Linear Free Energy Relationships. Local Empirical Rules – or Fundamental Laws of Chemistry. A Reply to Kamlet and Taft

Svante Wold* and Michael Sjöström

Research Group for Chemometrics, Institute of Chemistry, Umeå University, S-901 87 Umeå, Sweden

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In a recent article, Kamlet and Taft challenged our view that linear free energy relationships (LFER), and in particular linear solvation energy relationships (LSER), are best seen as locally valid linearizations of complicated functional relationships. Here we give evidence that our view is supported by observed data, while that of Kamlet and Taft is not.

We do *not* challenge the statement of Kamlet and Taft that their LSER fit a large number of solvent effect data with some statistical significance. We show, however, that in these data, as well as in other data measured on series of chemical reactions, *there are systematic parts which cannot be predicted by general models like the LSER of Kamlet and Taft.*

These system-specific regularities are often not negligible and sometimes substantial, which means, in our terms, that a given LFER or LSER is not generally applicable. Indeed, this was also found by Kamlet and Taft, who frequently discover "outliers" and unpredictable differences in behaviour between families of solvents when applying their LSER.

To be predictively efficient, a model should be recalibrated for each new investigated system. This is easily done with modern data analytic methods, such as PLS modelling.

Introduction

In a recent article in this journal,[1] Kamlet and Taft (henceforth abbreviated K-T) claim to present evidence that their linear solvation energy relationship (LSER) is generally applicable in "every area of chemistry, and many of biology, where physicochemical, biological, pharmacological, and toxicological properties depend on interactions between solutes and solvents".

This generality would be inconsistent with our previously presented statement, supported by rigorous statistical analysis of several pertinent chemical data sets, that empirical models including LSER have only local validity for classes of similar chemical systems or processes.[2]

In the present article, we try to disentangle the apparent inconsistencies between the views of K-T and our own. We propose that our different opinions are due to differing interpretations of the concept of applicability of a scientific model.

Recapitulation

Let us first briefly review linear free energy relationships (LFER), of which LSER is a particular case dealing with solvent-solute interactions. Originally,[3,4] LFERs were formulated as linear relations between the change in free energy in different reaction series subject to analogous modifications, e.g. the change of the pK_a of a reactant or the change of a substituent.

As shown by Higman,[5] Malinowski,[6] Palm[7] and Wold and Sjöström,[8] these models in their simplest form are factor or principal components (PC) models with one product term as follows:

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*To whom correspondence should be addressed.

$$x_{ik} = c_k + t_i b_k + e_{ik}. \tag{1}$$

Here x_{ik} denotes data measured on the k.th series in its i.th modification. The parameters c_k, t_i and b_k are chosen so that the deviations (residuals) e_{ik} are small.

In the early use of LFER, the custom was to define the "scales" t_i by means of measured values in standard series, but since the models have the form of factor or PC models, statistical estimation methods can be used to estimate parameter values c, t and b which makes a model optimally fit a given set of "calibration data".[9,10]

In the Hammett relation, for example, x_{ik} denotes the logarithmic rate or equilibrium constant in the k.th reaction series with the i.th substituent. The value for the "unsubstituted" compound of the series (substituent = H) defines the value of c_k. The parameters σ_i corresponding to t_i are called substituent constants and the parameters ϱ_k (b_k) are called reaction constants. The former (σ) are often interpreted as expressing the "inductive" effect of the i.th substituent on the reaction and the latter (ϱ) as expressing the sensitivity of reaction k to this effect.

$$(\log k)_{ik} = (\log k)_{0k} + \varrho_k \sigma_i + e_{ik}. \tag{2}$$

In the 1950s LFERs with several product terms were formulated and interpreted as modelling the influence of several effects on the reactions, one effect per product term. The K-T LSER is an example of this type of multiple term LFER.

$$x_{ik} = c_k + \sum_{a=1}^{A} t_{ia} b_{ak} + e_{ik}. \tag{3}$$

The statistical isomorphism between LFERs and statistical PC models inspired an alternative interpretation of LFERs as being linearizations of complicated unknown functional relationships, linearizations valid locally for similar reaction series and substituents (or other modifications, i.e. solvents in LSERs).[2,7,8] Thus, it can be shown that, provided the modifications corresponding to the index i are small, a few term LFER (PC-model) can always be found that well approximate to any measured data on the set of investigated reactions.

PC-models have the same approximation properties on data tables as polynomials on continous

data. In a small "local" domain, a good approximation can always be found, but the approximations differ between different domains.

The two views of LFER/LSER

Today there are, therefore, two interpretations of LFERs. First the traditional one supported by K-T, namely that one can specify a number of "effects" in chemistry and combine them linearly in any given application to a multiple term LFER. This means, among other things, that chemistry, like classic 19th century physics is theoretically finite, and that basic research at some future date no longer is needed because all effects are discovered and quantified.

In the second alternative interpretation – called that of chemometricians by Kamlet and Taft, but which actually originates with Polyani[11] and Hammett[12] – chemistry and other fields of science are seen as the study of infinitely complicated systems which, however, when only slightly modified, can be modelled by means of perturbation theory, i.e. linearized relationships based on Taylor expansions of continuous multivariate functions.

This more humble view of the theory of LFERs and other semiempirical models means that in any fresh problem area there will be regularities in observed data that cannot be inferred from the behaviour of previously investigated systems. This does not mean that new systems are totally unpredictable, but rather that the regularities in data observed in any system can be divided into two parts, one part common with other systems and one part which is system specific (Fig. 1). The larger the common part, the closer is the similarity between the new system and the ones previously investigated.

We can formulate the K-T viewpoint as being that the system specific regularities in their LSER are zero, i.e. that G (for generalizable information) in Fig. 1 is not significantly different from 1.0. Our view is that the system specific regularities are not zero and often not negligible with respect to the precision of the data, i.e. that G is often significantly smaller than 1.0.

Empirical evidence for LFER being local models
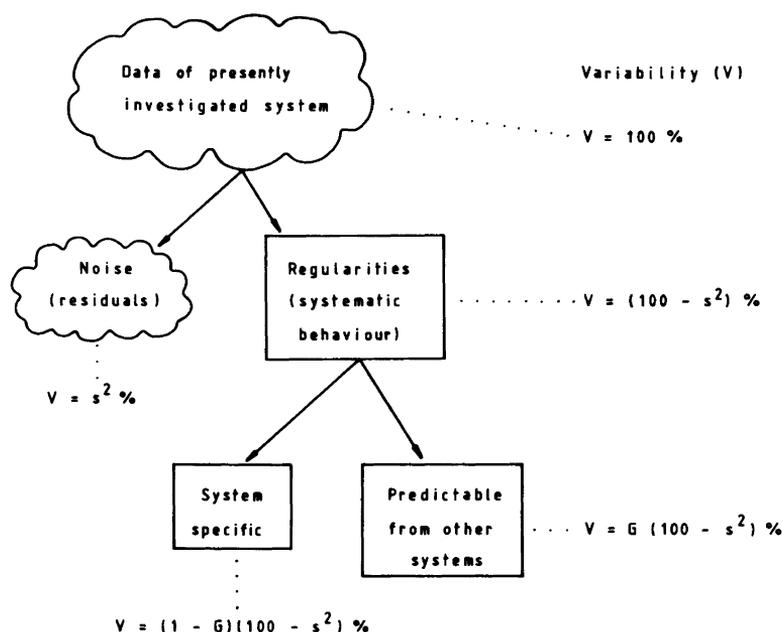
In this debate with K-T, we mainly use evidence

Figure 1. The variability of experimental data measured in a given series, process or system, can be divided into three parts. The present debate considers whether the system specific part (1-G), is significantly different from zero.

from the field of LSER, since this is the battleground chosen by these authors. Reading their own papers on LSERs, we repeatedly find statements in direct contradiction to the proposed generality of LSERs. For instance, many correlations are restricted to what they call "select solvents", e.g. no 6–11, 63–71 and others (numbering according to Table 1, Ref. 1). In Ref. LSER-4 (Table 1), it is stated: "For reasons stated above, correlations have been restricted to families of solvents with similar polarizability characteristics, *i.e.* only non-chlorinated aliphatic solvents

Table 1. Comparison between error of measurement and residual standard deviation in Kamlet-Taft examples (a)–(k). Except for sets (d) and (f), the error of measurement corresponds to an experimental precision is deliberately assumed to be *large* (2 SD = 5 %). For UV λ_{max} (set d) we assume a precision better than 1 mμ[25] and for ^{15}N NMR (set 10) we assume a precision of 0.3 ppm, being a compromise of the within experiment precision of 0.1 ppm and between lab precision of 1 ppm.[26]

Kamlet-Taft example (n)	Data type	Units	Experimental precision	KT-LSER-fit (residual SD)
a (93)	Molar solubility (H$_2$O)	log	0.03	0.144
b (25)	Molar solubility (blood)	log	?	0.16
c (18)	Free energy of transfer	kcal mol^{-1}	0.1–0.2	0.6
d (32)	Frequency of max UV-abs	cm^{-1}	10–30	100
e (23)	Rate of t-BuCl solvolysis	log	0.02–0.03	0.36
f (16)	^{15}N NMR shifts	ppm	0.2–0.3	0.42
g (37)	Adsorb. on activ. carbon	log	?	0.19
h (8)	Complex formation const.	log	0.02–0.03	0.06
i (36)	Bacterial EC_{50}	log	?	0.25
k (28)	HPLC capacity factors	log	0.02–0.03	0.07

or, in a few instances where sufficient data were available, only aromatic solvents".

This is a typical application of local models where the fit and prediction is good for solvents of the same type as those for which the model was calibrated, but less precise outside this domain.

In Ref. 2 we used, among other examples, data of K-T to show that a local LSER model with two product terms calibrated on solutes which are hydrogen bond donors (HBD) predicts significantly less than 100 % of the systematic behaviour of non-HBD solutes. The systematic behaviour of the non-HBD solutes is adequately modelled by a local one term LSER. The solvent scale in this latter LSER cannot be seen as a combination of the two scales of the HBD model. These results, which K-T prefer not to discuss, is inconsistent with a view which regards LFERs and LSERs as generally applicable models, at least in the way we interpret these terms.

The difference between fit and predictive power of a model

K-T usually express the success of their LSER applied to a given data set in terms of the *degree of fit* between model and data, the residual standard deviation (RSD). This measure is also a good estimate of the prediction power of the model provided that the RSD is based on a large data set with substantially more data than estimated parameters. Since K-T now have about 10 adjustable coefficients in their LSER, their use of multiple regression for the data analysis necessitates 40–50 data points per analysed series to make the RSD a good measure of the predictive power of the model. In the ten examples used by K-T in Ref. 1, only four have sufficiently many data (Table 1). The example with the largest amount of data (ex. *a*) indeed has a RSD which is substantially larger than the experimental error.

Modern statistics in combination with computers allow us to use better measures than the degree of fit to evaluate a model. Bootstrapping and cross-validation are methods that give direct estimated of the predictive power of the model.[13–15] With cross-validation this is accomplished by the recalculation of the model parameters several times, each time with part of the data kept out of the calculations and thereafter predicted by the resulting partial model.

Hence, we now have tools to judge models directly according to how they predict new data. Because of the mathematical properties of least squares fitting, invariably the degree of fit is apparently better than the predictive power calculated according to bootstrapping of cross-validation. This leads K-T to overrate the power of their model.

The choice of data analytic method

One reason why K-T fail to recognize that significant parts of their data are not explained or predicted by their model is that they use multiple regression[16] (MR) in their data analysis. This method is based on the assumption that the predictor variables (here π^*, δ, α, β, etc.) are 100 % relevant. This assumption is equivalent to the K-T statement that their scales are generally applicable. However, MR provides no tools or diagnostics for testing the validity of this assumption. Specifically, in MR one reaction series is analysed at a time, thus excluding the possibility of seeing systematic deviations from the model by the simultaneous analysis of several related data series.

Multivariate data analysis, such as factor analysis[9] (FA), PCA[10] and PLS (partial least squares models in latent variables)[17,10] analyse data from several reaction series simultaneously. The analysis can be made under a minimum of assumptions; the data need only be continuous and homogeneous. After the analysis, other assumptions can be checked for consistency with the results, such as the relation of estimated model parameters with previously established "scales".

With respect to the present debate, we use PC analysis and PLS analysis (partial least squares modelling in latent variables)[17] to calculate the total systematic part of a data set (PC) and how much of the data set can be explained and predicted by preestablished scales (PLS).

PC analysis gives for a given data matrix Y (see Fig. 2) a separation into "structure" expressed by the average vector $\bar{y}$ and the score matrix T times the loading matrix B, plus "noise" expressed by the residual matrix E. The variance of the latter divided by the variance of the original data matrix Y is a measure of s^2 in Fig. 1. The score vectors t_a have the character of "scales" and express the relation of the different subsystems to each
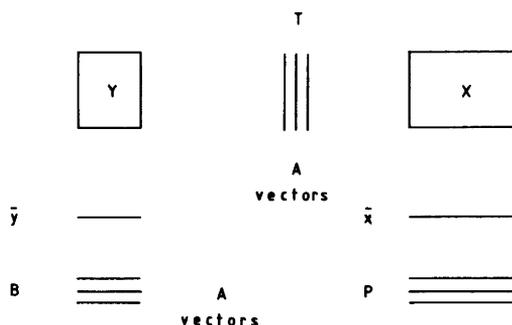
Figure 2. The multivariate analysis of chemical data Y results in a projection of the data (centered by subtracting the average vector ȳ) on a score matrix T times a loading matrix B. The number of components or factors, A, corresponds to the number of columns in T and rows in B.
In principal components analysis (PCA), the matrices T and B are estimated from the Y-matrix itself, for instance, by a singular value decomposition.[24]
In a PLS analysis,[10,17,18] the projection is computed from Y plus an auxilliary matrix X containing the a priori specified predictor variables (here π^*,δ,β, etc.).

other. The loading vectors b_a specify the combination of the original x-variables into the score vectors t_a. The number of significant dimensions of the model, A, – the number of factors in the data – is estimated by cross-validation (see below).

With PLS analysis, the data matrix Y is modelled in terms of "factors" of another "predictor matrix", X (Fig. 2). The results are similar to the ones of PC analysis, with the difference that the score vectors t_a are linear combinations of the X-columns instead of the Y-columns. Thus a PLS analysis gives a measure of how much of Y that can be explained by X in a way similar to multiple regression (MR).[18] The difference from MR is that PLS can handle multiple y-vectors simultaneously as well as collinearities in X, and gives a shrunk solution.[18] PLS includes MR as a limiting case.[18]

In both types of analysis, cross-validation (CV) plays a crucial part in the estimation of the significance of the results. With CV parts of the investigated data set are kept out of the model fitting and thereafter predicted by the resulting model. The sum of squares of the differences between predicted and actual values (denoted PRESS) is formed for the data kept out. Then another part of the data is kept out, a new model

calculated, predictions are made, new terms added to PRESS, etc., until each datum element has been kept out once and once only.

PRESS gives an unbiased measure of the predictive power of the given model. This PRESS can be compared with the PRESS of other models, for instance with higher complexity, or models with other predictor variables.

The interpretability of local models

Kamlet and Taft state that their "general"LSER is preferable to statistically estimated local LSERs because the "general" model gives an understanding of the system, while the local models in the form of PC models do not. To this we would like to give an answer on two levels.

First, since locally estimated models give better fits and better predictions, the "general" model is in some fundamental way incomplete and the "understanding" thereby reached is not, in our view, a good one. In order not to mislead users of LFERs and LSERs we have preferred to use locally estimated parameters which are not transferable to other systems.

Second, however, we realize man's desire to use generally applicable concepts and models. If we intend to understand the relations between the presently investigated system and other ones, we agree that the PC models and their score vectors t with loadings p do not immediately convey this "understanding". This can, however, be reached by a subsequent rotation of PC solution to agree as well as possible with established scales, so-called target rotation.[9]

Example

We briefly review the previously published analysis of a data set concerning the solvent effects on the ^{13}C NMR spectra of indenyllithium. The data consist of the five ^{13}C NMR shifts of indenyllithium in thirteen solvents. This type of data are advantageous in this type of debate since they are multivariate without always being subject to inter-laboratory variation. Hence, the precision of the data is well controlled.

The data were analysed in two ways. First, a PC analysis was made of the NMR shifts of the eleven solvents considered to have precise data. A significant two-component model was obtained, accounting for 96 % of the variance. The

first of these components was very similar to π^* of K-T, but the second showed no relation to any known solvent scale, indicating a significant system specific "effect".

Second, a PLS-analysis was made using the NMR-data as the Y-block and an X-block consisting of twelve empirical solvent scales including π^*. One significant dimension was obtained, explaining 66 % of the variance. An attempt to improve the model by including all available scales of K-T did not change the results. This is not surprising, considering the fact that the K-T scales correlate with all other solvent scales.[1] Hence, the unbiased estimate of the system specific "effect" is 30 % (96 % in the PC model minus 66 % in the PLS model).

We conclude that the general information G is considerably and significantly smaller than 1.0.

The difference between significant and exhaustive fit

Another way to express the difference in views between K-T's and our own is that the former regard a model applicable when it fits a data set better than chance (statistically significant fit). All their arguments in Ref. 1 are based on the fact that their LSER shows a statistically significant fit to a large number of data series. This fact we do not dispute. Their model shows a statistically significant fit to all these data.

Chemical data have good precision, usually better than 2–3 %. To be of any practical or theoretical interest a model must fit data considerably better than just on the level of statistical significance.[20]

The optimal level of fit where the model explains all regularities in the data we call the exhaustive level. We consider that K-T, in order to show that their model is generally applicable, should show that their model reaches this level of regularity exhaustion, at least closely.

K-T make no efforts to show how near the level of exhaustion their model comes. In fact, their own results indicate that the fit of their LSER to measured data is significantly less than exhaustive. In Table 1 we tabulate the residual standard deviations as given in Ref. 1 for the ten data sets (a through k) they use as illustrations of their LSER applicability. We do not discuss the Sunner-Kebarle set since evidently the K-T LSER fails ("Aromatics are excluded ..."). We

include in the same table the pertinent experimental precision of the data according to the stated reference.

We see that in all cases where the experimental precision is known, the fit of the K-T LSER is not close to this precision. In several cases the fit is much worse (e.g. a,c,d,e). Hence, even in the examples selected by K-T themselves, there are strong indicatons that the K-T LSER does not fit the data exhaustively.

Additional effects and the deletion of non-fitting cases

The last correlation discussed by K-T gives a clear example of another escape route often taken when a "fundamental" model does not fit given data as well as expected. As the footnote in Ref. 1 states: "Aromatics are excluded to exclude variable polarizability effects". How were these "variable polarizability effects" found? And why was there no term in the model from the beginning which explained them?

Our interpretation is that aromatics deviated strongly in a way impossible to rationalize with the given LSER. Thus, when a subset of the data (here aromatic ligands) does not, *in retrospect,* fit the model, a "new effect", *i.e.* a rationalization, is invented which explains away the unexpected deviations.

K-T in Ref. 1 give another example of the same type where Kupfer and Abraham find it necessary to "take into account such additional effects as may be operative for the specific XYZ studied, such as solvent viscosity in fluorescence relaxation processes". What is this if not local models where new "effects" are brought in when needed to explain the results?

In our view, for a model to be generally applicable, it should fit all pertinent data in a model form specified in advance. A posteriori rationalizations are, of cource, allowed in practice, but not with the simultaneous pretention that the model is generally applicable. Thus K-T in fact admit that their model is not generally applicable; systems showing "variable polarizability" or influenced by "solvent viscosity" are not possible to model adequately.

Moreover, the LSERs often give unexpected outliers, e.g. no 64, 121, 154, 184, 187, 189 and 208 (numbering as in Table 1, Ref. 1). We found these misfits by scrutinizing a small part of the

material of Table 1, Ref. 1. Many more outliers would probably be found by a rigorous and detailed inventory.

Finding and deleting outliers in empirical models is certainly to be permitted, but not in fundamental, "general" ones. In particular, if one or several observations are deleted from a correlation, one cannot thereafter state that the model correlates a property as done in Table 1, Ref. 1. For no 154, for instance, this gives the misleading impression that $\beta(2)$ contains the same information as Gutmann's donor number, which *it does not* because three points out of sixteen deviate strongly from the correlation!

Further evidence ignored by Kamlet and Taft

An interesting piece of evidence regarding the interpretation of LFERs and LSERs is Fig. 4 in Ref. 2, showing that the residual standard deviation is roughly proportional to the reaction parameter (ϱ) in the Hammett equation. This behaviour is to be expected if LFERs are seen as local linearizations of more complicated functions (F), because when ϱ increases so do the third degree and higher terms in the Taylor expansion of F. This, in turn, makes the model show a decreasing degree of fit with increasing ϱ, just as seen in the figure. It seems difficult to explain this figure if we see LFERs as fundamental models combining known and fixed chemical effects.

Conclusions

First we wish to express our appreciation to K-T who openly and boldly discuss the difficult problems connected with the applicability of scientific models. We find their work developing models for solvent effects admirable and their results useful in chemical research and practice. This is as long as it is clearly stated that their LSER is an empirical model which gives good fit and prediction for solvents similar to the ones where it was calibrated and which is expected to behave more poorly the further away one moves from these solvents.

To quote K-T (Ref. LSER-1 in Ref. 1, Table 1): "With the linear solvation energy relationships involving these other XYZs, however, the *r* and SD measures of statistical fit were significantly better when the correlations were re-stricted to families of solvents with similar polarization characteristics, *i.e.* (a) non-chlorinated aliphatic solvents, (b) polychlorinated aliphatics, and (c) aromatic solvents. In a subsequent communication we reported that correlations were better still (average r < 0.985) if restricted to a selected set of *ca* 30 aliphatic solvents for which π^* values are very nearly proportional to molecular dipole moments".

Hence, we interpret their claim that their model is of general scope as meaning that the model fits most data significantly better than chance. This claim we do not challenge.

However, if we adopt a more stringent meaning of the concept of "general applicability", *i.e.* that the model should fit the data exhaustively or nearly so, without the need to arbitrarily explain away parts of the data, then LFERs and LSERs cannot be said to be generally applicable. Rather, one must admit that in data observed in a series of reactions or compounds there are regularities that cannot be predicted from observations made on other systems. We call these the system-specific regularities. These can be estimated only by means of local models "calibrated" on the same system or very similar systems to the one we wish to predict. This we can summarize as chemistry having a fractal nature.[21] Indeed, we find that K-T also agree with this with their repeated statement that "It is also seen that the goodness of fit improves significantly for the select solvent set (SSS) correlations".

We agree with K-T (and everybody else) that this partly local behaviour of a series does not make the behaviour of new series totally unpredictable. As long as the new series bears some similarity to previously investigated series, these can be used to provide "generalizable" regularities for the new system. Our point is just that the system specific part of the regularities is not negligible. And that the regularities predicted from other systems are less important, the more dissimilar the other systems are to the new one.

The view that chemical models are, in part, only locally applicable does not lead to greater difficulties to interpret the results. Only the local part needs a local interpretation; the general part can, if one so wishes, be interpreted in the traditional way. One should, however, be cautious in such interpretations, since the general part is dominant only as long as the current system is fairly similar to the "reference systems".

A practical reason to be careful with the concept of generality is that if it is adopted for a given type of models, all deviations must be interpreted as new effects and soon one finds oneself in a morass of scales, corrections, exceptions and anomalies. The correct use of the model in a given situation is then difficult, and the sound idea of semiempirical models may (locally) fall into disrepute, as seems to happen in the field of LFER in organic reactivity.[22]

Sadly, the development of LSERs seems to conform to this line of development. The LSER of Kamlet and Taft, initially a sound and simple empirical model, now has ten adjustable parameters (see Ref. 1). Still, according to Ref. 2 in Ref. 1, there are effects not yet parametrized, such as steric effects in acid-base complexing, entropy effects, variable aromatic polarizability, and conjugative-electron donation. And the solvent viscosity effect mentioned in the footnote of Ref. 1 certainly remains too.

Finally, we might add a purely personal reason why we prefer the idea of local models to that of general ones. This makes the fields of future research infinite; Nature and the world will never be exhaustively investigated and modelled. All new situations and problem areas will demand partly new concepts and models, and make life interesting also for future generations of chemists.

We note that this desirable state indeed has been formally proven by Gödel.[23] He shows that within any sufficiently rich axiomatic system, statements can be formulated which cannot be shown to be true or false within this system. Hence, in complicated systems like the ones studied in chemistry, there will always be events that cannot be predicted from previous observations. This, in turn means that there will always be a need for experiments. And local models.

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