $x_1 = g(x_0)$, $x_2 = g(x_1), \ldots, x_m = g(x_{m-1})$, we have

$$
\begin{aligned}
|x_m - s| &= |g(x_{m-1}) - g(s)| \\
&= |\mathrm{d}g/\mathrm{d}x|_{\hat{x}\in(s,x_{m-1})}\,|x_{m-1} - s| \\
&\leqslant \alpha_m |x_{m-1} - s| \\
&= \alpha_m |g(x_{m-2}) - g(s)| \\
&= \alpha_m |\mathrm{d}g/\mathrm{d}x|_{\hat{x}\in(s,x_{m-2})}\,|x_{m-2} - s| \\
&\leqslant \alpha_m \times \alpha_{m-1} |x_{m-2} - s| \\
\ldots &\leqslant \alpha_m \times \alpha_{m-1} \times \ldots \times \alpha_0 |x_0 - s|.
\end{aligned}
$$

Because $\alpha_i < 1$ for all i, we have $\alpha_m \times \alpha_{m-1} \times \ldots \times \alpha_0 \to 0$, and therefore $|x_m - s| \to 0$ (convergence) as $m \to \infty$.

Received 13 May 1997/1 July 1997; accepted 14 July 1997