# Kinetics of Non-Equilibrium Metabolism-Coupled Passive Transport in Biosystems

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**Abstract**. Expressions for time course of solute concentration in an arbitrary compartment of a biosystem were derived using simplifying assumptions of unidirectional transport and first order metabolism kinetics. The coefficients of the resulting exponential-summation function comprise, in addition to the volumes and the connecting areas of individual compartments, the rate parameters of the processes mentioned. The equations presented were verified using results obtained in drug potency testing.

**Key words**: Biokinetics — Passive transport — Hydrophobicity — Structure-activity relationship — Metabolism-coupled transport

## Introduction

One of the problems concerning the kinetics of drug activity is the time-dependent concentration of the effector in the receptor region. Providing that only a negligible fraction of the total drug amount added to a biosystem is bound to the receptors, the distribution of the drug molecules can be treated separately from their interactions with the receptor sites (Baláž et al. 1985). So far attempts to solve this task have been made especially in the field of drug design, transport through membrane lipid bilayers (Penniston et al. 1969; Kubinyi 1979; Cooper et al. 1981; Baláž et al. 1984; Baláž and Šturdík 1984) and also the first order elimination (Dearden and Townend 1978; Kubinyi 1979; Aarons et al. 1982; Baláž and Šturdík 1985) being considered as major steps determining the fate of drugs in the system. Differential equations derived to describe the above processes had to be solved numerically since reversible transport was involved. However, for sufficiently large biosystems and/or when the rates of transport and metabolism are comparable, undirectional transport seems to be a good

representation of the in vivo situation. Thanks to this approximation the corresponding differential equations are completely integrable. This communication is aimed to present the explicit expressions for the solute concentration in arbitrary compartment, the cellular structure of biosystems being also considered. Under the cellular structure periodical alterations of compartments with identical properties are meant. In this context, an eucaryotic cell may also have cellular structure since it is subdivided by the endoplasmic reticulum and membranes of subcellular organelles into a series of compartments.

## Methods

An exact mathematical description of the solute distribution in biosystems would require the use of the 2nd Fick law for each aqueous and lipidic phase of the system, taking into account their inhomogeneity (interfacial diffusion layers more ordered than the bulks) as well as different solvation of substances in individual phases (discontinuous concentration gradients at the interfaces). Diffusion proceeds much more rapidly in the bulks than in the diffusion layers, the equilibrium being attained within 0.1 s under the real in vivo conditions (Baláž et al. 1984; Baláž and Šturdik 1984).

To simplify the situation we shall assume instantaneous diffusion in the bulks which seems quite plausible with respect to most experimental procedures in membrane research. In addition, the practically homogeneous composition of the bulks allows to use a common description for the reaction kinetics. There is quite a lot of reactants in real biosystems which are either present in sufficiently high concentrations or buffered, so that their changes in the course of the reaction can be neglected. Thus, the kinetics of metabolism in the $i$-th compartment is characterized by a global rate constant $k_i$:

$$k_i = \sum_{j=1}^{N} k_j c_j \tag{1}$$

where $k_j$ is the rate constant for the $j$-th reaction, the $j$-th reactant is present in concentration $c_j$, $N$ is the total number of reactants in the $i$-th compartment.

Transport through the interfaces with the diffusion layers can be characterized (Penniston et al. 1969) by the transport rate parameters $l$ ($l_1$ — direction from water to membrane, $l_2$ — backwards).

Under the above assumptions, the kinetics of transport coupled with chemical reactions in an $N$-compartment system (Fig. 1) is described by

$$-\dot{c} = Bc \tag{2}$$

where $c$ and $\dot{c}$ are the vectors of concentrations in the individual compartments and their time derivatives, respectively, the matrix $B$ ($N \times N$) has elements: $b_{i,i} = A_i l_x / V_i + k_i$ ($i = 1, 2, \ldots N$; $V_i$ is the volume of the $i$-th phase; $A_i$ is the contact area between the $i$-th and the $(i + 1)$-th compartments, $A_N = 0$; for the values of $x$ see table 1) and $b_{i+1,i} = A_i l_x / V_{i+1}$ ($i = 1, 2, \ldots N - 1$). At time $t = 0$ the solute ($n$ moles) is present in the 1st compartment only. The equation (2) was solved by standard methods (Benson 1960; Wolf et al. 1977).

The constants in empirical equations (10) and (12) (Table 3) were optimalized by non-linear regression analysis (Fletcher and Powell 1963). The number of constants used to calculate statistical parameters also involved the nonoptimalized values, the constant $E$ from equation (12) was taken once only.

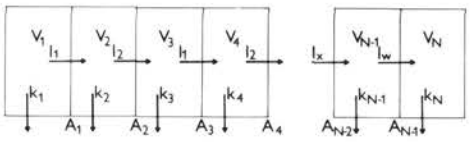


**Fig. 1.** Schematical representation of the $N$-compartment model system. $V$ — volumes of individual compartments, $A$ — interfacial areas, $l$ — transport rate parameters in direction water-lipid and vice versa (subscripts 1 and 2, respectively), $k$ — reaction rate constants.

## Results

There are two types of solution to equation (2) depending on whether the biosystem in question is cellular (i.e. composed of periodically alternating compartments with identical properties) or not. For the latter case, the time dependence of concentration ($c_m$) in the $m$-th compartment is given by

$$c_m = n\, l_1^y l_2^z \prod_{i=1}^{m-1} A_i \prod_{i=1}^{m} V_i^{-1} \sum_{j=1}^{m} \exp(-\lambda_j t) / \prod_{\substack{n=1 \\ n \neq j}}^{m} (\lambda_n - \lambda_j) \tag{3}$$

where

$$\lambda_i = b_{i,i} = A_i l_x / V_i + k_i$$

The values of $x$, $y$, $z$ are specified in Table 1.

**Table 1.** Symbol explanations

| $m, i, N$ | $w$ | $x$ | $y$ | $z$ |
|---|---|---|---|---|
| even | 1 | 2 | $m/2$ | $(m-2)/2$ |
| odd | 2 | 1 | $(m-1)/2$ | $(m-1)/2$ |

When certain compartments have identical properties the corresponding diagonal elements (i.e. eigenvalues in this case) of the matrix $B$ are also equal and, consequently, equation (2) is invalid. This phenomenon might not only be observable in tissues of higher organisms but also in eucaryotic cells, which are subdivided into a set of compartments by the endoplasmic reticulum and other intracellular membranes. Although the shapes of these compartments are less regular than those of the cells in tissues, identical properties may be quite frequent. When the cellular periodicity starts with the $M$-th compartment (which is obviously of lipidic nature and, consequently, $M$ is even), the diagonal elements $\lambda_M$ to $\lambda_N$ of the matrix $B$ can be written as follows:

$$A_M l_2/V_M + k_M = A_{M+2} l_2/V_{M+2} + k_{M+2} = \ldots A_{N+1-w} l_2/V_{N+1-w} + k_{N+1-w} \quad (4)$$

$$A_{M+1} l_1/V_{M+1} + k_{M+1} = A_{M+3} l_1/V_{M+3} + k_{M+3} = \ldots A_{N+1-x} l_1/V_{N+1-x} + k_{N+1-x} \quad (5)$$

The values of $w$, $x$ are summarized in Table 1. Under the above conditions, the time dependence of the concentration in the first $(M + 1)$ compartments is given by equation (3), and equation (6) holds for that of the $(M + m)$-th compartment:

$$c_{M+m} = E_{M+m}\left(\sum_{i=1}^{M+1} a_{i,M+m} e^{-\lambda_i t} + e^{-\lambda_M t} \sum_{i=1}^{y} a_{M+2i,M+m} t^i + e^{-\lambda_{M+1} t} \sum_{i=1}^{z} a_{M+2i+1,M+m} t^i\right) \quad (6)$$

where

$$E_{M+m} = (n/V_{M+2-x}) l_1^{(M+3)/2+z-w} l_2^{(M+3)/2+y-x} (A_M/V_M)^{y+1-x} (A_{M+1}/V_{M+1})^{z+1-w} \prod_{i=1}^{M+1} (A_i/V_i)$$

The coefficients $a$ are given by the recurrent formulae:

$$a_{i,M+m} = a_{i,M+m-1}/(\lambda_{M+2-x} - \lambda_i);\ i = 1, 2, \ldots (M-1)$$

$$a_{M+2i+4-x,M+m} = a_{M+2i+2-x,M+m-1}/(i+1);\ i = 0, 1, \ldots (y-1)$$

$$a_{M+m-1,M+m} = a_{M+m-1,M+m-1}/(\lambda_{M+2-x} - \lambda_{M+2-w});$$

$$a_{M+2i+2-w,M+m} = (a_{M+2i+2-w,M+m-1} - (i+1) a_{M+2i+4-w,M+m})/(\lambda_{M+2-w} - \lambda_{M+2-x});\ i = 0, 1, \ldots (z-1)$$

$$a_{M+2-x,M+m} = -\sum_{\substack{i=1 \\ i \neq M+2-x}}^{M+1} a_{i,M+m}$$

The expression for concentration in an arbitrary compartment can thus successively be derived starting with the solution to equation (2) for the first compartment:

$$c_1 = (n/V_1) e^{-\lambda_1 t} \quad (7)$$

and setting $\prod_{i=m}^{p} = 1$ and $\sum_{i=m}^{p} = 0$ for $m > p$.

To compare out results with biological reality we shall use data about effects of xenobiotics on biosystems. Our considerations were based on the idea that

under appropriate conditions the biological activity of a compound may monitor the concentration in the receptor region (Baláž et al. 1985). To avoid the difficult determinations of all the parameters $l$, $k$, $V$, $A$ in individual compartments we shall convert them, in accordance with the current practice in the field of drug design, into exactly measurable physicochemical properties, which can, in turn, be confronted with both the bioactivity indices and our results. The transport rate parameters have been shown to depend on the partition coefficient $P$ (Zwolinski et al. 1949):

$$l_1 = \alpha P/(\beta P + 1) \tag{8}$$

$$l_2 = \alpha/(\beta P + 1) \tag{9}$$

where $\alpha = D_L/h_L$, $\beta = D_L h_A/D_A h_L$, $D$ is the diffusion coefficient in the aqueous (A) and lipid (L) diffusion layers with and effective thickness $h$. Since values of $\alpha$, $\beta$ for actual biosystems are not available we could use values obtained with organic solvent-water model systems since there is a physical resemblance between solvent-water and membrane-water interfaces. The values of $\alpha$, $\beta$ in model systems are independent of the solute structure even if the permeants are not members of a congeneric series, if they are partially or completely ionized, or form ion pairs (Kubinyi 1978; Van de Waterbeemd et al. 1981). The quantities $\alpha$ and $\beta$ thus become properties of the model system characterizing the quality of the diffusion layers on both sides of its interface. As for certain congeneric series, the assumption of a constant rate for the metabolic processes is quite plausible, the partition coefficient $P$ can play the role of a "referent" physicochemical property, and we can try to compare the shape of the experimental dependence of bioactivity indices on $P$ with the respective relationship resulting from our description of the solute disposition in biosystems. The time development of such a relationship is shown in Fig. 2. The curves are bilinear

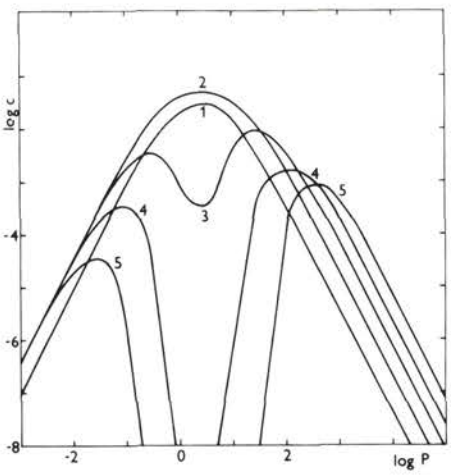


**Fig. 2.** The dependences of concentration $c$ in the 5th compartment on the partition coefficient $P$ after 3.2 (1), 10 (2), 32 (3), 100 (4) and 320 (5) hours. Model specification: $V_1 = 1\,dm^3$, $V_2 = V_3 = 0.5\,dm^3$, $V_4 = V_5 = 0.3\,dm^3$; $A_1 = A_2 \ldots A_5 = 1\,dm^2$; $k_1 = k_2 = k_4 = 0$; $k_3 = k_5 = 1\,h^{-1}$, $l_1$ and $l_2$ obey equations (8), (9) with $\alpha = 0.286\,dmh^{-1}$; $\beta = 0.245$ (Kubinyi 1978), $n = 1\,mol\,dm^{-3}$.

(i.e. composed of two linear parts connected by a curved portion) in the early stages of the distribution, and become distorted later in a characteristic manner (Dearden and Townend 1978). They have two maxima separated by a minimum and can be considered as consisting of four linear parts with curved joining portions, the leftmost and rightmost linears retaining the slopes of the short-term bilinear curves. The slopes are integer and their values are typical for individual compartments (Fig. 3, Table 2). This fact may significantly promote the elucidation of mechanisms of action of drugs since the shape of the bioactivity-lipophilicity profile can, under certain conditions, indicate the nature and the number of the receptor compartment.

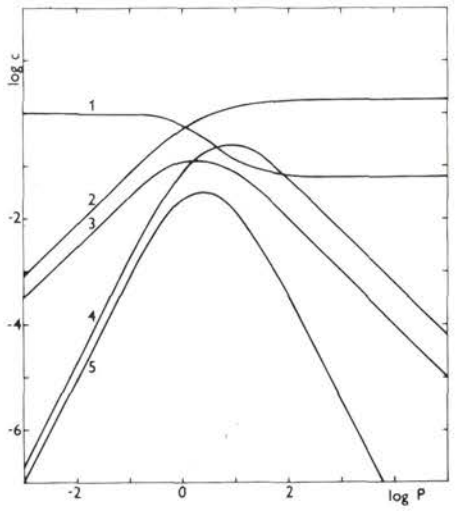


**Fig. 3.** The concentration-lipophilicity profiles in the first 5 compartments after 3.2 hours. For model specification see Fig. 2, the numbers of the compartments are indicated at the corresponding lines.

**Table 2.** The integer values of the slopes in the linear parts for the bilinear concentration-lipophilicity profiles in the $n$-th compartment and the corresponding values of the constants $A$ and $B_1$ in equation (10) ($N = 1$).

| Nature of the $n$-th compartment | Slopes | | $A$ | $B_1$ |
|---|---|---|---|---|
| aqueous | $(n-1)/2$ | $(1-n)/2$ | $(n-1)/2$ | $(1-n)$ |
| lipidic | $n/2$ | $(2-n)/2$ | $n/2$ | $(1-n)$ |

Fig. 4 illustrates the influence of metabolism rate (constant within the series studied) on the concentration — lipophilicity relationship. The shape of the curves remains generally unchanged although some minor deviations are observable.

In order to compare quantitatively our results with the biological reality it is indispensable to find and empirical formula describing both types of curves with a sufficient accuracy. For this purpose equation (10) proved to be useful:

$$\log(c/c_0) = A \log P + \sum_{i=1}^{N} B_i \log(C_i' P + 1) + D' \qquad (10)$$

where $c_0$ is the initial concentration in the entry compartment, $A$, $B$, $N$ are integer and $C_i'$, $D'$ non-integer constants. Their values depend on the parameters of the distribution system (volumes of individual phases, connecting areas, $\alpha$, $\beta$)

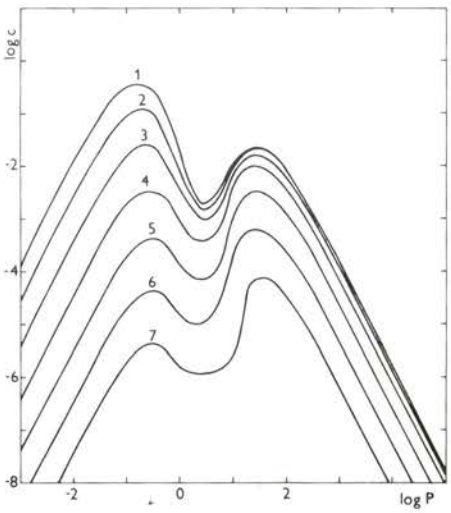


**Fig. 4.** The dependences of concentration $c$ in the 5th compartment on the partition coefficient $P$ after 32 hours. For model specification see Fig. 2., except: $k_3 = k_5 = 0.01$ (1), 0.1 (2), 0.32 (3), 1 (4), 3.2 (5), 10 (6) and 32 (7) $h^{-1}$.

from equations (8) and (9) and time. $N$ is 2 and 1 in the short-term bilinear curves for the 1st compartment and for those with higher numbers, respectively, and $N = 3$ for the curves with two maxima. $A$ and $B_i$ determine the magnitude of slopes in the linear parts, their values for the bilinear curves are given in Table 2. The constants $C_i'$ are coupled with the position of the curvatures. The relation between the individual constants in equation (10) and the curve parameters can be seen in Fig. 5. Equation (10) was fitted to data presented in Figs. 2—4 by non-linear regression analysis (Fletcher and Powell 1963), the magnitudes of individual constants are given in Tables 3 and 4. The values of statistical parameters indicate that an almost perfect fit was obtained.

To adapt equation (10) to biological reality the model partition coefficient $P$ has to be substituted by the membrane-water partition coefficient $P_M$ via equation (11) (Collander 1951)

$$P_M = \text{const } P^E \qquad (11)$$

This introduces an additional constant $E$ into equation (10). Assuming a one-step and reversible drug-receptor interaction with the same affinity constant for all the drugs in question, equations (10) and (11) can be rewritten for isotoxic concentrations $c_x$ (Baláž et al. 1985):

$$\log(1/c_x) = A \log P^E + \sum_{i=1}^{N} B_i \log(C_i P^E + 1) + D \qquad (12)$$

The empirical equation allows a comparison of dependences obtained in our experiments (Figs. 2—4) with results of drug potency testing.

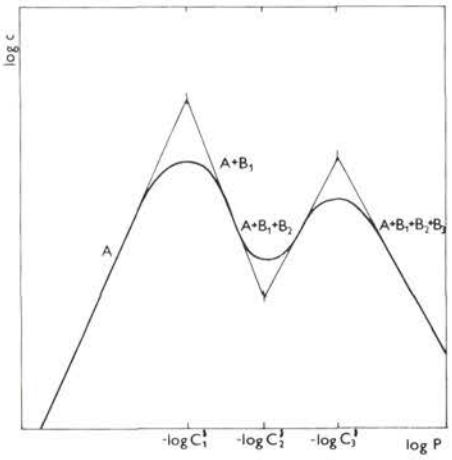


**Fig. 5.** The relation between the individual constants in equation (10) and the curve parameters. Expressions at the curve describe the slopes in the corresponding linear parts.

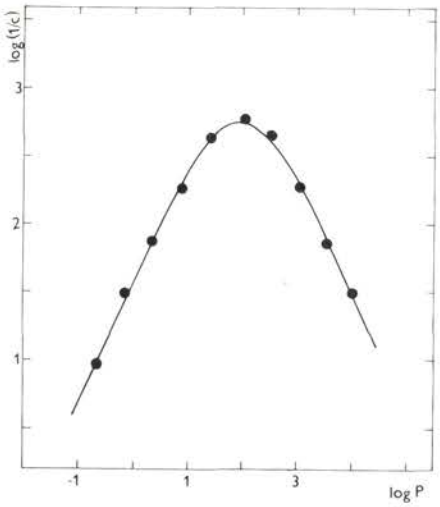


**Fig. 6.** The neurotoxicity-lipophilicity profile of homologous *n*-alcohols (Kubinyi 1979). The line corresponds to empirical equation given in Table 5.

**Table 3.** The constants in equation (10) with $N = 1$ describing the dependences given in Figs. 2 and 3. $A$ and $B_1$ were non-optimalized. Statistical parameters: 17 points in all cases (for $\log P = -3$ to 5 with the step 0.5), the lowest values of the correlation coefficient and of the $F$-test were $r = 0.998$ and $F = 298$, the highest value of the standard deviation $s = 0.145$.

| Fig. | Curve | $A$ | $B_1$ | $C_1'$ | $D'$ |
|---|---|---|---|---|---|
| 2 | 1 | 2 | −4 | $3.802 \times 10^{-1}$ | −1.080 |
| 2 | 2 | 2 | −4 | $3.311 \times 10^{-1}$ | $-9.032 \times 10^{-1}$ |
| 3 | 2 | 1 | −1 | $4.169 \times 10^{-1}$ | $-1.387 \times 10^{-1}$ |
| 3 | 3 | 1 | −2 | $4.467 \times 10^{-1}$ | $-5.892 \times 10^{-1}$ |
| 3 | 4 | 2 | −3 | $3.236 \times 10^{-1}$ | $-7.447 \times 10^{-1}$ |
| 3 | 5 | 2 | −4 | $3.802 \times 10^{-1}$ | −1.080 |

**Table 4.** Optimalized values of constants in equation (10) describing the dependences given in Figs. 2—4. Superscript a indicates non-optimalized values. Statistical parameters: 17 points in all cases, the lowest $r = 0.999$ and $F = 302$, the highest $s = 0.131$ (for symbols see text to Table 3).

| Fig. | Curve | $A^a$ | $B_1$ | $B_2$ | $B_3$ | $C'_1$ | $C'_2$ | $C'_3$ | $D'$ |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 3 | 2 | −3.790 | 4.942 | −4.153 | 4.667 | 0.309 | $3.890 \times 10^{-2}$ | −0.945 |
| 2 | 4 | 2 | −10.24 | 16.64 | −7.402 | 6.310 | 0.562 | $1.622 \times 10^{-2}$ | −2.976 |
| 2 | 5 | 2 | −10.26 | 18.06 | −8.800 | 69.18 | 0.398 | $5.754 \times 10^{-3}$ | 2.936 |
| 3 | 1 | 0 | $-1^a$ | $1^a$ | — | 1.995 | 0.032 | — | 0.213 |
| 4 | 1 | 2 | −5.281 | 5.282 | −3.021 | 5.495 | 0.389 | $2.884 \times 10^{-2}$ | 1.794 |
| 4 | 2 | 2 | −4.230 | 4.473 | −3.240 | 9.550 | 0.324 | $3.020 \times 10^{-2}$ | 1.512 |
| 4 | 3 | 2 | −3.731 | 4.422 | −3.695 | 6.166 | 0.275 | $3.311 \times 10^{-2}$ | 0.154 |
| 4 | 4 | 2 | −3.790 | 4.942 | −4.153 | 4.677 | 0.309 | $3.890 \times 10^{-2}$ | −0.945 |
| 4 | 5 | 2 | −3.645 | 5.590 | −4.955 | 4.266 | 0.295 | $4.169 \times 10^{-2}$ | −2.028 |
| 4 | 6 | 2 | −3.267 | 5.803 | −5.540 | 5.012 | 0.316 | $3.981 \times 10^{-2}$ | −2.888 |
| 4 | 7 | 2 | −3.186 | 6.861 | −6.682 | 5.495 | 0.144 | $3.311 \times 10^{-2}$ | −3.554 |

The first two examples were taken from an excellent paper by Kubinyi (1979). In Fig. 6, neurotoxicity of homologous *n*-alcohols in rats (expressed in terms of doses causing a certain degree of ataxia) was plotted against lipophilicity. The same relation for hemolytic activity of $\alpha$-monoglycerides is given in Fig. 7, curve 1 representing a 2 % ethanolic solution and curve 2 an aqueous solution. The lines correspond to empirical equations summarized in Table 5. As follows from the integer values of the coefficients $A$ and $B_1$ (also see Table 2), it can be inferred on the basis of the model used that the receptor compartment is of aqueous nature and it represent the third phase when counted from the site of application. Kubinyi (1979) suggested micelle formation as a possible explanation of a decrease in activity of higher homologs in aqueous solution as compared with those in ethanolic solution. In our context, however, it is the effect of the ethanol on the erythrocyte membrane rather than a break-up of micelles that seems to be a more plausible explanation for the observation. This hypothesis is especially supported by the fact that the coefficients $A$ and $B_1$ have the values 1 and $-2$, respectively and $E$ changes in both cases (Table 5). Kubinyi fitted the data with his bilinear equation allowing to adopt continuous values for the coefficients $A$ and $B_1$ with fixed $E = 1$. Our statistical parameters are comparable with those of Kubinyi as for the correlation coefficient; standard deviation and the Fischer test, however, have somewhat worse values. This is due to a higher number of coefficients included in our empirical equation. They were all used to calculate the statistical parameters neglecting the fact that some of them ($A$, $B_1$) have fixed values and are not optimalized.

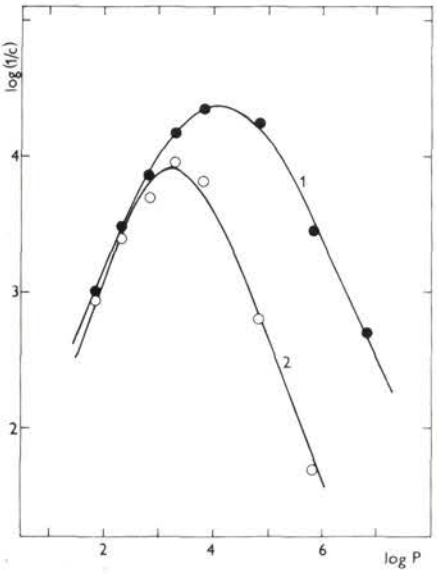


**Fig. 7.** The dependence on lipophilicity of hemolytic activity in a series of $\alpha$-monoglycerides in 2 % ethanolic (curve 1, full circles) and in aqueous solution (curve 2, open circles). The lines correspond to equations summarized in Table 5.

**Table 5.** Optimalized values of constants in equation (12) describing the bioactivity-lipophilicity data from literature given in Figs. 6—8. For meaning of the statistical parameters, see text to Table 4.

| Fig. | Curve | $A$ | $B_1$ | $B_2$ | $C_1$ | $C_2$ | $D$ | $E$ | $n$ | $r$ | $s$ | $F$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | — | 1[b] | −2[b] | — | $1.759 \times 10^{-2}$ | — | 1.606 | 0.904 | 10 | 0.998 | 0.109 | 21.9 |
| 7 | 1 | 1[b] | −2[b] | — | $2.768 \times 10^{-4}$ | — | 1.457 | 0.864 | 8 | 0.998 | 0.056 | 68.1 |
| 7 | 2 | 1[b] | −2[b] | — | $3.689 \times 10^{-4}$ | — | 1.079 | 1.054 | 7 | 0.997 | 0.096 | 30.4 |
| 8[a] | 1 | — | 1.784 | −1.534 | $3.565 \times 10^{-3}$ | $6.274 \times 10^{-4}$ | 7.339 | 1.017 | 8 | 0.981 | 0.204 | 3.25 |
| 8[a] | 2 | — | 5.015 | −4.888 | $6.257 \times 10^{-4}$ | $1.800 \times 10^{-4}$ | 6.475 | 1.125 | 8 | 0.931 | 0.691 | 0.82 |
| 8[a] | 3 | — | 9.526 | −8.852 | $4.971 \times 10^{-4}$ | $2.131 \times 10^{-4}$ | 5.757 | 1.087 | 8 | 0.909 | 1.066 | 0.61 |

[a] $10^{\Sigma\pi}$ is used instead of $P$, $\pi$ being a substituent lipophilicity constant (Hansch and Leo 1979)
[b] non-optimalized values

In Fig. 8, the analgesic activity of N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides in rats ($c$ is $ED_{50}$ in mol/kg) at various times (Van Bever et al. 1976) was plotted against lipophilicity represented by the sum of $\pi$-constants for the changing substituents (Hansch and Leo 1979). Five derivatives with $R_1 = CH_3$ and $R_3 = H$ or $COCH_2CH_3$ (numbering according to the original paper) were not taken for the correlation. The lines correspond to the empirical equations given in Table 5. Although statistical evaluation gave not very good results, the example is worth of being mentioned since it illustrates the time development of the bioactivity — lipophilicity profile which agreed with our model (also see Fig. 2).

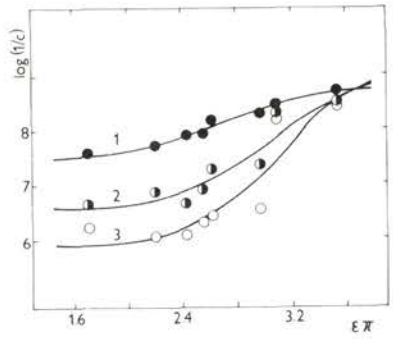


**Fig. 8.** Analgesic activity of N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides in rats, 2 (curve 1, full circles), 4 (curve 2, half-open circles) and 6 hours (curve 3, open circles) after i.v. injection (Van Bever et al. 1976) vs. lipophilicity expressed as the sum of $\pi$-constants of the changing substituents (Hansch and Leo 1979).

The presented quantitative comparison of biological data with our model suggest that equations (3) and (6) possibly describe the distribution kinetics of low-molecular solutes in biosystems.

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