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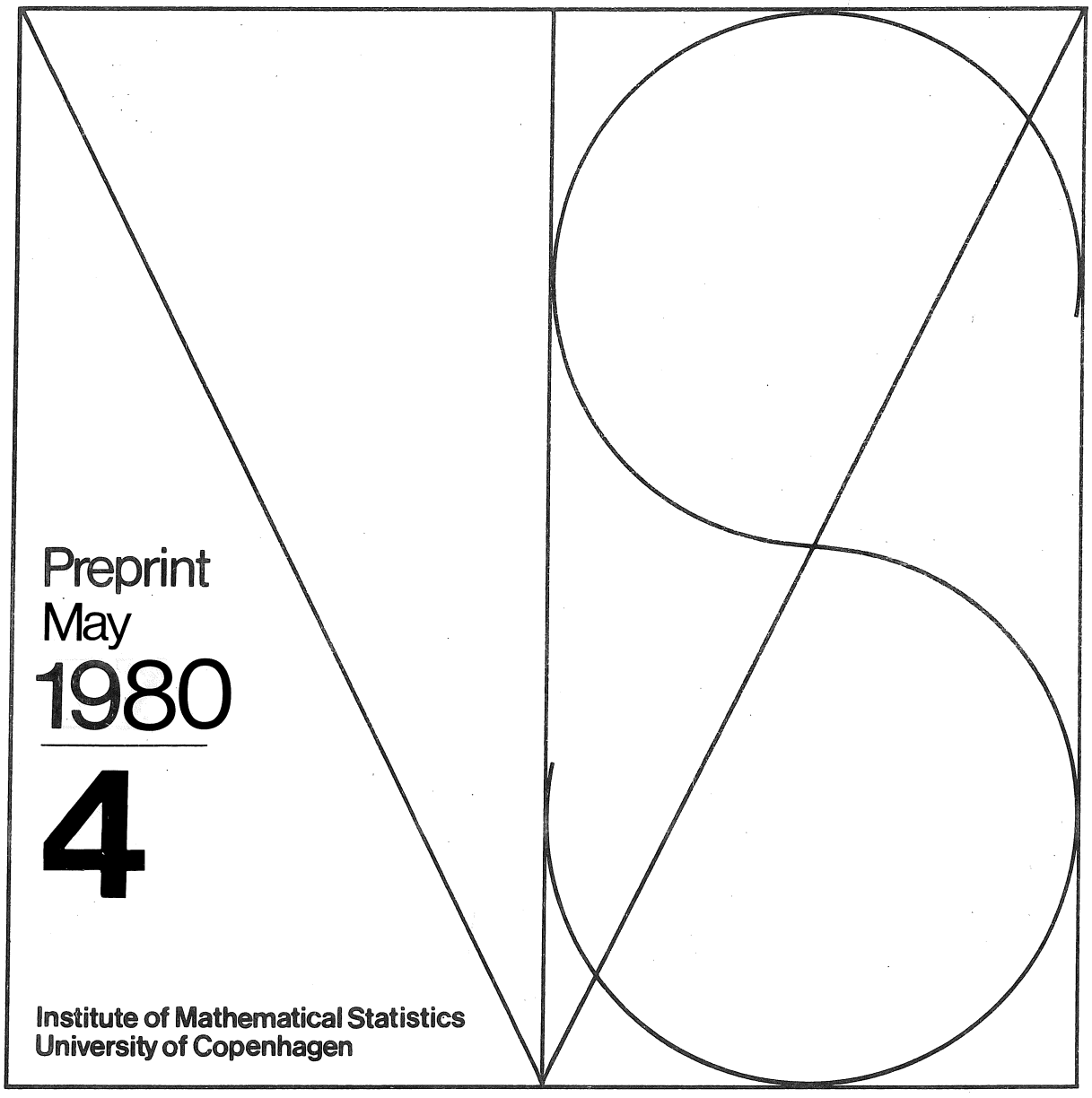
A Family of Models for the Elimination of Substrate in the Liver



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Abstract

A family of models describing the elimination of substrates from the blood by the liver is proposed. It is shown how it contains some previously proposed models for elimination in the liver, diffusion through the capillaries and absorption in the intestine, where the elimination is assumed to follow either first order or simple Michaelis-Menten kinetics.

Applications to allosteric reactions are suggested.

Running headline:

Models for elimination in the liver

1. Introduction

A model of the enzymatic elimination of substrates from the blood flowing through the liver has recently been proposed by Bass, Keiding, Winkler & Tygstrup (1976). It was assumed that the local elimination reaction in the hepatocytes follows Michaelis-Menten kinetics, and a mathematical model for the elimination kinetics of the whole liver was formulated. In the present paper we describe a family of models for cases where the local reaction in the hepatocytes follows other types of enzyme kinetics.

In the model by Bass et al. it was assumed that in the liver parallel and identical vascular passages (called sinusoids) are perfused with unidirectional blood flow carrying the substrates. The sinusoids are lined with cells (hepatocytes) in which the elimination (v') takes place according to a Michaelis-Menten relation at the local concentration (c) at each place along the sinusoid

$$v' = \frac{V'_{max}\, c}{K_m + c} \quad . \tag{1}$$

Here V'_{max} is the maximal elimination rate for the sinusoid and K_m the Michaelis-Menten affinity constant. The elimination creates a decreasing blood concentration from the inlet (c_i) to the outlet (c_o) of the sinusoid. It was shown that for the whole liver the relation between c_i, c_o and the blood flow rate F is given by

$$F\{(c_i - c_o) + K_m(\ln c_i - \ln c_o)\} = V_{max} \quad , \tag{2}$$

where V_{max} is the maximal elimination rate for the whole liver.

This relation can be reformulated as

$$(3) \qquad v = \frac{V_{max}\,\hat{c}}{K_m + \hat{c}} \;,\; \hat{c} = \frac{c_i - c_o}{\ln c_i - \ln c_o} \;,\; v = F(c_i - c_o)$$

see Keiding, Johansen, Winkler, Tønnesen & Tygstrup (1976).

Hence the relation between F, c_i, and c_o can be reformulated as a Michaelis-Menten reaction using the concentration $\hat{c}$, which can be interpreted as an average sinusoidal concentration.

Thus the model combines a physiological aspect of the liver perfusion with a local enzymatic reaction (1) and integrates these into a global relation for the whole liver (3) of the same type for a suitably chosen average value of c_i and c_o. An important consequence of this is that one can use the usual linear Lineweaver-Burk plot of $\frac{1}{v}$ against $\frac{1}{\hat{c}}$ as a graphical check of the model, since

$$\frac{1}{v} = \frac{1}{V_{max}} + \frac{K_m}{V_{max}} \frac{1}{\hat{c}} \;.$$

In the present study it is shown that the same qualitative conclusions hold for a whole family of different local reactions, each one giving a new type of average sinusoidal concentration to be considered.

The investigation was prompted by an attempt to replace the local reaction (1) with the Hill equation, which is used as an approximate description for allosteric reactions. This equation was used as a tentative explanation of some curved Lineweaver-Burk plots of $\frac{1}{v}$ against $\frac{1}{\hat{c}}$ by Vilstrup (1980).

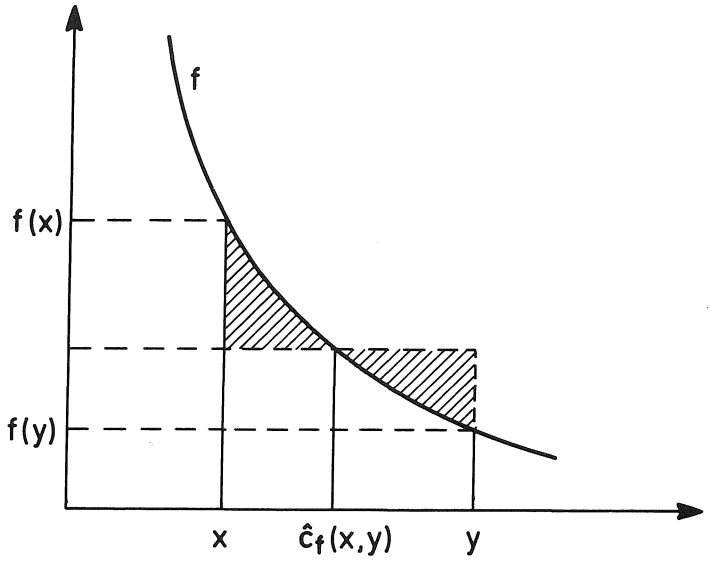
2. Main Result

Let $f(u)$ be a decreasing continuous function, defined for $u > 0$. For any $x < y$ we define the "f-average" of x and y by

$$\hat{c}_f = \hat{c}_f(x,y) = f^{-1}\left(\frac{1}{y-x}\int_x^y f(u)\,du\right) \tag{4}$$

where f^{-1} denotes the inverse function of f.

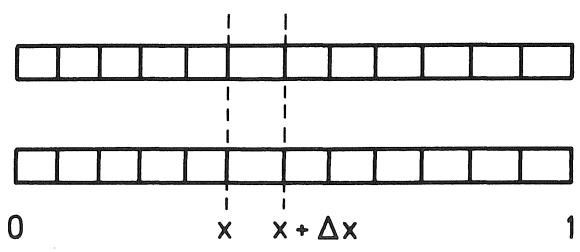
Figure 1



The definition of $\hat{c}_f$ is such that the two shaded domains have the same area.

As a model for the liver we consider a tube of unit length lined with hepatocytes and we let x denote the distance from the inlet to a point along the tube, $0 \leq x \leq 1$

Figure 2



Schematic model of a sinusoid lined with hepatocytes.

We assume that the reaction in the hepatocytes is governed by the relation

$$v' = \frac{V'_{max}}{1+f(\frac{c}{K_m})} \quad . \tag{5}$$

In case $f(u) \to 0$, $u \to \infty$, we see that V'_{max} has the interpretation as the maximal elimination rate for the hepatocyte.

Now the balance between input and output between the cross sections at x and $x + \Delta x$ gives

$$Fc(x) = Fc(x + \Delta x) + \frac{V_{max}\ \Delta x}{1+f(\frac{c(x)}{K_m})}$$

where again V_{max} is the maximal elimination rate for the liver in case $f(u) \to 0$, $u \to \infty$. The concentration $c(x)$ depends on x, and we have $c_i = c(0)$ and $c_o = c(1)$.

The above equation can be reformulated as

$$F\ \frac{dc(x)}{dx} = -\ \frac{V_{max}}{1+f(\frac{c(x)}{K_m})} \quad . \tag{6}$$

Now separate the variables c and x by multiplying by $(1 + f(\frac{c}{K_m}))dx$. Integration gives

$$F[(c_o - c_i) + K_m \int_{c_i/K_m}^{c_o/K_m} f(u)\,du] = -\ V_{max}$$

or

$$v\left(1+\frac{K_m}{c_i-c_o}\int_{c_o/K_m}^{c_i/K_m} f(u)\,du\right) = V_{max}$$

which can be written

$$(7) \qquad v=\frac{V_{max}}{1+f(\hat{c}_f)}\,,\ \hat{c}_f = f^{-1}\left(\frac{K_m}{c_i-c_o}\int_{c_o/K_m}^{c_i/K_m} f(u)\,du\right)\ .$$

Thus the global equation (7) is of the same form as the local equation (5), and the function f defines the proper average concentration to use.

3. Applications

We shall illustrate the above results by some special cases.

3.1. The first application is obviously the original model proposed by Bass et al. which we get for $f(u) = \frac{1}{u}$. In this case the local reaction (5) is just the Michaelis-Menten reaction (1) and the average concentration is

$$\hat{c} = \hat{c}_f(x,y) = [\frac{1}{y-x} \int_x^y \frac{1}{u}\, du]^{-1} = \frac{y-x}{\ln y - \ln x} .$$

3.2. The following first order reaction was used by Crone (1963) to describe the diffusion of substances from the capillaries into the tissue. The local reaction is

$$v' = PS'c$$

This equation can be brought into the formulation by considering the function $f(u) = \frac{1}{u} - 1$, which again gives the average

$$\hat{c}_f(x,y) = \frac{y-x}{\ln y - \ln x} = \hat{c}$$

Thus for the whole capillary the elimination due to diffusion is described by the equation

$$v = PS\,\hat{c} .$$

The coefficient PS has in this case the interpretation as a permeability coefficient times the surface area of the capillary (with the dimension being flow).

Note that this equation could be obtained as a limiting case from the relation (3) for $V_{max}/K_m = PS$ and $c_i/K_m \to 0$.

3.3. The model that started the present investigation was the Hill-equation

$$v' = \frac{V'_{max}\, c^n}{K_m^n + c^n}$$

which is used as a model to describe the sigmoid relation between elimination rate and concentration, due to allosteric enzyme reactions, Segel (1975).

If we define $f(u) = \frac{1}{u^n}$ and denote the corresponding avarage by $\hat{c}_n$, we get

$$\hat{c}_n = \hat{c}_n(x,y) = \left[\frac{1}{y-x} \int_x^y \frac{1}{u^n}\, du\right]^{-\frac{1}{n}}$$

$$= \left[\frac{x^{-n+1} - y^{-n+1}}{(y-x)\ (n-1)}\right]^{-\frac{1}{n}}$$

where the expression is interpreted as $\hat{c}$ if $n = 1$.

Thus for the Hill-equation we get the global relation

$$v = \frac{V_{max}\ \frac{(n-1)\,(c_i - c_o)}{c_o^{-n+1} - c_i^{-n+1}}}{K_m^n + \frac{(n-1)\,(c_i - c_o)}{c_o^{-n+1} - c_i^{-n+1}}} \tag{8}$$

or in the linearized form

$$\frac{1}{v} = \frac{1}{V_{max}} + \frac{K_m^n}{V_{max}} \frac{c_o^{-n+1} - c_i^{-n+1}}{(c_i - c_o)\,(n-1)} = \frac{1}{V_{max}} + \left(\frac{K_m}{\hat{c}_n}\right)^n \frac{1}{V_{max}} \tag{9}$$

which shows how the Lineweaver-Burk plot should be modified to accommodate for an allosteric effect.

One may note that if $n \to \infty$ then $\hat{c}_n(c_i, c_o) \to c_o$, but the reaction equation (8) has no limiting value of interest as $n \to \infty$, since

$$\frac{V_{max}(\hat{c}_n)^n}{K_m^n + (\hat{c}_n)^n} \underset{n\to\infty}{\to} \begin{cases} V_{max} & \text{if } c_o > K_m \\ 0 & \text{if } c_o < K_m \end{cases} .$$

Thus the model proposed by Rowland, Benet & Graham (1973)

$$v = \frac{V_{max}\ c_o}{K_m + c_o}$$

is not contained among the models considered here.

3.4. The elimination of a substrate in the hepatocytes may follow two parallel pathways. Ethanol for example is metabolized in the liver by at least two enzyme systems, alcoholdehydrogenase (with a low value of K_m) and the microsomal ethanol oxidizing system described by Lieber & DeCarli (1972) (with a high value of K_m). The latter reaction can be approximated by first order kinetics at low substrate concentrations compared with K_m with $K_D = V_{max}/K_m$, and the local reaction accordingly has the form

$$v' = \frac{V'_{max}\ c}{K_m + c} + K'_D\ c \tag{10}$$

For this to take the form (5) we define

$$f(u) = \frac{1}{1+r}\{\frac{1}{u} + \frac{1}{ur+1+r}\} - 1 ,$$

where $r = K'_D K_m / V'_{max}$.

One can in principle work out $\hat{c}_f$ and insert it into (10). One then obtains the global equation

$$v = \frac{V_{max}\ (1+r)}{K_m}\ \{\frac{1}{\hat{c}(c_i, c_o)} + \frac{1}{\hat{c}(rc_i + (1+r)K_m, rc_o + (1+r)K_m)}\}^{-1} \tag{11}$$

Note that in this case there is no simple linearization, like the Lineweaver-Burk plot, because K_m enters into the expression in a complicated way.

The model (10) has also been used to describe the uptake of amino-acids in the intestines, see Antonioli, Joseph & Robinson (1978), where the equation (11) can be found.

3.5. A model for inhibition by high substrate concentrations can be found in Dixon & Webb (1967) (p. 75), where the local reaction is of the form

$$v' = \frac{(ke)'}{1 + \frac{K_s}{c} + \frac{c}{K'_s}} .$$

This can be brought into the form (5), by

$$f(u) = \frac{1}{u} + Ru ,$$

where $R = K_s/K'_s$. Note that $f(u)$ is not monotone in u and hence that $\hat{c}_f$ can not be defined. We can, however, still perform the basic integration and find the global relation

$$v = \frac{ke}{1 + \frac{K_s}{\hat{c}} + \frac{\bar{c}}{K'_s}}$$

where $\bar{c} = (c_i + c_o)/2$. Note also that ke does not have the interpretation of a maximal capacity, since $f(u) \to \infty$, $u \to \infty$.

4. Time dependence of enzyme reactions in vitro

The same type of mathematics will solve the seemingly unrelated problem of the time dependence of the substrate concentration in a one compartment system with enzyme conversion of a substrate.

Let the volume be V and the basic enzyme reaction be given by

$$v' = \frac{V'_{max}}{1 + f(\frac{c}{K_m})}$$

The concentration c(t) will decrease with time from the initial value c(0) according to the differential equation

$$V \frac{dc}{dt} = - \frac{V_{max}}{1 + f(\frac{c(t)}{K_m})}$$

which can be solved in exactly the same way as above. If we let $v(t) = \frac{V(c(t) - c(0))}{t}$ denote the total amount metabolized per time unit in [0,t], then

$$v(t) = \frac{V_{max}}{1 + f(\hat{c}_f(t))} \quad , \quad \hat{c}_f(t) = \hat{c}_f(\frac{c(0)}{K_m}, \frac{c(t)}{K_m})$$

which describes c(t) implicitly as a function of t.

These equations have been developed by Henri (1902) for the Michaelis-Menten reaction, see also Bass & Bracken (1977) and Segel (1975) (p.54). For the two pathway model (10) the integrated equation has been given by Antonioli, Joseph & Robinson (1978).

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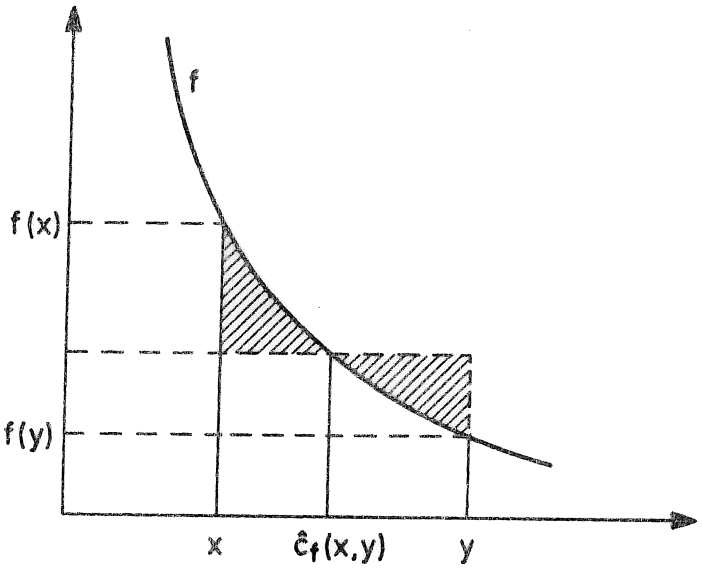
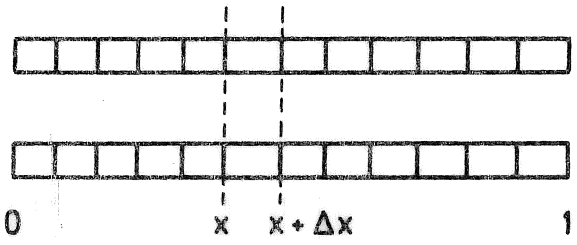

f
f(x)
f(y)
x
$\hat{c}_f(x,y)$
y


0
x
x + Δx
1

Legend for Figure 1

The definition of $\hat{c}_f$ is such that the two shaded domains have the same area.

Legend for Figure 2

Schematic model of a sinusoid lined with hepatocytes.