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Tutorial

Expert Discussion of the Role of Rate Constant Versus Clearance Approaches to Define Drug Pharmacokinetics: Theoretical and Clinical Considerations

Marilyn N. Martinez,^{1,4} Roger W. Jelliffe,² and Johannes H. Proost³

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Abstract. This article provides a dialogue covering an ongoing controversy on the use of clearance versus rate constant approaches for model parameterization when assessing pharmacokinetic (PK) data. It reflects the differences in opinions that can exist among PK experts. Importantly, this discussion extends beyond theoretical arguments to demonstrate how these different approaches impact the analysis and interpretation of data acquired in clinical situations. By not shying away from such dialogues, this article showcases how dissimilarity in well-grounded perspectives can influence how one applies PK and mathematical principles.

KEYWORDS: Clearance; Rate Constant; Parameterization; Discussion.

Dr. Martinez

By way of introduction, this dialogue is the result of an ongoing controversy with respect to the use of clearance versus rate constant parameterizations for the assessment of pharmacokinetic (PK) data. As an onlooker, it seems that much of the disagreement is grounded in parties talking past each other without fully understanding the evidence and perspectives within which each argument is grounded.

The controversy between the “clearance approach” and the “rate constant approach” has a long history after the introduction of the clearance concept in pharmacokinetics by Rowland and colleagues more than 40 years ago (1–9). The current dispute was initiated after Jelliffe *et al.* published a manuscript in 2016 advocating the use of volume of distribution (V) and elimination rate constant (K) rather than V and total systemic clearance (CL) when caring for patients (10). In response to that publication, Dr. Proost published a commentary countering this position (11). He stated that he disagrees with the position of Dr. Jelliffe that CL, V, and K are “all interdependent.” Rather, he stated that V and CL are independent of each other, reflecting different PK processes,

i.e., distribution and elimination, respectively. Consequently, K is dependent on both V and CL.

Drs. Bayard and Jelliffe later published a paper showing that both parameterizations are mathematically equally valid and equivalent (12), because of the principle of invariance (13) which provides mathematical proof that all three parameterizations, V and CL, V and K, and CL and K, are equally valid, indistinguishable, and equivalent. Dr. Proost did not disagree with the mathematical arguments associated with this principle but rather provided reasons for the position that from a mechanistic perspective, V and CL need to be modeled as separate processes of distribution and elimination, respectively.

The resulting disagreement leaves young researchers and clinicians with misunderstandings and misconceptions, reflecting a need to improve our communication on the use of clearance and rate constant approaches. There is also a need to describe situations when each of the respective approaches may be applicable. For example, in a research situation, there is an opportunity to use sophisticated methods to describe how the drug is eliminated from the body and the impact of genetic polymorphisms (transporter, enzymes), disease, diet, stress, and other medications on elimination processes. This is the foundation of mechanistic models. However, how does one handle the challenging clinical situation where dosages need to be determined/adjusted for a patient within an intensive care unit when all the attending physician has access to are occasional plasma drug samples?

Within the framework of collaborative discussion, Drs. Jelliffe and Proost have been invited to respond to some questions and to submit questions of their own. Both scientists were provided an opportunity to review the other’s responses and to add further clarification as needed. Ultimately, this commentary was produced with the common goal

This communication reflects the opinion of the author and does not reflect views or policy of the FDA.

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of creating an educational experience and to clarify the importance of identifying the intended purposes of model application.

To begin, it is important that all discussions share the same definition of the basic PK parameters (in this case, assuming a 1-compartment body model and linear kinetics):

- Elimination rate (amount/time): amount of drug removed from the body over a stated period of time.
- Elimination rate constant (K, 1/time): this describes the infinitesimally small fraction of a substance that is eliminated over an infinitesimally small period of time. It thus describes the instantaneous rate of removal of a drug from the body over an infinitely small time (in the limit, as in calculus, not over any stated period of time). It is usually denoted by a rate constant K in a differential equation.
- Clearance (CL, volume/time): this describes the capacity of the body to eliminate the drug. CL is defined as the elimination rate divided by the plasma or serum concentration. This corresponds to the volume of plasma totally cleared of the drug over a specified unit of time (e.g., hour, minute).
- Volume of distribution (V): the term used to describe the apparent volume into which a drug is distributed. V is defined as the amount of drug in the body divided by the plasma or serum concentration. This apparent volume may also reflect distribution into body water as well as binding to or partitioning into various tissues and organelles.
- Therapeutic drug monitoring (TDM): measurement of drug concentrations in blood, plasma, or serum at specified times. This is coupled with an analysis of the resulting data with the aim to predict the dosing regimen achieving the target concentration as precisely as possible.

The key equations of interest are

$$CL = V \times K \quad (1)$$

$$K = CL/V \quad (2)$$

$$V = CL/K \quad (3)$$

There is also agreement that these three parameterizations are mathematically equivalent and interchangeable (12,13). However, differences in opinion exist in terms of the mechanistic basis of the three equations and their applications in terms of describing the effect of physiological changes on drug PK.

Position of Dr. Jelliffe:

- 1) Since the three parameterizations are mathematically equally valid, indistinguishable, and equivalent, there is no scientific preference in Eqs. (1–3). There is no

debate any more whether or not one is somehow “better.” Mathematics describes relationships between various entities. It never implies any mechanism. However, some parameterizations are useful in some situations while others may not be.

- 2) Many clinicians and mathematicians prefer parameterization in K and V.
- 3) Any predictions are always speculative. Getting data is essential.

In short, choice of parameterization is whatever is most useful or convenient for an intended purpose, due to the principle of invariance (13).

Position of Dr., Proost:

- 1) Although the three parameterizations are mathematically equally valid, indistinguishable and equivalent, this does not imply that there can be no hierarchical order or preference in Eqs. (1–3).
- 2) Mechanism-based models and parameterization are preferred over purely empirical mathematical models and parameterization.
- 3) Since the elimination rate is proportional to the plasma or serum concentration, where the proportionality constant equals clearance, parameterization of CL and V is mechanistically preferred over K and V.
- 4) CL and V are independent parameters, whereas K is dependent on CL and V (Eq. (2)).
- 5) Parameterization in terms of CL and K is counter-intuitive and probably never used in practice.
- 6) Parameterization in CL and V allows predictions of the changes in PK parameters and plasma concentration profile in the case of changes in physiological and pharmacological processes and is helpful in understanding basic and clinical PK. This cannot be done in the case of parameterization of K and V.

In short, parameterization in CL and V is mechanistically superior and is helpful to understand basic and clinical PK.

Questions:

Dr. Martinez: The focus of this discussion is the basis for the individual preferences for defining drug PK from a mathematical versus mechanistic perspective.

Although these three equations are interchangeable from a mathematical perspective, Dr. Proost argues that they are different from a mechanistic perspective. In that regard, his argument is that the concentration of drug rather than the amount of drug that constitutes the “driving force” for elimination through the liver and kidney. Amount per se does not ever serve as a “driving force” for elimination. Furthermore, he contends that the application of Eqs. 1–3 mechanistically assumes that CL and V are inter-related. In other words, he has stated that when using these equations, one assumes that “knowing two of the parameters allows for a determination of the third requires an assumption of mechanistic inter-relationships.”

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: First, this *not* a debate of V and CL versus V and K. That debate is *resolved* and is *over*. This is because of the principle of invariance (13). The point is that *all three*

parameterizations are now proven *equally* valid mathematically, with no one any “better” or “worse” than any other.

Our following discussion therefore centers on what are the most useful ways of describing events. Mathematics is the language with which we describe PK/PD behavior. One of its theorems is the principle of invariance mentioned above. The descriptive language of mathematics is not intended to consider any process from a “mechanistic” perspective any more than is the use of differential equations in general. There is no assumption in mathematics of any mechanism or “driving force.” This is what makes math so useful—its ability to describe such an enormous variety of different phenomena, regardless of any particular mechanism. Math simply would not be as useful as it is if it were not for this total generality. For example, we still do not know the mechanism of gravitational attraction, but we have been using Newton’s mathematical descriptions of gravitational attraction to fit data and predict planetary orbits since his time, until Einstein modified them.

Newton used the famous phrase “Hypotheses non fingo” (Latin for “I feign no hypotheses”, “I frame no hypotheses”, or “I contrive no hypotheses”). He used this phrase in an essay, “General Scholium”, which was appended to the second (1713) edition of the *Principia*. (see Wikipedia). I do not understand where Dr. Proost gets his idea of “mechanistic” mathematical equations, or of mathematics mechanistically assuming any “driving force”.

I also believe that the current “mechanistic” approach described by Dr. Proost has isolated PK, much drug research, and certainly optimal drug dosage, from other areas of science which now use better mathematical ways to describe drug behavior that are not part of the usual mechanistic and statistical repertoire. There has been much work done to achieve better modeling of PK/PD processes and adaptive control of dosing regimens (12,14–16,18). I have not seen them considered by the “mechanistic” community. Such isolation is counter to good science, to optimal and maximally precise understanding of the mechanisms governing drug behavior, and to optimal patient care.

Dr. Proost: Although these relationships can be viewed from the mathematical perspective, there are important consequences for the relationship between the parameters CL, V and K to be considered when viewed from a mechanistic perspective.

CL is the measure of the total capacity of the eliminating organs such as liver and kidneys and is defined by the following equation.

$$\text{Elimination Rate} = \text{CL} \times C \quad (4)$$

Where C is the plasma (or serum) concentration, which is the concentration perfusing the eliminating organs and the driving force for drug elimination. This approach is mechanistically supported by the knowledge that the rate of drug metabolism as well as the rate of renal excretion is proportional to the drug concentration perfusing the eliminating organs. Equation (4) defines CL as the unique parameter describing drug elimination, independent of drug distribution.

Alternatively, one might define the elimination rate constant K in a similar way, resulting in:

$$\text{Elimination Rate} = K \times A \quad (5)$$

Where A is the amount of drug in the body. Although Eqs. (4) and (5) are mathematically identical and interchangeable, there is an essential difference between these equations. In Eq. (5), A is assumed to be the driving force for drug elimination. However, this does not make sense from a mechanistic point of view. This implies that Eq. (5) does not describe the elimination rate in a mechanistically logical way, in contrast to Eq. (4).

It should be noted that mathematics, albeit essential for understanding PK, is not helpful in differentiating between Eqs. (4) and (5) since it does not consider the mechanistic basis. Equations (4) and (5) are mathematically identical and interchangeable, but mechanistically, they are not the same.

Because CL is a unique parameter describing elimination and V is a unique parameter describing distribution, CL and V are independent parameters, and it follows that K is dependent on CL and V (Eq. (2)). Mechanistically, this implies that an observed change in CL cannot be due to a change in K, nor to a change in V. It also implies that an observed change in K can be due to a change in CL or V or both. On the other hand, when considering the principle of invariance, when K and V are treated as independent parameters, it would follow that CL is dependent on K and V (i.e., $\text{CL} = K \times V$). This would imply that an observed change in K cannot be due to a change in CL, nor to a change in V. It would also imply that an observed change in CL might be due to a change in K or V or both.

This reasoning demonstrates that both approaches result in fundamental differences with respect to the relationship between CL, V and K.

Dr. Martinez: Dr. Jelliffe, in your 2018 AAPS J manuscript (12) you state that “the choice of one parameterization over the other is based on preference or usefulness for research or clinical practice, but no longer, because of this analysis, on science.” Those who believe that a mechanistic approach dictates the need to focus on CL rather than rate constants have criticized this perspective. The argument is that the use of rate constants implies that the drug amount in the body is the driving force for drug elimination (Eq. (2)) rather than the plasma concentration (Eq. (1)), which does not make sense from a mechanistic perspective.

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: First, as it is written, Eq. (5) above describes compound interest, (an exponential growth rate), not an exponential elimination rate. K should be a negative value with a minus sign in front, to indicate loss. Because of this, in Eq. (4), CL should also be negative because it is describing a loss. Why should it be negative? Because K is, and $\text{CL} = V$ times (-K). This comes from basic differential equations, where for example, if the amount of money in your savings account is denoted by A, then $dA/dt = -kA$ in describing drug excretion, and $dA/dt = kA$ in describing the growth rate of your money. This also illustrates the total generality of

mathematics in describing events, with no reference at all to “mechanism.”

Second, if CL is the unique parameter, as in Eq. (4), there is an immediate contradiction in Eq. (5), below, stating that that $CL = V \times K$. Clearly, CL is not at all a unique parameter. It depends on V and K.

Third, we can also write that

$$\text{Elimination rate} = V \text{ times } (-K) \text{ times } C \quad (6)$$

It is equally as valid as Dr. Proost's Eq. (4).

Fourth, the statement above that “Mechanistically, this implies that an observed change in CL cannot be due to a change in K, nor to a change in V” is something I simply cannot understand. I have tried my very best to understand this, but I simply cannot.

Fifth, the principle of invariance is an implication of a mathematical theorem and therefore cannot be so summarily disregarded.

Sixth, I cannot find any evidence for what Dr. Proost says above, that “CL and V are independent parameters, and it follows that K is dependent on CL and V”? Simply saying that they reflect different physiological processes does not make them mathematically “independent” without further mathematical evidence. I cannot find any evidence for this view except that many appear to believe so, probably because of the way they were trained. Why are CL and V “independent”, and why should K be “dependent”? Equations 1–3 above clearly show that all three parameters are intimately and inextricably inter-related. Each parameter (CL, V or K) is clearly dependent on the values of the other two. Viewing Eqs. (1–3) from a “mechanistic” perspective is not part of math.

Seventh, since $K = CL/V$ as in Eq. (2), it really does not matter if one writes K or CL/V on a piece of paper. This is just one example. V and CL are simply stated to be independent at the beginning of several books, but without any further mathematical evidence that I can see. Using a mathematical approach based on science, employing any of the three equally valid parameterizations, has great significance when it comes to the real-life world of bedside utility in clinical care.

Eighth, Rowland, Benet, and Graham (1) describe “Clearance concepts” in pharmacokinetics. Concepts are ways of thinking about something. The V and CL parameterization has been found useful by those devoted to studying mechanisms governing drug behavior. It has influenced generations of students who have been trained in these particular ways of thinking. For many years, the pharmaceutical industry has been the principal area in which these ways of thinking have been used, almost totally with a view to understanding mechanisms governing drug behavior.

However, pharmacokinetics is only a part of the wider mathematical area of compartmental analysis. It employs the basic mathematics of compartmental analysis, including the *world-wide use of amounts and rate constants*. The recent insight provided by the principle of invariance (13) now serves to reconcile any remaining controversy between these two areas. Not “clearance concepts” and ways of thinking, but rather the full scientific tools of mathematical descriptions, are the real foundations of the study of drug behavior.

Furthermore, while concentration is the main driving force for passive drug movement across a membrane, it still is a true statement that the amount of drug A_t remaining after excretion for a certain period of time t is correctly expressed as $A_t = A_0 e^{-kt}$. Just as it does not matter if one writes K, for CL/V on a piece of paper for example, one can write with equal validity that $A_t = A_0 e^{-(CL/V)t}$, one can also write $(\text{Conc} \times V)$ instead of A. All expressions preserve exactly the same meaning and obtain exactly the same numbers, with the same likelihood values, using maximum likelihood estimation.

In mathematics there is no assumed “driving force.” The assumption of a “driving force” seems to me to be a big (and unnecessary) issue here. We start with a certain data set which we wish to model. If one parameterization might give results that are more likely mathematically, using the method of maximum likelihood estimation, that parameterization truly would be a better and more valid one. However, that is not the case. All three parameterizations give results that are equally likely given the data. That is the meaning of the principle of invariance (13).

One additional comment. This concerns the general approach of adaptive control of a system, described long ago by Bellman for example (17). The “mechanistic” school, usually devoted to “pharmacometrics,” talks about monitoring and dosage adjustment but has given little serious consideration to the power and potential of methods to *learn* optimally about a system (the PK/PD drug system in a patient) while *controlling* it at the same time.

Adaptive control is designed to develop inputs to learn about and control a system to achieve a desired target goal or output, first by providing an input to the system such as a dose, by monitoring the responses of the system, and by adjusting the input to more precisely control it to achieve the desired target goal. Aircraft, missiles, trains, oil refineries (controlling the composition of hydrocarbons in gasoline), and even economic systems, are just a few examples. Adaptive control is a totally general approach used in widely different fields (including self-driving cars and PK/PD) for planning both the dosage and the TDM strategy in a coordinated manner to optimize learning about the patient while having to treat him/her at the same time (14–16).

Further, lack of consideration of newer and improved methods of modeling and monitoring has isolated the current “mechanistic” approach to PK/PD from optimal patient care, and very likely from optimal quantitative mechanistic understanding of drug behavior as well. Much thought has correctly been given to such understanding for the pharmaceutical industry and drug development. However, little thought has been given to what is always the final product—practical bedside care of a patient. I think that if the field can be freed from the constraints of its current reliance on outdated parametric models and their associated statistical approaches, it is likely that the newer and better methods, including nonparametric (NP) modeling and multiple model (MM) dosage design (14,15), can further enhance not only our understanding of drug behavior but also of how to achieve optimal therapeutic precision.

These methods deserve more consideration than they have received to date. All this can be done using any of the three parameterizations, if the data to be modeled permit.

Dr. Proost: The evidence that “CL and V are independent parameters” has been given above. Consequently, K must be dependent on CL and V, according to Eq. (2). Furthermore, the statement that “one can substitute ($\text{Conc} \times V$) for A” implies that the rate of elimination is proportional with the plasma drug concentration, with proportionality constant $K \times V$, which equals CL according to Eq. (2). This demonstrates (again) that CL is dependent on K and V.

Equations (4) and (5) describe the rate of elimination and are identical to the equations used elsewhere, e.g., in reference 12. The rate of elimination is a positive quantity, according to the definition given above. Therefore Dr. Jelliffe’s comment that K and CL should be negative is not correct, and, to my knowledge, never used in practice. As stated above, Eqs. (4) and (5) are mathematically equivalent and interchangeable. Therefore, there can be no contradiction, nor is there any argument against CL being a unique parameter describing elimination, as follows directly from Eq. (4). Mathematically, it is correct that $\text{CL} = K \times V$. However, the mechanistic approach in Eq. (4) demonstrates that CL is a unique parameter describing elimination, independent of distribution.

I agree with Dr. Jelliffe’s statement that in mathematics there is no assumed “driving force”. However, from our knowledge about the kinetics of the elimination processes we conclude that the plasma concentration is the driving force for elimination. So it is logical, and useful, to apply this knowledge in our models by a mechanism-based parameterization. There is no future in PK modeling for optimal patient care if such opportunities are ignored.

Indeed, mathematics is the language used to describe drug behavior. But this does not imply that each mathematically correct approach is equally appropriate for understanding the relationship between drug and patient. In my view, a mechanistic approach, if available, is preferred over an empirical mathematical approach.

I fully agree that denying math and its principles is denying science, but denying fundamental mechanisms governing PK leads to scientific isolation as well. I disagree that the “mechanistic” school basically ignores the most important clinical subject of adaptive control as described long ago by Bellman (17). Rather, adaptive control can be applied based on both the clearance approach and on the rate constant approach. Most certainly, I contend that mechanistic models provide the preferred approach for predicting the effect of changes in the PK in individual patients. Please note that a mechanistic approach is complementary to, and not excluding, the mathematical approach.

Dr. Martinez: One of Dr. Proost’s expressed concerns with the “rate constant approach” is that “since K is assumed to reflect elimination, if V decreases, e.g. by displacement of drug from tissue binding, then K will not change. Mathematically, it would then be assumed that CL must have decreased, which implies that the daily dose should be decreased.” However, in examining the Jelliffe manuscript, it seems that this argument is not consistent with what he stated. Rather, if there was knowledge of a change in V, TDM would allow for insights into the change’s PK and its consequences to the patient. With TDM, PK parameters can be estimated and as such, can be used to determine if changes in dose are needed. The mathematical relationships are used to facilitate an

understanding of what is happening within the patient. Thus, there does not appear to be any contradiction with the mechanistic perspective on this issue.

Drs. Jelliffe and Proost, please comment on this perspective (i.e., use of the mathematical relationships to support dose optimization as informed through TDM).

Dr. Jelliffe: First, I wish to emphasize the importance of fundamental understanding. I am sure that our mutual desire is to enhance knowledge of the relationship between drug and patient. However, I also wish to emphasize that much has happened in mathematics that now removes PK from the constraints imposed upon it by conventional outmoded parametric population models. The newer and more capable mathematical tools seem not to have been considered by the current mechanistic community. They are, however, worthy of close attention (14–16,18).

Second, the mechanistic approach has *similar and equal* validity. Equal. No more, no less. While as a clinician I prefer V and K myself, one parameterization may be useful in a certain situation while another may not. However, all three parameterizations have *equal* scientific validity. I generally prefer V and K myself for convenient bedside use and I find V and K generally more useful for my job. If one parameterization were better scientifically, or gave more likely results mathematically, I would use it.

Third, I prefer treating patients without making assumptions. Specifically, I do not wish to speculate about whether or not K changes if V does, and everything else stays the same. I do not wish to mix the descriptive and nonmechanistic language of mathematics with any assumed “mechanism” or “driving force”. TDM is the way you acquire data about a patient’s model parameters - without assumptions - and obtain a Bayesian posterior model, using any of the three parameterizations above, V and CL, V and K, or even CL and K. The Bayesian posterior then becomes the Bayesian prior for the next cycle of planning the upcoming maximally precise dose and a new optimal TDM strategy.

With that in mind, for maximally precise dosage, the clinician must begin individualized therapy by first setting a specific individualized point target therapeutic goal for each patient. This goal can be a therapeutic target concentration in the central (serum concentration) compartment, a specific AUC, or a specific profile for that particular patient according to the clinician’s perception of what that patient needs. However, the target also can be a specific amount or concentration in a peripheral compartment. There is also an associated and inevitable risk of toxicity one must decide to accept in order to obtain the hoped-for benefit of the drug, but above which the clinician feels it is too risky to exceed. This is where clinical judgment is required in setting the specific point target goal for each patient.

Once that patient’s target goal has been set, the task is to dose to hit it with maximum precision, and to monitor response optimally and most cost-effectively, to get the best quality information about the patient’s response for use in planning the next therapeutic cycle of dosage and TDM to come. There are general mathematical methods for optimizing how one learns best about the patient and his/her response while having to treat him/her at the same time (14,17).

Dr. Proost: As a clinician, Dr. Jelliffe correctly states that one needs data to be able to detect a change in one or more PK parameters. However, in many cases a change can be expected, e.g., after a change in glomerular filtration rate (GFR), a change in metabolic clearance after co-administration of an enzyme inhibitor or inductor, or a change in plasma protein binding or tissue binding after co-administration of a displacing drug.

When using the clearance approach, the mechanistic basis allows predicting how the PK will change in the case of a change of one or more physiological or pharmacological processes, even in a clinical setting if no plasma concentration data are available, e.g., to predict the changes in PK in the case of renal impairment. Using the correct theoretical interrelationship of the PK parameters is not “speculation” nor does it “confuse math with a so-called “mechanism.” Mathematics alone will not be helpful in such situations, since it does not provide a mechanistic understanding of the relationship between patient physiological changes and alterations in drug PK.

There are many situations where such a prediction may be useful, such as in the case of changes in tissue binding. The clearance approach predicts that CL is not affected by a decrease in V due to displacement of tissue binding by a competing drug since CL and V are independent and the processes governing elimination (i.e., renal excretion and hepatic biotransformation) are likely to be unaffected. I fully agree that TDM is valuable for optimal treatment of the patient, but the need for TDM is not related to the question “clearance approach or rate constant approach.”

Dr. Martinez: One of Dr. Jelliffe’s expressed concerns is that with a change in V, we cannot exclude the possibility of simultaneous changes occurring in other processes. To that end, he relates the challenges associated with treating critically ill patients found to have augmented renal clearance. In this first article in the AAPSJ theme issue within which Dr. Jelliffe and colleagues discuss perspectives on the use of modeling and simulation in a clinical environment (two of the three manuscripts are still works in progress), he states that when evaluating patients with “augmented renal clearance”, it is important to know how much of this “augmented renal clearance” is due to changes in K and how much is due to V. If the rate limiting factor is organ blood flow, then a change in V (e.g., hemorrhage) could alter CL. Alternatively, changes in CL would occur, irrespective of changes in V and organ blood flow, for a low extraction ratio drug. Thus, it seems that this kind of questioning is consistent with a framework of individualized patient care.

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: First, if math alone will not provide help in the situations Dr. Proost describes above, what will? Is writing “CL/V” really somehow “better” than writing “K”? Or is writing “Concentration x V” somehow “better” rather than writing “Amt”? I simply cannot understand this. Dr. Proost himself acknowledges that Eqs. (1–3) are all equally valid, and also that one can always get K by simply dividing CL by V. We must now keep in mind that getting K this way is only permissible because of the principle of invariance. We have not been used to thinking of that, but there it is now, for all to see, and to respect.

Second, I do not trust assumptions or predictions such as those which are made above using a “mechanistic” approach, for example, as “if V decreases, CL remains the same and therefore K *must* increase”. If V should decrease, perfusion might also, and that might also decrease K. Further, what is the quantitative degree of the change? By how much should a dose be changed? At the bedside, I try not to assume what *must or must not happen* concerning any individual patient. Getting data is the key.

Third, I have seen examples given in which CL is *assumed to remain constant* and K increases upon a decrease in V, just as Dr. Proost states. However, I also have seen just the opposite example given, where K is *assumed to remain constant after a decrease in V*, with a resulting decrease in CL.

Which is correct? It all depends on what is assumed. I do not trust such assumptions. Especially when dealing with a patient having high intra-patient (inter-occasional) variability with changing model parameters and renal function over time, my bedside experience using the Bestdose clinical software employing Interacting Multiple Model (IMM) estimation (16) has shown me that V and K, for example, change independently and unpredictably over time, and may not follow *at all* the above predictions described by Dr. Proost.

Fourth, we monitor serum creatinine, and may or may not get timed urine collections to estimate creatinine clearance as clinically indicated and feasible. This has been done for years. It is easy to link these estimated changes in renal function either to K or to CL. We have been doing this for decades with the free Bestdose software, and so have many other commercial software programs.

Dr. Proost: The use of any PK model is based on a number of, often not explicitly mentioned, assumptions.

The assumption that a change in V by hemorrhage could alter CL needs some further analysis. Hemorrhage will result in a decrease of the circulating blood volume. Because most drugs have a volume of distribution that is much larger than the blood volume, even a severe decrease of the blood volume is unlikely to result in a significant decrease of V. The decrease of the circulating volume may indeed result in a decrease of CL for drugs with a high extraction ratio due to a reduced organ blood flow. However, such a change is not due to the decrease of V per se, but rather to the decreased perfusion because of the reduced circulating volume. This does not imply that CL is dependent on V, albeit that both changes may have the same primary cause, e.g., when plasma protein binding changes.

The influence of a change in plasma protein binding is quite different from that of a change in tissue binding. Again, however, the clearance concept allows a solid prediction of the expected changes in PK parameters.

Finally, while I fully agree that TDM is valuable for optimal treatment of the patient, TDM should be performed with measurement and modeling of the unbound concentration to control the unbound concentration. TDM based in total concentration may result in serious overdosing.

Dr. Jelliffe: First, models are made from data. While measurements of unbound drug clearly are best, useful models are also made from whatever response it is possible to measure. Many clinical models are based on measured total concentrations in serum, and even on whole blood. The

model parameter values obtained from such data reflect the relationship between doses given and whatever response is measured. The relationship to dosage will be correct as long as unmodeled relationships do not change. It depends on how you perceive, model and control the system. As long as binding remains constant, for example, the relation between dose and measured response will remain the same, whether what is measured is unbound concentration, total serum concentration, or whole blood. And if binding changes, we need to get data to clarify *and quantify* what is happening to the patient. That is one of the important reasons we do TDM—to discover and quantify such changes.

Second, even the *directional* predicted changes as described above by Dr. Proost often are not correctly predicted, and do not occur as he states. That has been my bedside experience using IMM analysis, as discussed above. Data (and often IMM analysis) are essential to best track (not predict) changing model parameters over time. As Yogi Berra, the great baseball player, once said, “predictions are hard, especially about the future.” I would add that this is doubly hard at the bedside of an acutely ill and unstable patient.

Third, to categorize extraction ratios and to make assumptions and predictions concerning dosage reflects a speculative rather than a quantitative and clinically responsible approach to the patient. I think that is poor medicine. While a “mechanistic” approach may (but may not) help a physician relate changes in physiology to directional changes in drug PK, it is only a mathematical approach, employing any of the three parameterizations if the data permit, by which a clinician can see, quantify what is going on with a patient, and dose optimally, based on that data, to hit a target therapeutic goal with maximum precision and minimal uncertainty. Maximum precision requires nonparametric (NP) models and MM dosage design. It cannot be achieved by using current parametric models based on single point summary “group values” (5,14,18).

Dr. Proost: In the case of a change of plasma protein binding, when modeling total plasma concentration, predicted dosages will be correct only if the target concentration is based on the unbound concentration, as follows from a mechanistic approach. This stresses the need for a mechanistic approach, which is complementary to, and not excluding, the mathematical approach.

Dr. Martinez: Considering a slightly different objective, when we seek to understand drug PK from a population perspective (i.e., without the use of TDM but rather from an initial set of blood concentration profiles from animal models or from normal human subjects), we typically seek to obtain a mechanistic understanding of the variables that can influence in vivo drug behavior. Such information is essential from the perspective of drug product development and labeling to inform the practitioner. In that situation, we find it most convenient and useful to employ mechanistic approaches for estimating CL and V (e.g., based upon drug physicochemical parameters, tissue composition as a function of age and body weight, clearance pathways as described by in vitro microsomal or hepatocyte studies, impact of enzyme polymorphisms, likelihood of drug-drug interactions, transporters involved in absorption, elimination, organ partitioning, etc).

It would seem that this viewpoint is consistent with the comment posted by Dr. Nick Holford that “The important reason to parameterize in terms of clearance and volume comes when applying pharmacokinetics in a population context. Covariates usually influence clearance and volume independently. Clearance and volume are reasonable population constants whose group values can then be sensibly adjusted in light of covariate information such as weight, renal function, other drugs, etc.” (4).

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: First, developing covariates for CL and V is done quite as reasonably and easily for V and K, and for CL and K. However, V is often related to body weight, surface area, or allometric scaling, while CL, because it is the product of, and therefore dependent on, the individual values of V and K, is also related to renal function, for example. To me, the situation becomes confusing because CL is a joint product, which is dependent on both V and K. This is one reason I generally prefer V and K. They help me understand these things separately, not mixed together.

Second, as to information in a drug label, statements about “half-life”, are enormously helpful to me, and are quite intuitive to everyone at any level of training. Similar statements about CL are less intuitive for almost everyone in a hospital setting. Half-life is simple and useful for nurses and untrained personnel as well.

Third, another important point concerns Dr. Holford’s stated wish above to obtain single summary “group values” for population modeling. Parametric models based on such “group values” simply do not get the most likely results given the data (18,27).

We can do better now than simply getting “group values”. We can start by recognizing that a population is really a collection of *individual subjects*. The true ideal population model would obtain each subject’s model parameter values exactly, rather than summarizing them with single point “group values” (18). It is much closer to the ideal and to the truth to try to estimate *each subject’s* model parameter values using the NP population modeling approach (14,15,18,27). Direct comparisons have been made, with results favoring the NP approach (27). However, it has received relatively little attention.

Further, maximally precise achievement of a target goal can never be achieved by the parametric population models in much current use, employing such summary “group values”. NP models and MM dosage design are required for maximally precise dosage (14,15,18). This has been known for years (I presented the first NP approach in Dr. Holford’s presence, probably about 1987, in Sydney). However, the NP approach seems not to have been recognized by the “mechanistic” community. This will be discussed further in a subsequent communication.

Dr. Proost: I fully agree with the statements made by Dr. Martinez. Besides, it is not clear how Dr. Jelliffe concludes that “CL is dependent on V and K.” This is in clear contradiction to the principle of invariance, which proves that the three parameterizations are mathematically equivalent and interchangeable.

Dr. Martinez: Dr. Jelliffe, one of the issues raised by Dr. Proost is that physicians should not be reluctant to use CL concepts. Are you implying that clinicians prefer rate constants to CL? If yes, why, and how does this influence dosing recommendations?

Dr. Jelliffe: First, all three parameterizations are equivalent and *interdependent*, as shown in Eqs. (1–3). Knowing any two permits estimation of the third. Each one is dependent on the values of the other two. This is why CL is dependent on V and K.

Second, clinicians are often comfortable using V and CL, perhaps in part because of their training. However, some, like myself, find it often inconvenient, and prefer the equally valid V and K. We should be free to do so without unwarranted and unscientific criticism, especially now, because of the principle of invariance. More information on this topic is below in the discussion on augmented renal clearance.

Dr. Proost: Please note that “the clearance approach” is fully compatible with the use of the elimination rate constant in clinical applications. K can always be obtained using Eq. (2), so there is no criticism in the use of “V and K.” My criticism with respect to “V and K” refers to situations where the question about independence of the parameters is relevant, e.g., in predictions. In other cases, while one is free to use a parametrization of choice, it is the preference of a nonmechanistic versus mechanistic approach that is, in my view, questionable.

The notation that the use of clearance is less intuitive to clinicians is indeed sad. Actually, clearance is directly related to the daily dose, using the simple and fundamental relationship, which follows from Eq. (4) at steady state:

“average dosing rate IN = average elimination rate OUT”

This can then be expressed as follows:

$$\frac{F \times \text{Dose}}{\tau} = \text{CL} \times C \quad (7)$$

where F is bioavailability, dose is the administered dose, τ is the dosing interval, and C is the average plasma concentration at steady state.

Dr. Martinez: Dr. Jelliffe, Dr. Proost asks why you suggest that augmented renal clearance should not be interpreted as an enhanced ability to eliminate the drug? He continues with the statement that “how much of this augmented renal clearance is due to changes in K, and how much is due to V” is the wrong question. He has expressed the position that the correct question is: what is the change in K and what is the change in V? It seems that based upon the fact that $K = \text{CL}/V$, he is in fact stating the same questions that you are raising. In a hospital setting, one needs to inquire about the pieces of information readily acquired by the physician. These include drug concentrations and amount of drug and fluids given. The patient in an acute care facility may not be a candidate for studies of drug CL and even if that were possible, this value would likely shift over the course of therapy. Knowing amounts of drug given and using models that can support dose adjustments can then be used to estimate the rate of drug elimination.

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: First, it is only because of the principle of invariance that Dr. Proost can say what he does about getting K from Eq. (2).

Second, Eq. (7) applies only when everything is in a nice steady state, and one can somehow know the average serum concentration over that time. The problem is that sick patients all too often are not so obliging and stable!

Third, returning to the example of patients with augmented renal clearance - yes, augmented renal clearance certainly exists and should be correctly interpreted as increased renal function (19,20).

However, I am more skeptical than Dr. Proost. This is because there are also *apparent* increases in creatinine clearance due to reduced creatinine production, with lowered serum creatinine concentrations, in similar acutely ill patients. Both can occur, and perhaps together. That is the problem. The problem can only be resolved by carefully timed urine collections in each patient if clinically required and feasible. Carefully timed urine collections are essential to document augmented renal clearance and to distinguish it from apparent increases due to reduced creatinine production.

At the bedside, I generally prefer to know V and K separately. K, and the slope of its relationship to either measured or estimated creatinine clearance, whether based on urinary data or not, tells me more about half-life. That is intuitive and useful to me. In addition, I would very much like to understand how a sick patient’s renal function can be increased (or appear to be) when someone gets so sick, only to have it decrease (or appear to decrease) later on, as he/she gets well.

A decrease in V with recovery from illness was first described for aminoglycoside therapy by Haug and Slugg at the Cleveland Clinic many years ago. They called it “Vd collapse” (21). As a patient recovers, creatinine production may well increase up to that patient’s baseline, and such “Vd collapse” may well take place.

We still have much to learn about both processes, and about their evolution throughout the course of a patient’s illness. This requires data, not speculation about what also changes if V changes. We also need to quantify the degree of such changes, not just to speculate about them.

Because of changing V, it is not wise to assume automatically that there is a direct translation between augmented renal clearance and the magnitude of dose adjustment needed to hit the patient-specific target concentrations. Only by obtaining carefully timed urine collections can one get “true” values of creatinine clearance.

It is also interesting to note that the 95% confidence limits in the classical gold standard “true” determination of creatinine clearance using a 24-h urine collection, even in a total research setting, are quite large, about $\pm 22\%$. This is due to serum creatinine and urinary creatinine assay errors, to the errors in urine volume collection, and to the way these errors propagate to become the overall error (26).

Further, in the clinical setting, whether clearance or GFR is correctly estimated (with the above error) or not, mathematically and empirically linking the renal excretion of drugs to various less precise but usually systematically biased

estimates of creatinine clearance based on serum creatinine (and other covariates such as age, gender, weight, and body surface area) is often most useful at the bedside. While not as reliable as measurements based on timed urine collections, these simpler equations often provide a useful clinical link between the empirical behavior of a patient's serum creatinine concentration and that of the drug in question, regardless of whatever the true GFR may be. They are most helpful to guide bedside dosing in the many patients from whom urine cannot be collected.

Dr. Proost: I do not think that Dr. Jelliffe is in fact stating the same questions that I am raising. Augmented renal clearance implies that clearance is increased. So, the question is still what is the change in CL and what is the change in V? Dr. Jelliffe's question follows from the "rate constant approach." In the "clearance approach," a change in CL can never be explained by a change in K, since it is the other way around: K is dependent on CL (and V).

Besides, I'm impressed by the clinical comments of Dr. Jelliffe about augmented renal clearance and I fully accept his extensive expertise in this topic.

Dr. Martinez: Dr. Proost, if all one can get from a patient is the information mentioned above, how will V and CL, or changes thereof, be assessed over the course of therapy? Ultimately, would it not be, as suggested by Dr. Jelliffe, a mathematical analysis of drug concentration, amount of drug added, and K to estimate CL?

Dr. Proost: Modeling for the individual patient (as well as for the population) should be done in terms of clearance and volume, so CL and V are directly obtained from the modeling. There is no "mathematical manipulation" to estimate CL using K.

Dr. Martinez: Dr. Jelliffe, please provide an example of how you have used TDM, and the use of K within the framework of clinical practice.

Dr. Jelliffe: First, there is no current way I know to follow or track a patient's changing model parameters *as they evolve over time* except by using the IMM approach (16). All other methods assume that the model parameter values are fixed, constant, and unvarying over the period of time covered by the TDM analysis.

I remember a telephone consultation some years ago concerning a 60-year-old patient, 68 in tall, weighing 76 kg, with a stable serum creatinine of 0.8 mg/100 mL, (estimated creatinine clearance of 97 mL/min/1.73 square meters body surface area), who was in another center, and who was in regular sinus rhythm (RSR). He was on an oral maintenance dose of 0.25 mg of digoxin daily.

One day he missed his dose of digoxin and developed atrial fibrillation (AF). He was titrated with 0.25 mg of IV digoxin, each given over about 5 min, and after four doses, he converted to RSR. He was then placed back on his daily maintenance dose. However, he went into AF again about 2 days later. A serum digoxin level drawn when he had gone back into AF was 1.0 ng/mL.

He was titrated with IV digoxin again. This time it required only two doses of 0.25 mg, and RSR was restored again. The results of a second serum digoxin level, drawn after RSR was restored, gave everyone a big surprise, as it was exactly the same as the first one—1.0 ng/mL!

How could this be? How can a patient be in AF at one time and RSR soon after, with exactly the same serum concentration? Hmmm. A puzzle.

The patient was again placed back on his daily maintenance dose of 0.25 mg, and did well for another three days, when AF returned again. He was again titrated with IV digoxin, and after 5 doses of 0.25 mg, he again converted to RSR. A serum digoxin level drawn after RSR was restored was 1.2 ng/mL. At this point, we were called to analyze his situation.

Many cardiologists will look at the three serum levels of 1.0 ng/mL in AF, and 1.0 and 1.2 in RSR, and quickly (and correctly) conclude that there is no correlation between serum concentrations and effect or clinical behavior. They are quite correct. They have also generally concluded that monitoring serum digoxin is a waste of time. In this they are incorrect. Serum digoxin concentrations do NOT correlate with clinical behavior unless the patient is in a stable steady state, trough concentrations for example, on a fixed daily dose, or in a steady state on a fixed rate IV infusion.

The useful clinical tool here was the LAPK Bestdose clinical software, employing a two-compartment model of digoxin (22,23,25) to reveal the time course of events in both the central (serum concentration) compartment and also in the peripheral nonserum compartment, *where the amount of digoxin is well correlated with clinical effect* (see the references above).

First, after fitting the population model to his three serum concentrations, we could estimate and reconstruct the entire course of his serum digoxin concentrations, and also the computed total amount of drug in his peripheral, nonserum, compartment.

We could first see that back before he first developed AF, when he was on oral digoxin, 0.25 mg/day, quite low serum concentrations were retrospectively estimated at peaks of 0.7 and troughs of 0.5 ng/mL. When he missed his dose and developed AF, they had fallen to an estimated 0.25 ng/mL. During his various titrations with IV digoxin, there were also transient serum peaks estimated as high as 2.5 to 3.0 ng/mL. There was no correlation between serum digoxin concentration and clinical effect.

However, by use of this 2-compartment model, it was possible to see what was taking place outside his serum compartment. The clinical effect of digoxin is known to take place in the peripheral, *nonserum*, compartment, on the many different cell membranes throughout the body to which digoxin is bound (22,23,25).

First, before he had developed AF, the calculated total amount of digoxin in his peripheral compartment, normalized by body weight and expressed in units of μg of drug per kg of body weight, to which the inotropic and its other clinical effects are related (22,23,25), were already somewhat low at a peak of 6.5 and a trough of 5.5 $\mu\text{g/kg}$. He developed AF when his weight-normalized peripheral compartment amounts fell to 2.5 $\mu\text{g/kg}$.

The first of the three IV titrations increased his peak peripheral compartment amount (PPCA) to 10 $\mu\text{g/kg}$. This was associated with his conversion to RSR the first time. AF returned when his PPCA fell to 8 $\mu\text{g/kg}$. RSR was achieved for the second time when the PPCA reached 11.8 $\mu\text{g/kg}$, after the second titration. AF returned when it fell to 7 $\mu\text{g/kg}$. RSR was achieved again when his PPCA rose after the third titration to 13 $\mu\text{g/kg}$.

Relating his clinical behavior to his PPCA provided the key to managing his AF. By his behavior, the patient was telling us what he did and did not like. The 2-compartment model let us listen to the patient and to “hear” what he had been trying to tell us. We were able now to realize that he was doing well in RSR when he was achieving PPCA’s between 10 and 13 µg/kg.

Because of this, a specific PPCA target goal of 11.5 µg/kg was chosen, to be achieved by an oral dose. This PPCA is usually reached about 7 h after each daily oral dose.

The ideal maximally precise dosage to achieve this target PPCA of 11.5 µg/kg was 468 µg the first day, 578 µg the next, followed basically by 572 µg/day afterward. Knowing this ideal dosage, a revised and more practical regimen was given of 250 µg the first day, followed by 625 and 500 µg on alternate days thereafter. On this regimen, his predicted peak PPCA’s were 10.28 µg/kg on the first day, followed by 10.85, 10.65, 11.17, 10.88, 11.33, 10.99, and 11.52 on the first 8 days, quite close to the target of 11.5 µg/kg.

RSR continued. He was discharged home and was still in RSR when seen in the clinic 2 weeks later. No serum concentrations were obtained, however, and no further follow-up was possible. All this was done using the Bestdose clinical software, using the V and K parameterization.

Now, let us proceed as Dr. Proost says we should, analyzing his situation using the “mechanistic” V and CL parameterization. For the central, (serum concentration) compartment (C), either parameterization V and CL, or V and K, can be used equally well.

For the peripheral compartment (P). Let us also use V and CL here, as Dr. Proost says we should, and see where this takes us. We will have.

$$\text{Rate out} = \text{Conc Central} \times \text{CL}_{cp} \quad (8)$$

and

$$\begin{aligned} \text{Rate back} &= \text{Conc Periph} \times \text{CL}_{pc} \\ &= (\text{AmtP}/V_{\text{periph}}) \times (\text{Kpc} \times V_{\text{periph}}) \end{aligned} \quad (9)$$

where

Conc Central	drug concentration in the central (serum) compartment,
CL _{cp}	clearance out from the central to the peripheral compartment,
CL _{pc}	clearance back from the peripheral to the central compartment,
K _{pc}	the rate constant back from peripheral to central compartment.
AmtP	the amount of drug in the peripheral compartment,
V _{periph}	volume of peripheral compartment, and
Conc periph	concentration in the peripheral compartment.

The problems with this approach are with Eq. (9), combined with the fact that only the central compartment

serum concentrations can be measured. It is not possible to measure a concentration in the totally abstract peripheral compartment. Specifically, the term V_{periph} (which is needed to use the V and CL parameterization), is known *NOT* to be mathematically identifiable for a two-compartment model without observations in the peripheral compartment (24). The volume of this totally abstract, nonanatomic, peripheral compartment (all the rest of the body that is not in the serum compartment, consisting of cells and cell membranes in many different tissues throughout the body) cannot possibly be known. The peripheral compartment is a totally abstract mathematical compartment which is unobservable (22,23,25). The CL and V parameterization is simply not possible for this model when only serum TDM measurements can be made. One cannot use the approach advocated by Dr. Proost in this setting. The V and CL parameterization simply will not work.

What will work? When the changes out to and back from the peripheral compartment are parameterized using V and K, the rate of drug transfer from the central out to the peripheral compartment is described as:

$$\text{Rate out} = d\text{AmtC}/dt = \text{AmtC} \times \text{Kcp} \quad (10)$$

and the rate back from the peripheral (P) compartment to central is described as

$$\text{Rate back} = d\text{AmtP}/dt = \text{AmtP} \times \text{Kpc} \quad (11)$$

where

AmtC	amount of drug in the central compartment,
AmtP	amount of drug in the peripheral compartment,
K _{cp}	rate constant from the central compartment out to the peripheral compartment,
K _{pc}	rate constant back from the peripheral compartment to the central compartment.

The amounts of drug in both the central and peripheral compartments are easily calculated when the system is parameterized as Amounts, V and K. However, there is no way to calculate either the volume or concentration of drug in this peripheral compartment using CL and V.

How do we proceed when what we have are amounts, V, and K? The central compartment serum concentrations are measured as ng/ml, but the peripheral compartment can only be evaluated as total AmtP, here stated in total ug. This total amount is then normalized by total body weight in kg to correct it for large and small patients. Body surface area might be another index to consider for normalizing the amount, or allometric scaling, but we chose body weight. When stated as Amounts in the two compartments, and using the V and K parameterization, the estimated amount and volume of the central serum compartment can readily be estimated, as well as the total amount in the peripheral compartment, normalized to body weight. All calculations are easily done, permitting management of his digoxin therapy using this clinically oriented, clearly nonmechanistic but highly useful PK model (22,23,25). It is not necessary to

know the peripheral compartment volume V_{periph} using the V and K parameterization. This is one of the reasons I generally prefer V and K .

Dr. Proost: In my opinion, this interesting clinical case demonstrates that a purely mathematical model does not add to our understanding of what happens in the patient and therefore it is not helpful in solving the case. We need mechanistic models for understanding and to treat the patient optimally.

The statement that this case could not have been solved using the “CL and V ” approach for the peripheral compartment is not correct. In the case of the “CL and V ” approach, the model parameters for the peripheral compartment are CL_{cp} , CL_{pc} and V_{periph} , as follows from Eqs. (8) and (9). {note that I raise point because Dr. Jelliffe uses the amount of drug in the peripheral compartment as the driving force for the drug pharmacodynamics}. Dr. Jelliffe correctly states that these three parameters cannot be estimated from data if there are no observations in the peripheral compartment. Similarly, the three parameters of the “ K and V ” model, K_{pc} , K_{cp} and V_{periph} , cannot be obtained for the same reason. So, for both approaches, an additional constraint is required. In the “ K and V ” approach as suggested by Dr. Jelliffe, this problem is circumvented by leaving V_{periph} unknown, since it is not needed in the presented case, relating the amount of drug in the peripheral compartment to the drug effect.

In the “CL and V ” approach the same procedure can be used by replacing the ratio $CL_{\text{pc}}/V_{\text{periph}}$ by a single parameter K_{pc} . Then, Eq. (9) may be written.

$$\text{Rate back} = \text{Conc Periph} \times CL_{\text{pc}} = \text{AmtP} \times K_{\text{pc}} \quad (12)$$

Now, Eqs. (8) and (12) can be solved in a similar way as Eqs. (10) and (11).

Alternatively, using the equity $CL_{\text{periph}} = CL_{\text{cp}} = CL_{\text{pc}}$, CL_{periph} and V_{periph} can be estimated from the data. Note that the constraint $CL_{\text{cp}} = CL_{\text{pc}}$ is not critical and may be replaced by any constraint of the ratio $CL_{\text{cp}} / CL_{\text{pc}}$, providing the same amount in the peripheral compartment. The constraint $CL_{\text{cp}} = CL_{\text{pc}}$ is the “natural” choice, since it implies that the distribution clearance is identical in both directions, implying that the concentrations in both compartments are equal in the case of steady state. Similarly, V_{periph} may be obtained using the “ V and K approach” with a constraint $K_{\text{cp}} \times V_{\text{c}} = K_{\text{pc}} \times V_{\text{p}}$, which is identical to the constraint $CL_{\text{cp}} = CL_{\text{pc}}$.

Dr. Jelliffe: First, one cannot use a steady state to describe this patient’s situation and his management. That option is not available when caring for patients. For example, this patient’s dosage was changing over time, and so was his clinical (and PK/PD state). So, it is not possible to use the constraints suggested by Dr. Proost.

Second, what he has done in Eq. (12) is to convert back to the V and K approach, as in Eqs. (10) and (11). However, in order to do this, he has needed to introduce an ad-hoc choice for the unobservable parameter V_{periph} . This is an example of why the CL and V approach fails in this situation.

Dr. Martinez: I would like to proffer the following as a proposed conclusion to this debate: *How one elects to parameterize a model should be considered from the perspective of “fit for*

purpose”. Ultimately, whether evaluated mathematically or mechanistically, knowledge of drug elimination and distribution behavior is essential for dosage adjustments or for understanding disease processes on systemic drug exposure. The important question is not how CL , V , or K are estimated but rather that the necessary supportive information is available to calculate the dosage recommendations/adjustments.

Drs. Jelliffe and Proost, please provide your thoughts and comments on this perspective.

Dr. Jelliffe: I agree. I think people will use a particular parameterization based on its convenience or fitness for a particular task. To do this properly, one must appreciate the mathematical foundations, theorems, and differential equations of compartmental analysis which we use to model PK/PD processes. We should study and do research on how various genetic and metabolic factors influence V and CL or V and K , or CL and K . For bedside use, nonmechanistic PK models are often necessary, highly useful, and mathematically rigorous.

Data (not speculations or assumptions) are key in research, in the industry, and at the bedside. Data should be analyzed using optimal tools for research and bedside adaptive control of PKPD systems to do the desired job best.

The point of the present discussion relates to long-held views that a so-called “mechanistic” approach, based on V and CL , has been superior. Rowland outlined a good description of the V and CL approach (1). This approach has generally been used by those doing research on drug behavior and mechanisms of action. However, less thought has been given to practical clinical use of PKPD models, especially effect models of clinical response as described here (22,23,25).

Because of this, I generally prefer for my own clinical use the now proven conclusion that since CL and V , K and V , and K and CL are all equally valid, how one parameterizes a model depends on convenience, suitability for the task, or simple preference. I really do not believe I should be criticized for my general clinical preference for V and K any longer.

I am also most fortunate to have been mentored by Richard Bellman, and by his colleagues, Drs. Alan Schumitzky, Mark Milman, and David Bayard, who are mathematicians, and whose outlook is far from being limited to “mechanistic” PK.

Dr. Proost: I agree, except for the first statement: “How one elects to parameterize a model should be considered from the perspective of fit for purpose.” Modeling in terms of CL and V is mechanism-based and therefore the preferred approach for any situation. There is no obvious reason to model nonmechanistically in terms of rate constant and volume.

Dr. Jelliffe: And similarly, I contend that there is no reason not to use any of the three parameterizations, except when one parameterization permits the job to be done but another does not, as in the management of the above patient on digoxin, where V and CL did not work but V and K did. I am very much indebted to Dr. David Bayard for his analysis of the problem of parameter identifiability concerning the digoxin model discussed here.

Dr. Proost: As explained above, this case could have been solved using the “CL and V approach” as well. Because of the principle of invariance, both parameterizations are mathematically equivalent and interchangeable. Therefore, a problem that can be solved using the “ K and V approach” can also be solved using the CL and V approach, and vice versa,

providing the same results. So, there is no need to use a nonmechanistic parameterization.

Dr. Martinez: Upon embarking on the creation of this discussion paper, my goal was to allow for Drs. Proost and Jelliffe to expand upon the basis and application of their two divergent perspectives and to focus the discussion purely on the corresponding scientific underpinnings. My hope was that through this dialogue, there could be a better appreciation of how the approach to PK analysis may vary as a function of situation and application. However, what has emerged is that two brilliant scientists and PK thought leaders continue to hold strong divergent perspectives.

This discussion in fact highlights that the beauty of our discipline is that we need to make room for and appreciate markedly different expert opinions. I am convinced that such controversies can provide an incentive for growth.

Finally, these kinds of lively discussions are healthy and need not be shied away from. I hope that this effort provides an encouragement for expert dialogue on other topics. Accordingly, our responsibility is to expose future scientists to divergent perspectives and encourage them to utilize their own experience, their own evaluation of the special needs of a particular project, and to choose what and how they will apply the varying PK and mathematical principles.

I wish to express my sincere appreciation to Dr. Roger Jelliffe and Dr. Johannes Proost for their willingness to participate in this challenging endeavor.

Drs. Jelliffe and Proost: And we thank you so much, Dr. Martinez, for all your careful thoughts and hard work in making this discussion possible.

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