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Frequency Response Method in Pharmacokinetics

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The paper presents the demonstration of applicability of the frequency response method in a bioavailability study. The frequency response method, common in system engineering, is based on an approximation of the frequency response of a linear dynamic system, calculated from input–output measurements, by a frequency model of the system transfer function in the frequency domain. In general, the influence of the system structure on the form of the system frequency response is much more distinct than on the form of the system output. This is of great advantage in modeling the system frequency response instead of the system output, commonly used in pharmacokinetics. After a brief theoretical section, the method is demonstrated on the estimation of the rate and extent of gentamicin bioavailability after intratracheal administration to guinea pigs. The optimal frequency model of the system describing the gentamicin pathway into the systemic circulation and point estimates of its parameters were selected by the approximation of the system frequency response in the frequency domain, using a noniterative algorithm. Two similar estimates of the system weighting function were independently obtained: the weighting function of the selected frequency model and the weighting function estimated by the numerical deconvolution procedure. Neither of the estimates of the weighting function does decrease monotonously after the maximum of about 2.2–2.5 unit of dose · hr^{-1} recorded approximately 0.1 hr after drug administration. Both estimates show a marked additional peak approximately at 0.3 hr after administration and possible peaks in the further time period. We hypothesized that the loop found in the frequency response calculated and in the selected optimal frequency model, the high-order of this model, and several peaks identified in the estimates of the system weighting function indicated the complexity of the system and the presence of time delays. Three estimates of the extent of gentamicin intratracheal bioavailability obtained by the three different ways: directly from the calculated frequency response, calculated using the selected frequency model, and by the deconvolution method were 0.950, 0.934, and 0.907 respectively. Thus the conclusion can be made that gentamicin injected intratracheally to guinea pigs is almost completely available.

KEY WORDS: linear dynamic system; frequency response; frequency response method; weighting function; bioavailability; gentamicin.

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INTRODUCTION

System modeling is usually done in the time domain, especially for pharmacokinetic purposes. Frequency domain methods are complementary to these procedures. The frequency response method is based on an approximation of a frequency response of a linear dynamic system measured or calculated from the system input–output measurements by a model of the system transfer function in the form of a ratio of polynomials in the complex domain (1). In spite of its positive features used to advantage, e.g., in system engineering or in some medical fields (2,3,4), the method is not commonly applied to pharmacokinetics. The frequency response method was introduced into pharmacokinetics several years ago (5,6,7). The utilization of the frequency response method is limited to the identification of pharmacokinetic models of linear systems consisting of subsystems without time delays, which are connected in serial (5). The frequency response method presented in our paper does not have such a limitation, and so it can be used for modeling any linear pharmacokinetic system consisting of several subsystems arranged in serial and/or parallel fashion, with or without time delays. The intent of our communication is to provide a methodological addition to previous papers (5,6,7) and to demonstrate the applicability of the frequency response method in a bioavailability study, using our own software CXT (CompleX Tools for Linear Dynamic System Analysis), written in TURBO PASCAL for a personal computer. The example employed was that of gentamicin bioavailability assessment after intratracheal administration to guinea pigs.

THEORETICAL

Behaviour of a system with respect to a deterministic input signal is dependent on the static and dynamic properties of the system.

If the harmonic signal

$$C_{in}(t) = A_1 \sin(\Omega \cdot t) \tag{1}$$

with the constant amplitude A_1 and frequency Ω, is introduced into a linear dynamic system, the behaviour of the system in steady state is represented by the harmonic output signal

$$C_{out}(t) = A_2(\Omega) \sin(\Omega \cdot t - \Phi(\Omega)) \tag{2}$$

with the amplitude $A_2(\Omega)$ and the lag $\Phi(\Omega)$. The symbol t represents time.

The complex function

$$F(\Omega) = A_2(\Omega) \exp(-i \cdot \Phi(\Omega))/A_1 \tag{3}$$

for the real argument $\Omega \in [0, \infty)$ is the frequency response of the system. The symbol i represents the imaginary unit.

If a deterministic nonperiodic signal is introduced into a linear dynamic system, the frequency response of the system can be determined as

$$F(\Omega) = C_{out}(\Omega)/C_{in}(\Omega) \tag{4}$$

for the real argument $\Omega \in [\Omega_{min}, \Omega_{max}]$. $C_{in}(\Omega)$ and $C_{out}(\Omega)$ are the Fourier transforms of the system input and output signal, respectively.

The system frequency response in the frequency domain, or the system weighting function in the time domain (8,9) provides all characteristics of the linear dynamic system. In the frequency domain, the system static properties are represented by the $F(0)$ value and dynamic properties by the dimensionless function $\hat{F}(\Omega)$

$$\hat{F}(\Omega) = F(\Omega)/F(0), \ (\hat{F}(0) = 1) \tag{5}$$

called the normalized frequency response of the linear dyanmic system. In the time domain, the static and dynamic properties of the system are represented by the area under the system weighting function and by the weighting function, respectively.

One of the conventional plots of the system frequency response is its polar plot in the complex plane. As an example the inherent frequency response of the first-order linear dynamic system described by Eqs. (6) and (7)

$$H(s) = \frac{G}{1 + T \cdot s} \tag{6}$$

$$C_{out}(t) + T \cdot \frac{dC_{out}(t)}{dt} = G \cdot C_{in}(t) \tag{7}$$

in the Laplace s domain and in the time domain, respectively, is presented in Fig. 1. G is the system gain and T is the system time constant.

The form of the system frequency response is strongly dependent on the system structure. In general, the influence of the system structure on the form of the system frequency response is much more distinct than on the form of the system output. This is of great advantage in modeling the system frequency response instead of the system output, commonly used in pharmacokinetics (10).

A linear pharmacokinetic system whose frequency response has been calculated from the input-output measurements according to Eq. (4), can be described by the ferquency model whose properties are similar to those of the calculated frequency response. The model transfer function $H_M(s)$

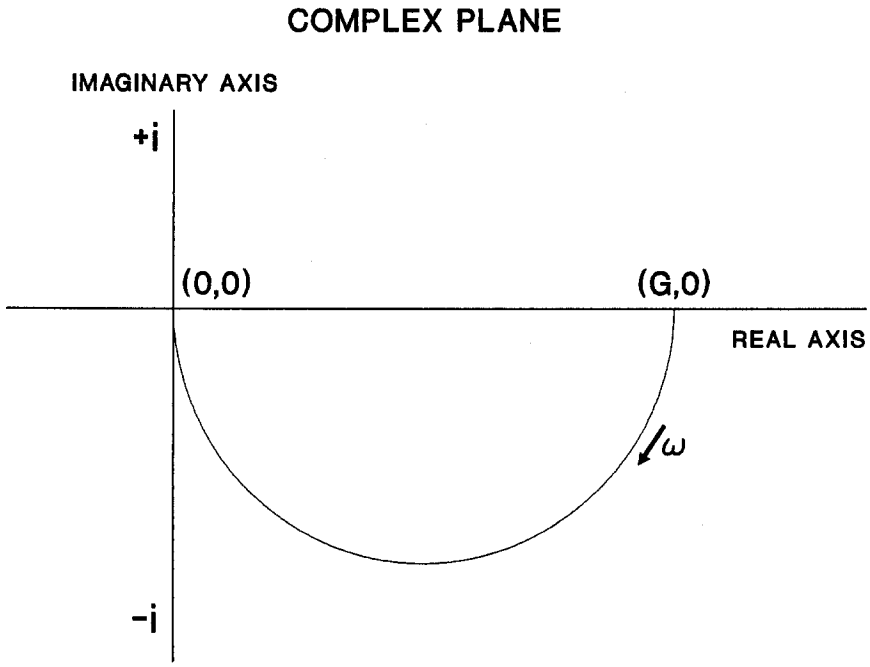

Fig. 1. Polar plot of the frequency response of the first-order linear dynamic system, defined by Eq. (6) and/or (7), in the complex plane.

may have the form

$$H_M(s) = \hat{H}_M(s) \cdot G \tag{8}$$

where $\hat{H}_M(s)$ is the model of the normalized frequency response, i.e., the model of the system dynamic properties and the gain G is the estimator of the static model parameter.

The linear pharmacokinetic system that does not contain a time delay can be approximated by the model

$$\hat{H}_M(s) = A(s)/B(s) \tag{9}$$

where $A(s)$ and $B(s)$ are polynomials (1). The linear pharmacokinetic system that contains a time delay can be approximated by the same model, however, only by high-order numerator and demoninator polynomials with complex conjugated roots (11).

The system frequency model $H_M(\Omega)$ can be formally obtained by the substitution $s = i \cdot \Omega$ into Eqs. (8) and (9). The optimal frequency model, optimal frequency range, G value, and values of the polynomial coefficients

can be selected by fitting variable frequency models $H_M(\Omega)$ to the calculated frequency response of the pharmacokinetic system (1).

Since $F(\Omega)$ is a complex function of the real argument Ω, the imaginary unit i is not stated in its symbolic representation.

MATERIAL AND METHODS

The published plasma concentrations of gentamicin were used (10). Gentamicin was administered intravenously and intratracheally in the same doses to guinea pigs (10). The drug plasma concentrations were determined in samples taken from the left side of the heart.

System Equations

The plasma circulatory system after intravenous administration was described by

$$C_{iv}(s) = H_c(s) \cdot I_{iv}(s) \tag{10}$$

where $I_{iv}(s)$ was the intravenous input, $H_c(s)$ and $C_{iv}(s)$ were the corresponding transfer function and system output, respectively.

The plasma circulatory system after intratracheal administration was described by

$$C_{it}(s) = H_c(s) \cdot H_{it}(s) \cdot I_{it}(s) \tag{11}$$

where $I_{it}(s)$ was the intratracheal input, the product of $H_c(s) \cdot H_{it}(s)$ and $C_{it}(s)$ were the corresponding transfer function and system output, respectively.

For the same inputs, $I_{iv}(s) = I_{it}(s)$ (10), $H_{it}(s)$ was expressed as

$$H_{it}(s) = C_{it}(s)/C_{iv}(s) \tag{12}$$

In this case, $C_{it}(s)$ and $C_{iv}(s)$ were the respective output and input functions of the system defined by Eq. (12). $H_{it}(s)$ was the system transfer function and the corresponding inverse transform $H_{it}(t)$ was the weighting function of the system (1).

The arguments presented were based on the assumption that the disposition kinetics of gentamicin in guinea pigs was linear. Linearity was assumed in the sense that all responses adhered to the superposition principle and time invariance with respect to the input rate.

Frequency Response Method

The frequency responses $F_{it}(\Omega)$ of the system defined by Eq. (12) was calculated according to Eq. (4) for varying sets of the Ω values. Each set

contained $N=20$ values of Ω, ranging from Ω_{min} to Ω_{max}, generated by the geometric series. The $C_{it}(\Omega)$ and $C_{iv}(\Omega)$ functions were determined as the Fourier transforms of the straight lines approximating the corresponding drug concentrations between two adjacent sampling points and as the Fourier transforms of the exponentials approximating the concentration–time courses in the interval from the last sampling time to infinity. $F_{it}(0)$ was determined as

$$F_{it}(0)=\lim_{\Omega\to 0} F_{it}(\Omega) \tag{13}$$

where

$$\lim_{\Omega\to 0} F_{it}(\Omega)=AUC_{it}/AUC_{iv}$$

with AUC_{it} and AUC_{iv} representing the areas under the plasma concentration–time curves from time 0 to infinity after intratracheal and intravenous administration, respectively. The $F_{it}(0)$ value was used for the calculation of the normalized frequency response $\hat{F}_{it}(\Omega)$ according to Eq. (5).

To approximate the normalized frequency response $\hat{F}_{it}(\Omega)$ of the system defined by Eq. (12) the following frequency model was employed

$$\hat{H}_{M,it}(\Omega_j)=\frac{a_0+a_1 i\Omega_j+a_2(i\Omega_j)^2+\cdots+a_n(i\Omega_j)^n}{1+b_1 i\Omega_j+b_2(i\Omega_j)^2+\cdots+b_m(i\Omega_j)^m} \tag{14}$$

The point estimates of the polynomial coefficients of variable frequency models with varying polynomial degrees n and m were obtained by fitting the respective models $\hat{H}_{M,it}(\Omega)$ to the calculated $\hat{F}_{it}(\Omega)$, using the noniterative algorithm in the complex domain, based on the Levy method (12). The formal description of this algorithm, used in the CXT program was as follows (13):

$$f_1(\Theta_1, i\Omega_j)=a_0+a_1 i\Omega_j+a_2(i\Omega_j)^2+\cdots+a_n(i\Omega_j)^n$$
$$f_2(\Theta_2, i\Omega_j)=b_1 i\Omega_j+b_2(i\Omega_j)^2+\cdots+b_m(i\Omega_j)^m$$

where

$$\Theta_1=\begin{pmatrix} a_0 \\ a_1 \\ \cdot \\ \cdot \\ a_n \end{pmatrix} \qquad \Theta_2=\begin{pmatrix} b_1 \\ b_2 \\ \cdot \\ \cdot \\ b_m \end{pmatrix}$$

were the vectors of unknown parameters. The j value of the calculated normalized frequency response $\hat{F}_j, j \in [1, N]$ was expressed as

$$\hat{F}_j = \frac{f_1(\Theta_1, i\Omega_j)}{1 + f_2(\Theta_2, i\Omega_j)} + Z_j \tag{15}$$

where Z_j was the random variable describing the error. Eq. (15) was rewritten into Eq. (16)

$$\hat{F}_j = f_1(\Theta_1, i\Omega_j) - F_j \cdot f_2(\Theta_2, i\Omega_j) + Z_j \tag{16}$$

under the condition that the term $Z_j \cdot f_2(\Theta_2, i\Omega_j)$ converged to zero (12,13).

The minimal frequency Ω_{min} was selected according to the empirical condition lag $\Phi(\Omega_{min}) = \pi/120$ rad (13). To decide on the optimal Ω_{max} value and on the numerator and denominator polynomial degrees of the frequency model optimally describing $\hat{F}_{it}(\Omega)$ the criterion

$$CC = 2 \cdot N \ln(R_{real} + R_{imag}) + 2 \cdot (n + m + 1) \tag{17}$$

was applied, assuming the normal distribution of the random variable Z_j. R_{real} and R_{imag} represented the real and imaginary parts of the residual sum of squares, respectively. To test the null hypothesis that the observed distribution of the residuals $Z_{j,real}$, $Z_{j,imag}$ can be regarded as the normal distribution, the χ^2 test was used (14). The frequency model with minimum CC was regarded as the best representation of the system frequency response.

The static model parameter G_{it} was estimated as

$$G_{it} = a_0 \cdot F_{it}(0) \tag{18}$$

The weighting function $H_{M,it}(t)$ of the selected optimal frequency model was obtained as the response of this model to the Dirac-delta pulse using the numerical Euler method (13).

Numerical Deconvolution Method

The numerical deconvolution method (15) was modified as follows: The initial drug concetrations in the plasma circulatory system were assumed to be

$$C_{iv}(t = 0) = C_{it}(t = 0) = 0 \tag{19}$$

The interpolated points obtained by Lagrange cubic polynomials fitted to the logarithms of the measured concentration data were used. The step of the interpolation was equal to the first sampling time. The static parameter of the system defined by Eq. (12) was estimated as the area under weighting function in the time interval from the first to last sampling time, using the

linear trapezoidal method. The first and last sampling time intervals were the same in both modes of administration (10).

The calculations were done by the TURBO PASCAL programs: CXT and DND (Direct Numerical Deconvolution); BIO-LAB Bratislava. (DEMO versions of the programs will be sent on receipt of a floppy in a self-addressed floppy disk mailer.)

RESULTS

The points in Fig. 2 show the calculated normalized frequency response of the system defined by Eq. (12) determined for the selected interval from $\Omega_{min} = 0.058$ rad · hr^{-1} to $\Omega_{max} = 30.42$ rad · hr^{-1}. The selected optimal frequency model had the numerator and denominator polynomial degrees $n = 4$ and $m = 5$, respectively. It is presented as the solid line in Fig. 2. The calculations of the goodness-of-fit statistics yielded the dispersion values σ^2_{real} and σ^2_{imag} of 0.00037 and 0.00016, respectively. The χ^2 test of the null

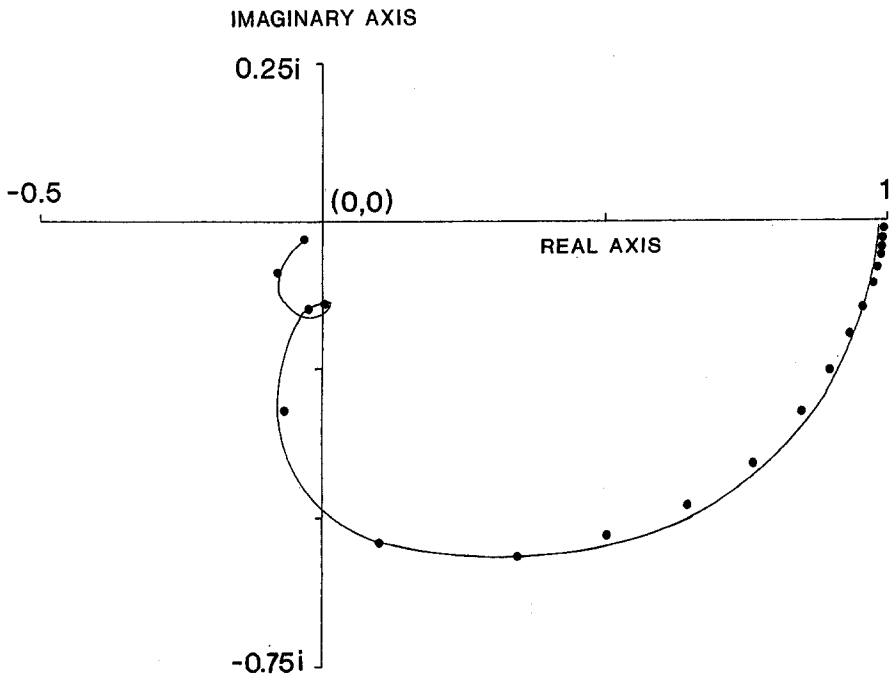

Fig. 2. Calculated normalized frequency response (points) of the system defined by Eq. (12) for the selected interval of Ω values from $\Omega_{min} = 0.058$ rad.hr^{-1} to $\Omega_{max} = 30.42$ rad.hr^{-1}. Model approximation by the selected optimal frequency model (solid line) with the numerator and denominator polynomial degrees $n = 4$ and $m = 5$, respectively.

Table I. Point Estimates of the Polynomial Coefficients of the Optimal Frequency Model of the System Defined by Eq. (12)

Numerator polynomial $A(s)$	Denominator polynomial $B(s)$	Dimension
$a_0 = 0.983$	—	—
$a_1 = 0.127$	$b_1 = 0.477$	hr
$a_2 = 0.014$	$b_2 = 0.0661$	hr^2
$a_3 = 0.000597$	$b_3 = 0.0087$	hr^3
$a_4 = 0.0000176$	$b_4 = 0.000275$	hr^4
—	$b_5 = 0.0000177$	hr^5

hypothesis that the observed distribution of the corresponding residuals $Z_{j,\text{real}}$, $Z_{j,\text{imag}}$ can be regarded as the normal distribution yielded the following values: $\chi^2(3) = 7.0232$, $P = 0.0711$. Since the probability level was greater than the conventional 0.05 level, the null hypothesis that the distribution of the observed residuals was normal was not rejected.

The point estimates of the fitted coefficients of the numerator and denominator polynomials of the selected optimal model are assembled in Table I. The calculation of the roots of the numerator (r_1, r_2, r_3, r_4) and denominator (q_1, q_2, q_3, q_4, q_5) polynomials yielded the values of $r_{1,2} = -12.319 \pm 16.938i$, $r_{3,4} = -4.654 \pm 10.283i$, and those of $q_{1,2} = -3.477 \pm 18.635i$, $q_{3,4} = -2.866 \pm 6.892i$, $q_5 = -2.818$, respectively. The loop of the frequency response, determined for the high values of Ω, seen in the bottom left quadrant of the complex plane in Fig. 2, the high order of the selected optimal frequency model, and presence of the complex conjugated roots indicate the complexity of the system and the presence of system time delays (1,11).

The open squares in Fig. 3a illustrate the mean concentrations of gentamicin in plasma after its intravenous administration, representating the input of the system defined by Eq. (12). The filled squares in Fig. 3b show the time course of the mean concentrations of gentamicin in plasma after its intratracheal administration, representing the output of the system defined by Eq. (12). The approximations of this time course by the output of the selected optimal frequency model and by the three-exponential function published in our previous study (10) are shown as the solid and dashed line, respectively, in Fig. 3b.

The estimate of the weighting function of the selected optimal frequency model and the estimate obtained by the deconvolution method are shown as the solid and dashed line, respectively, in Fig. 4. The estimates, approaching the rate of gentamicin bioavailability after intratracehal administration, did not decrease monotonously after their maxima, of about 2.2–2.5 unit of dose · hr^{-1}, recorded approximately 0.1 hr after administration, but showed marked additional peaks approximately at 0.3 hr after administration, and

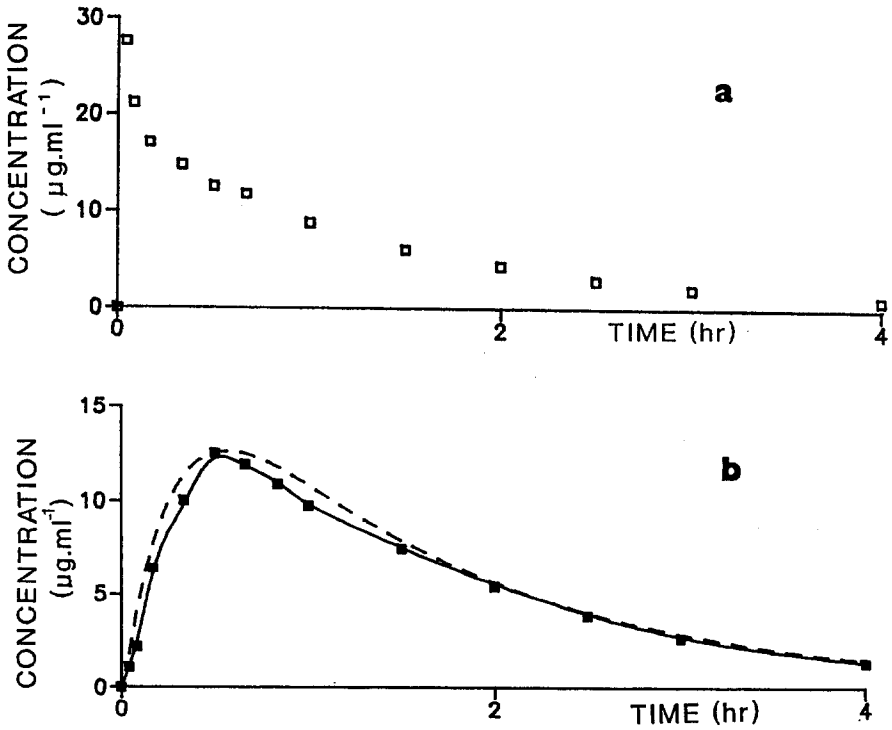

Fig. 3. Open squares (a); filled squares (b) are the time courses of the mean plasma concentrations of gentamicin after intravenous and intratracheal administration, respectively. Simulations of the latter profile by the output of the selected optimal frequency model and three-exponential function published previously (10) are shown as the solid and dashed lines respectively.

possible peaks in the further time period. The estimates of the extent of gentamicin intratracheal bioavailability obtained according to Eqs. (13) and (18) and that obtained by the deconvolution method are listed in Table II.

DISCUSSION

In pharmacokinetics much attention has been paid to modeling the output of the pharmacokinetic system in the time domain. In general, frequency domain methods are more suitable than time domain methods for building very accurate models of complex systems which permit physical interpretation of the parameters. The advantages of the frequency domain methods are, e.g., the methods can be applied to high-order systems, the *s*-domain transfer function may be directly identified, quality of a system approximation by a model of its transfer function can be visually checked for a wide range of system inputs, both input and output noises can be

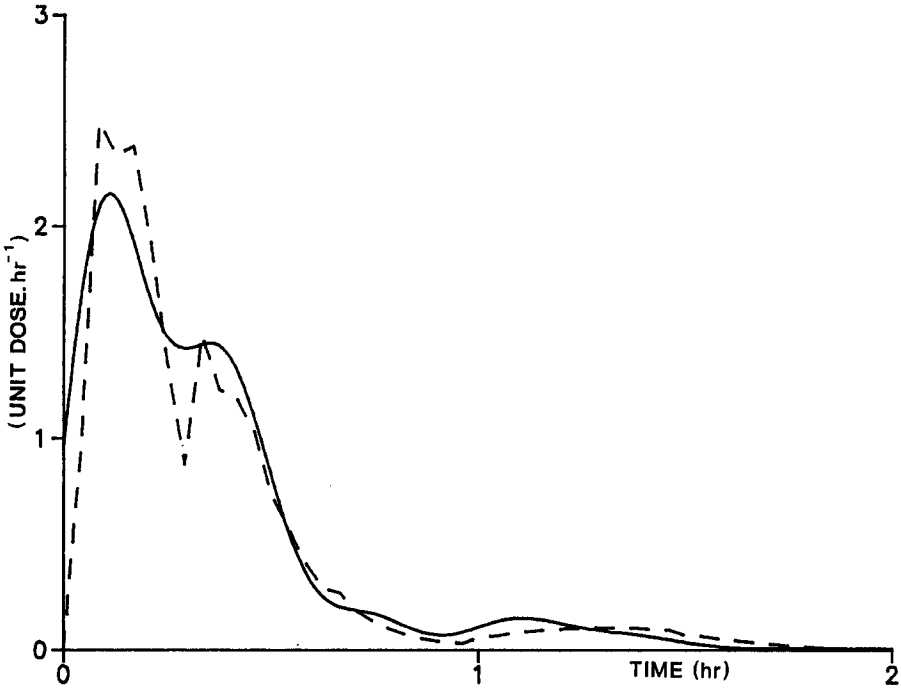

Fig. 4. Estimate of the weighting function of the system defined by Eq. (12) obtained by the simulation of the selected frequency model (solid line) and that obtained by the numerical deconvolution method (dashed line).

considered, and signal-to-noise ratio can be improved by an appropriate frequency band (1). In pharmacokinetics noise from three sources is included in the frequency response calculated from input–output measurement: measurement noise, noise generated by the pharmacokinetic system, and noise originating in numerical calculations of the Fourier transforms of the data with insufficient information density for the model building. In our study, in which mean concentration data were used, also noise from inter-individual variability among the animals contributed to the measurement noise, which represented the most difficult case of a contribution. Pitfalls of pharmacokinetic analysis of mean concentration data are discussed in the

Table II. Estimates of the Static Parameter of the System Defined by Eq. (12)

Parameter	Estimate
$F_{it}(0)$ obtained according to Eq. (13)	0.950
G_{it} obtained according to Eq. (18)	0.934
Area under the weighting function calculated by the deconvolution method	0.907

literature (e.g., ref. 16). Since the experimental design utilizing different sets of small animals has been used very frequently in experimental pharmacokinetics, an example with mean concentration data was used in our methodological study.

In the complex plane, the inherent frequency response of a linear dynamic system is a continuous curve (1), as shown for a linear first-order system in Fig. 1. This response is a semicircle located only in the bottom right quadrant of the complex plane (1). The points of the frequency response presented in Fig. 2 can be considered as lying on a continuous curve. The continuity of the calculated frequency response, shown in Fig. 2, is in agreement with our basic assumption of the possibility of approximating gentamicin disposition kinetics by a linear model. Comparing the responses presented in Fig. 1 and 2 it is obvious that the response calculated for the system defined by Eq. (12) is substantially different from the inherent response of a first-order linear system.

The model represented by Eq. (14) is non-linear-in-the-parameters, and thus it is not possible to use the linear least squares algorithm to obtain the model parameter estimates. To obtain point estimates of the model parameters the fast noniterative algorithm based on the Levy (12) approach is employed by the CXT program. The algorithm mentioned can be used to estimate model parameters under the following conditions: System and model orders are approximately similar; and the calculated (i.e., not measured) frequency response is approximated (13). In other cases the algorithm can select starting values of the model parameters for iterative search routines.

Utilization of different statistical criteria to selecting optimal models of the calculated frequency responses is discussed in the literature (1,17). The equivalence between the minimization of the Akaike information criterion (18) and the criteria similar to that defined by Eq. (17) is stated for small data sets (1).

The deviation of the selected optimal frequency model from the frequency response calculated, seen in the region of the small Ω values in Fig. 2, is pertinent to the estimation of the model numerator polynomial coefficient a_0, which yielded a value of 0.983 (see Table I). In a theoretically ideal model approximation of a normalized system frequency response this value equals 1 (1).

The two approximations of the data shown in Fig. 3b are substantially different. The first one (solid line) is the response of the selected optimal frequency model to the input data presented in Fig. 3a. The second one (dashed line) is the data approximation by the three-exponential function published in our previous study (10). It is important to stress that the solid line represents the output of the model of the system defined by Eq. (12),

but the dashed line represents only the model of the measured concentration data.

The two estimates of the weighting function of the system defined by Eq. (12), approaching the rate of gentamicin intratracheal bioavailability, the first obtained as the response of the selected frequency model to the Dirac-delta pulse, and the second obtained by the deconvolution method, are similar as shown in Fig. 4. The weighting function does not decrease monotonously after the maximum but shows additional peaks. In the numerical deconvolution method we impose constraints similar to that used by Veng-Pedersen and Gillespie (19). Our constraints, represented by Eq. (19), are consistent with the physically obvious fact that the initial value of drug concentration in plasma is zero, whatever the route of administration. Based on the similarity of the two estimates of the system weighting function, obtained by two different ways, the possibility of the artificial impact of the algorithm of the frequency response calculation can be excluded.

The value of the system and model static parameter approaches a fraction of the total intratracheal gentamicin dose bioavailable systemically in steady state. The estimates of this parameter obtained according to Eqs. (13) and (18) and that obtained by the numerical deconvolution method were 0.950, 0.934, and 0.907, respectively. The values of 0.950 and 0.907 were calculated directly from the experimental data. The value of 0.934 is a model-based estimate. Thus the conclusion can be made that gentamicin injected intratracheally to guinea pigs is almost completely available.

In principle, the loops in the frequency response and several peaks in the weighting function can be caused by the system time delays, as well as by different sources of noise, described above. We hypothesize that the fifth-order optimal frequency model, the model loop determined for the high values of Ω, and the complex conjugated roots of numerator and denominator polynomials with substantial imaginary components, indicate the complexity of the system and the presence of subsystems with time delays in the system described by Eq. (12) (1,11). The trend of both estimates of the system weighting function may also support this hypothesis.

It is important to note the following advantages of the frequency response method in pharmacokinetics: The results obtained by the frequency model implicitly contain very useful information concerning the system structure, which may be utilized in buidling a structured pharmacokinetic model; the frequency response method enables testing the possibility of approximating a pharmacokinetic system by a linear dynamic model. If a calculated frequency response is a continuous curve, the system can be approximated by a linear model; different pharmacokinetic systems, e.g., systems defined similarly as the system described by Eq. (12), systems containing time delays, systems describing the fate of a drug after intravascular

or extravascular administration, during and after short and long time infusion, after loading dose followed by infusion, after termination of steady state, and after many other inputs when the Fourier or the Laplace transforms of the inputs exist, can be analyzed by the frequency response method in the simple common way.

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