good initial estimates are available for the latter. Our method does not involve iteration and, as we showed, it performs well in the deconvolution problem. The programs proposed (1) are not simple, but once they are prepared, they save the user from the difficulties associated with ill-conditioning.

As in "Nonnegativity of the Input Rate," there remains a question of methodology with no unique answer. Our view is that, while the method Verotta discusses can be programmed readily, the technique we described (1) offers long-term advantages for the frequent user of deconvolution methods. The additional initial programming effort is likely to be offset by increased efficiency as more applications are run through.

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Reply to "Comments on Two Recent Deconvolution Methods." II

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The article by Verotta brought out some valuable comments about deconvolution methods, but unfortunately made some statements about assumptions, features, and properties of the deconvolution methods discussed that appear somewhat misleading. Additionally the possibility of "negative input" (drug removal) was not considered.

1. The gastrointestinal (GI) tract must be considered an important, integral part of the disposition space of drugs. Sizewise this space is significant. The diffusional transfer out of *and* into this space is greatly facilitated by the large interfacial area. The variability in drug affinity for the GI space appears mainly due to the GI content, but the GI motility,

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including frequency and extent of defecation, also plays a role. The variability in this GI affinity may have a pronounced effect on the absorption kinetics as commonly realized. Less recognized is the fact that the variability in the GI affinity may have a similar pronounced disposition kinetic effect (6,7). When doing deconvolution the "GI disposition effect" may be a possible explanation for evaluations of "negative input" in the terminal/postabsorption phase.

Clearly it does not make much sense to talk about a negative input if input is defined as the first appearance of drug molecules in some part of the body (e.g., the first appearance in "the general systemic circulation"). However, if it is assumed that the negative input is solely due to a GI disposition effect then a negative input may be quite meaningful. This can be seen as follows. A difference in disposition functions present during test administration (po) and reference administration (iv) caused by the GI disposition effect can be compensated for by a "push-pull function," $f_{pp}(t)$, that simple reflects the *relative* affinity of drug for the GI tract between the two administrations. A negative value for $f_{pp}(t)$ indicates a greater GI affinity of free (released) drug molecules in the test administration than in the reference administration. The push-pull is then in the pulling mode. Relatively speaking drug appears to be more trapped in the GI lumen in the test case. This trapping due to a higher affinity appears kinetically as a pulling of drug into the GI lumen. Thus $f_{pp}(t)$ is defined as negative in this case. A positive value for $f_{pp}(t)$ indicates the alternative, namely, a higher GI affinity in the reference administration. This higher affinity can be thought of as equivalent to the drug molecules more readily being pushed out of the GI space in the test administration. The push-pull is in the push mode in this case, corresponding to the push-pull function being defined positive in the push mode. Let $R(t)$ denote the function evaluated by deconvolution of the test response. It can readily be shown that a different GI affinity between test and reference administrations will result in $R(t)$ becoming the sum of the input function $f(t)$ and the input function convoluted by the push-pull function

$$R(t) = f(t) + f_{pp}(t) * f(t) \tag{1}$$

The push-pull function can be directly evaluated by analyzing the difference between two unit impulse responses when it is assumed this difference is caused by a GI disposition effect. Deconvolution of the difference in the unit impulse responses using one of the unit impulse responses as the reference gives directly the push-pull function. A very pronounced push-pull function caused solely by difference in GI content can be readily demonstrated experimentally (6,7).

2. It is important to fully realize the generality of the deconvolution concept. First, it is not necessary to assume that the input site [denoted S_i by Verotta (3)] and the sampling site (also denoted S_i by Verotta) are the same or located in the same part of the kinetic system. For example, it may under general linearity assumptions be possible by deconvolution to evaluate the input of drug into the general systemic circulation from urinary excretion of the drug or one or more of its metabolites. Second, it should be realized that deconvolution requires very little in terms of model assumptions. *It is essentially misleading to associate the use of an empirical sum of exponentials with the assumption that such an expression is the solution of ordinary linear differential equations* (*ODEs*). Such association is unnecessary and should be strongly discouraged because a dynamic system description in terms of ODEs normally is associated with a particular unnecessary model assumption, e.g., linear compartmental. The linear compartmental model assumptions introduce unnecessary misleading abstractions and limit the generality of the analysis. To do deconvolution it is not necessary to assume first-order transfer processes and homogeneous compartments. Deconvolution is mathematically derived from the linear superposition property (4). The linear superposition principle is based fundamentally on a *stochastic independent kinetic behavior* of the drug molecules. First-order transfer processes and homogeneous compartments are model abstractions not necessary for superposition, convolution, and deconvolution. Furthermore the compartmental/ODE approach introduces unnecessary functional restrictions that limit the analysis. For example, a two-compartmental disposition model with central input restricts the disposition function (the central bolus response) to be $c(t) = A_1\, e^{-\alpha_1 t} + A_2\, e^{-\alpha_2 t}$ with *both* A_1 and A_2 positive. However, the only thing we know with real certainty about the disposition function is that $c(t) > 0$, $c(t) \to 0+$ for $t \to \infty$ and that $c(t)$ nearly always is monotonically decreasing soon after the rapid initial cardiovascular mixing phase. These conditions obviously leave a lot of flexibility in the choice of functional approximation of the disposition function. For example, in the two-exponential approximation it should not be necessary to restrict A_1 and A_2 to be *both* positive as in the compartmental approach. It is possible to get a monotonically decreasing function with one of the As being negative, resulting in shapes of $c(t)$ not admitted by classical compartmental principles. If the disposition is treated in a noncompartmental physiologically more meaningful sense considering cardiovascular recirculatory aspects of the drug disposition then the limitation of the compartmental approach becomes very obvious. Recirculatory systems may give rise to disposition functions of complex shapes described by integro-differential equations that cannot be converted to ODEs, showing the kinetic limitation of the ODEs approach in the analysis. A linear disposition may, generally speaking, be

considered a realization of disposition kinetic processes governed on the molecular level by independent stochastic principles. Such analysis is "structure free" and appears more intrinsic than alternative modeling approaches by providing the most elementary and intrinsic foundation for the superposition principle (4) that forms the basis for all convolution and deconvolution methods. In the structure free stochastic modeling context the disposition function is simply proportional to a statistical distribution function and as such leaves a lot of choice and flexibility in its functional representation.

Thus, it appears most rational in dealing with biological systems and deconvolution to adopt a general and flexible attitude and not subscribe to a specific modeling approach, or to subscribe to a specific dynamic representation such as ODEs. In practical terms the deconvolution problem should be considered more an approximation/estimation problem than a modeling problem. In the choice of the functional form for the estimation/approximation in deconvolution it is advisable to be as flexible and general as possible under the given obvious physiological constraints.

3. Verotta (3) claims that the methods of Vajda *et al.* (5) and Veng-Pedersen (6) make similar assumptions on S (the system) and $I(t)$ (the input function). It is also stated (3) that the method of Vajda *et al.* assumes that "the input to S is a linear first-order process." These two statements together may be interpreted to mean that the method by Veng-Pedersen (6) assumes a linear first-order input process. This is certainly not the case. *When doing deconvolution using DECONV (3) and most other deconvolution programs it is not necessary to assume that the input is linear.* Nonlinear inputs are considered equally well. The DECONV program intrinsically represents the input as a sum of exponentials. A sum of exponentials is *not* the same as a first-order input. It is only when the input rate is assumed to be proportional to the amount remaining to be absorbed that one in a conventional kinetical sense can say that the input is first order. This condition is satisfied mathematically when the rate of input is a simple one-exponential function. The DECONV program considers this as a simple special case but is certainly not limited to this special case. As explained above it would be advisable not to associate DECONV (3) or DCON (4) with ODEs or compartmental structure principles. *DCON considers functional forms that simply cannot be represented in a classical linear compartmental sense.*

4. Verotta (3) incorrectly interprets the results presented by Veng-Pedersen (6) and states that according to Table II in ref. 6 the calculated input function diverges to $-\infty$ for $t \to \infty$. This is not the case as simply verified from the exponential coefficients in Table I and Eq. 23 (6). *DECONV is a mathematically exact analytical inversion deconvolution algorithm.* It is *numerically stable* and exact in contrast to numerical deconvolution

methods. The algorithm is completely stable and will never diverge to infinity provided the user does not make the fundamental mistake of describing the disposition function or the absorption drug level curve by expressions containing meaningless exponential terms with positive time coefficients.

5. Verotta's statement of assumptions A1-A3 (3) is in conflict with the arguments presented under Item 2. Assumptions A1-A3 (3) address only the functional/dynamic representation of the input function, $I(t)$, and the unit impulse response function, H(t). The less initiated reader may believe that one or more of these assumptions are assumptions necessary for doing deconvolution, which is not the case.

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Rejoinder

Davide Verotta

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I first wish to thank S. Vajda, K. R. Godfrey, P. Valko, and P. Veng-Pedersen for commenting on my paper. I will reply to some of the comments, and I summarize a few conclusions.

VENG-PEDERSEN

1. My paper considers situations where the assumptions underlying the use of deconvolution hold, but still one runs into estimation problems.