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Power-law modeling based on least-squares minimization criteria

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Abstract

The power-law formalism has been succesfully used as a modeling tool in many applications. The resulting models, either as Generalized Mass Action or as S-systems models, allow one to characterize the target system and to simulate its dynamical behavior in response to external perturbations and parameter changes. The power-law formalism was first derived as a Taylor series approximation in logarithmic space for kinetic rate-laws. The especial characteristics of this approximation produce an extremely useful systemic representation that allows a complete system characterization. Furthermore, their parameters have a precise interpretation as local sensitivities of each of the individual processes and as rate-constants. This facilitates a qualitative discussion and a quantitative estimation of their possible values in relation to the kinetic properties. Following this interpretation, parameter estimation is also possible by relating the systemic behavior to the underlying processes. Without leaving the general formalism, in this paper we suggest deriving the power-law representation in an alternative way that uses least-squares minimization. The resulting power-law mimics the target rate-law in a

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wider range of concentration values than the classical power-law. Although the implications of this alternative approach remain to be established, our results show that the predicted steady-state using the least-squares power-law is closest to the actual steady-state of the target system.

Keywords: S-systems; Sensitivity analysis; Enzyme kinetics; Biochemical system theory; Metabolic control analysis

1. Introduction

The construction of a mathematical model of a metabolic pathway requires using an appropriate formalism allowing system characterization and simulation. Although models based on enzymatic kinetic rate-laws, such as the classical Michaelis–Menten and Hill functions, appear as a logical alternative, they result in a mathematical representation that is too complicated for practical purposes. Moreover, a compilation of the available kinetic data does not guarantee that the resulting model does accurately represent the target steady state properties [1–7]. This is especially true if we consider that kinetic experiments are performed in vitro and that the derived parameters and mechanisms are far from representing the in vivo situation [8–10]. The complex structure of the intracellular media determines that in vivo conditions differ from the ideal in vitro conditions in which the rate-laws of isolated enzymes are derived. In vivo, the heterogeneous media in which a chemical reaction occurs may involve deviations from classical kinetics, making it necessary to consider fractal kinetics as a much more natural generalization for deriving the corresponding rate-law [11,12].

With all these points in mind, the search for an appropriate mathematical representation is an important issue in modeling metabolic pathways. In this context, the power-law formalism based on a Taylor series approximation in a given operating point provides an efficient alternative for representing the actual rate-law in situ. To produce a non-linear representation, this approximation is derived in logarithmic space, so that a power-law representation is obtained in normal coordinates [13–15]. This leads to models that appear to be accurate over a wide range for the steady-state values of the system as a response to changes in external variables [16–20].

The power-law representation is the best possible according to the criterion of using a Taylor series approximation for the actual rate-law. As a natural improvement, the use of second-order terms in the Taylor series approximation was explored [21]. Although the resulting representation results in an increased accuracy, the problems in experimentally determining the required second-order derivatives make this approach unpractical.

In this paper we suggest an alternative way of deriving the power-law representation without leaving the general structure of the formalism. The method

is based on a least-squares criterion that minimizes the quadratic deviation between the actual rate-law and its corresponding power-law representation. This minimization can be performed over an arbitrary range of variation of the system variables. The resulting optimum power-law will be thus dependent on this range, even for a fixed operating point.

We compare the resulting least-squares power-law with the corresponding Taylor-series power-law in the case of the Michaelis–Menten rate-law for a sample of operating points and minimization intervals. Our results show that the former does increase the accuracy of the representation and that the Taylor-series power-law is a limit case when the range of minimization tends to be a single point. The implications of this new strategy for deriving a power-law representation are explored by comparing the steady-state predictions in a simple model. We shall again confirm that the predicted steady-state using the least-squares power-law is closer to the actual steady-state of the target system.

2. Least-squares power-law fitting of functions

Let us consider for the sake of simplicity the case of a one-variable function $v(X)$. The standard power-law methodology approximates $v(X)$ by a power-law around an operating point X_0 assuming a first-order Taylor expansion in logarithmic space. Its goal is to derive an approximate representation that accurately models the target process in the vicinity of the nominal operating point but that has the advantage of simplifying the mathematical representation. Such a method produces automatically a power-law approximation of $v(X)$ at X_0 which is correct to first order in the sense of Taylor, i.e., the value of the power-law and v, as well as their first derivatives at the operating point, do coincide:

$$\gamma X_0^f = v(X_0) \quad \text{and} \quad \frac{\mathrm{d}}{\mathrm{d}X}(\gamma X^f)\bigg|_0 = \frac{\mathrm{d}}{\mathrm{d}X}v(X)\bigg|_0. \tag{1}$$

In what follows, we shall denote as γ_T and f_T the rate constant and the kinetic order found according to a Taylor's type criterion, respectively.

However, from the theory of approximation of functions [22] it is known that the concept of 'best approximation' is, in general, criterion-dependent. Therefore, the best power-law fitting, in the sense of Taylor, may be eventually improved if we are able to recognize another criterion which ameliorates the estimation of some features we are interested in. For instance, we can look for a criterion providing an overall accurate approximation of the target function within a given operating range.

We shall thus consider the effect of substituting 'the best approximation', in the sense of Taylor, by 'best approximation' in the sense of least-squares within a given operating range. Let us clarify the precise meaning of the new criterion:

given an operating point X_0 and an arbitrary interval $(X_0 - L, X_0 + U)$ around it, we shall approximate a rate-law $v(X)$ by a power-law γX^f in this interval in such a way that:

1. $\gamma X_0^f = v(X_0)$, namely the power-law equates $v(X)$ at the operating point.
2. The quadratic deviation between both curves within the interval $(X_0 - L, X_0 + U)$ is minimal. This is equivalent to imposing the following condition:

$$\int_{X_0-L}^{X_0+U} (\gamma X^f - v(X))^2 \, \mathrm{d}X \to \text{Minimum}. \tag{2}$$

Some remarks are in order after this definition. First, the apparent kinetic order in the sense of least-squares depends not only on the operating point X_0, as usual, but on a whole interval $(X_0 - L, X_0 + U)$ over which we define the minimization criterion. Consequently, $f \neq f_T$ in general. Second, note that this is an *integral* criterion. This implies that $v(X)$ needs not be differentiable at the operating point, as in the case of Taylor's approximation, but only integrable [23], which is a much less restrictive condition. In particular, according to the least-squares criterion, an optimal power-law may exist even if $v(X)$ is not continuous at the operating point – piecewise continuity is a sufficient requirement. This situation may not arise in enzyme kinetic models but it may be relevant when modeling other dynamical systems.

Let us now concentrate on determining the optimal kinetic order and rate constant according to the least-squares definition. We shall denote them as f and γ, respectively. Notice that we can always write the power-law approximation of $v(X)$ as

$$v(X) \doteq v(X_0)\left(\frac{X}{X_0}\right)^f. \tag{3}$$

Expressed in this way, the problem is reduced to finding f. Contrarily to Taylor's case, it is not possible to give a closed expression for f, but it must be estimated in an appropriate way.

Although a specific minimization algorithm for (2) can be derived, for practical purposes it sufices to use any standard tool for numerical minimization such as those available in *Mathematica*© or similar software. The least-squares f can be obtained as follows:

1. Define an operating point X_0 and choose the operating range (U and L).
2. Compute numerically the integral in Eq. (2) using some starting value for f. Although the choice is not as critical as it may seem, a good rule is to use f_T as a first guess for f.
3. Iterate the minimization algorithm, using the least-squares integral as the objective function and f as the unknown parameter.
4. Stop the minimization when an appropriate minimum is reached.

This procedure has been implemented in *Mathematica*© *v.3.0*, using the function **NIntegrate** for evaluating the integral (2) and the procedure **FindMinimum** for obtaining the least-squares kinetic-order f. The extension of the algorithm into the case of several variables rate-laws is obvious and we omit it for the sake of conciseness. Although the method for obtaining the power-law representation is somewhat less intuitive than in the Taylor case, the resulting approximation is optimal in the sense of least-squares and provides a power-law representation that preserves the formalism. Moreover, a least-squares minimization is in closer relationship with data analysis. Suppose the actual $v(X)$ is unknown, and that a set of experimental points (X_i, v_i) is measured. Then, for a given operating point (X_0, v_0) we can obtain the corresponding $\hat{f}$ value as follows:

$$\sum_{i=1}^{n}\left(v_i - v_0\left(\frac{X_i}{X_0}\right)^{\hat{f}}\right)^2 \rightarrow \text{Minimum}. \tag{4}$$

The resulting $\hat{f}$ will be an estimation of the actual least-squares f corresponding to fitting $v(X)$ in a range within the minimum and maximum values of the corresponding (X_i, v_i) data points. In general, this value will differ from the corresponding f_{T} value. Because the power-law representation derived from a least-squares criterion is a variant in comparison to the classical formulation, it would be useful to explore how does it compare with the Taylor representation and which are the consequences when modeling the whole system. We shall try to answer these questions by an example.

3. Comparison of different power-law approximations for the Michaelis–Menten rate-law

The meaning of the least-squares criterion for obtaining the power-law representation of a target process can be best understood if we choose an appropriate reference function $v(X)$. For the sake of illustration, we shall do this for the Michelis–Menten rate-law

$$v_{\mathrm{MM}}(S) = \frac{V_m S}{K_m + S}. \tag{5}$$

Notice that the general Michaelis–Menten rate-law (5) for a substrate S can always be rewritten in the normalized form

$$v(X) = \frac{X}{1+X} \tag{6}$$

after introducing the dimensionless quantities $X = S/K_m$ and $v = v_{\mathrm{MM}}/V_m$. We can thus consider the rate-law (6) as a prototypical representative of the general process (5).

We thus compare the rate-law (6) with both power-law approximations for a sample of operating points and minimization intervals. The results are summarized in Fig. 1. A feature which is apparent at first sight is that the least-squares approximation remains closer to the function, on the average, over the minimization interval. This was to be expected, since the traditional approach does only depend on a single operating point. In particular, the least-squares

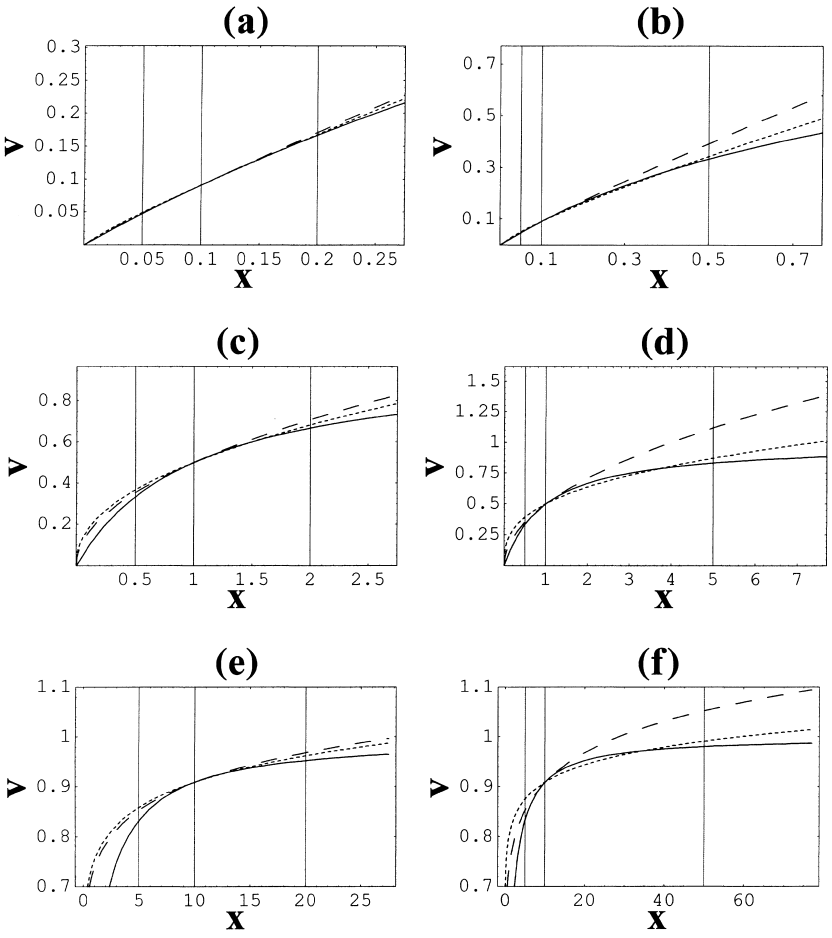

Fig. 1. Power-law representation of the Michaelis–Menten rate-law $X/(1+X)$ at different operating points and minimization intervals. The exact rate-law (continuous line) is displayed together with the Taylor (– – –) and the least-squares (- - - - -) approximate power-laws. The vertical grid indicates the points (X_0-L, X_0, X_0+U). (a) $(X_0, L, U) = (0.1, 0.05, 0.1)$; (b) $(X_0, L, U) = (0.1, 0.05, 0.4)$; (c) $(X_0, L, U) = (1, 0.5, 1)$; (d) $(X_0, L, U) = (1, 0.5, 4)$; (e) $(X_0, L, U) = (10, 5, 10)$; (f) $(X_0, L, U) = (10, 5, 40)$.

power-law, not being a saturating function, is able to reproduce better the saturation property of (6) over the corresponding interval. For a fixed operating point, the required least-squares kinetic order f is lower than the corresponding f_T value for operating regions with U well above the nominal operating point. For asymetrical regions with L well below X_0 and U close to zero, the corresponding f is greater than f_T.

In order to better visualize the average gain when representing the target function within the operating region, we may define the following ratio

$$R(X_0, L, U, v) = \frac{\int_{X_0-L}^{X_0+U} (\gamma X^f - v(X))^2 \, dX}{\int_{X_0-L}^{X_0+U} (\gamma_T X^{f_T} - v(X))^2 \, dX}, \tag{7}$$

where γX^f and $\gamma_T X^{f_T}$ are the least-squares and the traditional power-law approximations of $v(X)$ at X_0 over the interval $(X_0 - L, X_0 + U)$, respectively. Expression (7) is just the ratio of the quadratic deviations of both approximations (note that the minimization of such quadratic deviation is the criterion followed in the determination of γ and f). Thus, given a rate-law v and a combination of arguments $\{X_0, L, U\}$, function $R(X_0, L, U, v)$ gives a measure of the extent to which the least-squares power-law remains closer to $v(X)$ than the Taylor power-law over the corresponding interval. Therefore, we can verify the way in which we have a greater gain by calculating R for a sample of minimization intervals. This is done in Fig. 2 for the rate-law (6). As it can be seen, the Taylor and the least-squares approximations remain quite similar in the case of symmetrical minimization intervals. When the interval width tends to zero, f becomes equivalent to f_T. However, when we deal with asymetrical intervals, R decreases quickly to values of less than 0.1, thus showing that the least-squares approximation leads to an improvement of more than 90% in such cases. This can be especially useful if we want to explore the system's behavior within a wide range. For instance, if X is an external effector that can vary in a wide range, the least-squares representation may be more adequate than the Taylor representation if the goal is to explore the dynamic response related to the dynamic variation of X.

4. Comparison of the steady-state predictions in a simple model

The power-law formalism is especially suited for modeling a whole system. In that sense, the price to be paid for using an approximated representation of the underlying processes is compensated by the possibility of efficiently analyzing the system's properties. Moreover, the final set of equations will be, in general, able to model the target system in a wider region than we would expect from the use of an approximation [16–20]. Because the least-squares algorithm increases, on the average, the accuracy of the representation within the desired

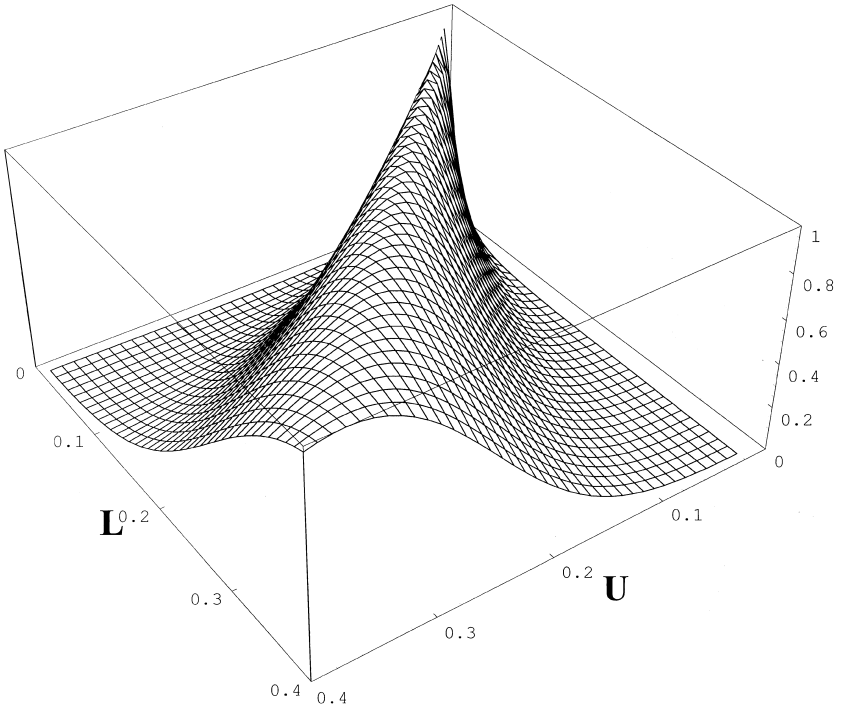

Fig. 2. Plot of the ratio $R(X_0, L, U, v)$ for the Michaelis–Menten rate-law (6), $v(X) = X/(1+X)$ at $X_0 = 1$ for different values of L and U.

operating region, it is expected that the system behavior will be better approximated by a model incorporating this strategy.

As an illustrative example, we compare the steady-state prediction for both alternative power-law descriptions of the simple mechanism

$$X_2 \to X_1 \to P.$$

The rate of variation of X_1 along the process is given by $v = v_S - v_D$, where v_S and v_D are the rates of synthesis and degradation of X_1, respectively. X_2 is assumed to be in excess, in such a way that its concentration can be taken as constant. We can then set $v_S = X_{20} = \text{constant}$. For v_D we shall consider the rate-law (6) used in the previous section. This leads to the following simple differential system:

$$\dot{X}_1 = X_{20} - \frac{X_1}{1+X_1}. \tag{8}$$

We can then approximate the Michaelis–Menten rate-law in (8) by either its Taylor or its least-squares approximation for a sample of operating points

and minimization intervals. Then, a comparison of both approximations is provided by the corresponding predictions of the steady-state of the system, when such steady-state is considered as a function of the operating point – which is given by parameter X_{20}. The advantage in taking such simple example is that the steady-state can be determined exactly as a function of X_{20}. Thus the comparison of the approximations with the actual solution is easily available.

Such comparison is displayed for system (8), for a sample of operating points and minimization intervals, in Fig. 3. Again, it is apparent that the prediction of the steady state is improved with respect to the Taylor method within the selected range. The fact that such range can be conveniently chosen case by case gives to the least-squares approximation an extra degree of flexibility not present in the classical approach. The appropriate operating range will depend on the particular problem and, to some extent, on the expected use of the model. This is similar to the choice of an appropriate operating point in the Taylor method.

5. Discussion

The power-law formalism based on a Taylor approximation provides a general framework for modeling complex systems. In this paper, we have suggested that a power-law derived by a least-squares minimization criterion is a valid alternative to the classical formulation. The power-law derived using this alternative criterion has several advantages. First, we are approximating the target function over a whole interval that can be chosen at will. This is convenient, since it allows improving the goodness of the representation in the most relevant range of the variables. For example, we have shown that some of the limitations of the power-law approximation (such as the overshoot of the rate-laws, which are usually saturating [24]) can be to great extent overcome with the new method. Second, the traditional power-law based on a Taylor-like approach, appears to be the limit of the least-squares approximation when the width of the optimization interval tends to zero – i.e., when the interval is just reduced to the operational point. From a practical point of view, we have shown (see Fig. 2) that the Taylor approach does almost coincide with the new one in the case of symmetrical intervals around the operating point. On the contrary, when the relevant range of the system is not symmetrical around the operating point, the least-squares method provides a more accurate representation of the rate-law. Third, the least-squares criterion is directly related to fitting a power-law from data points. In this sense, if we use experimental data points the resulting representation is an estimation of the corresponding least-squares power-law of the actual rate-law. As we have shown, this can be quite different from the corresponding Taylor power-law.

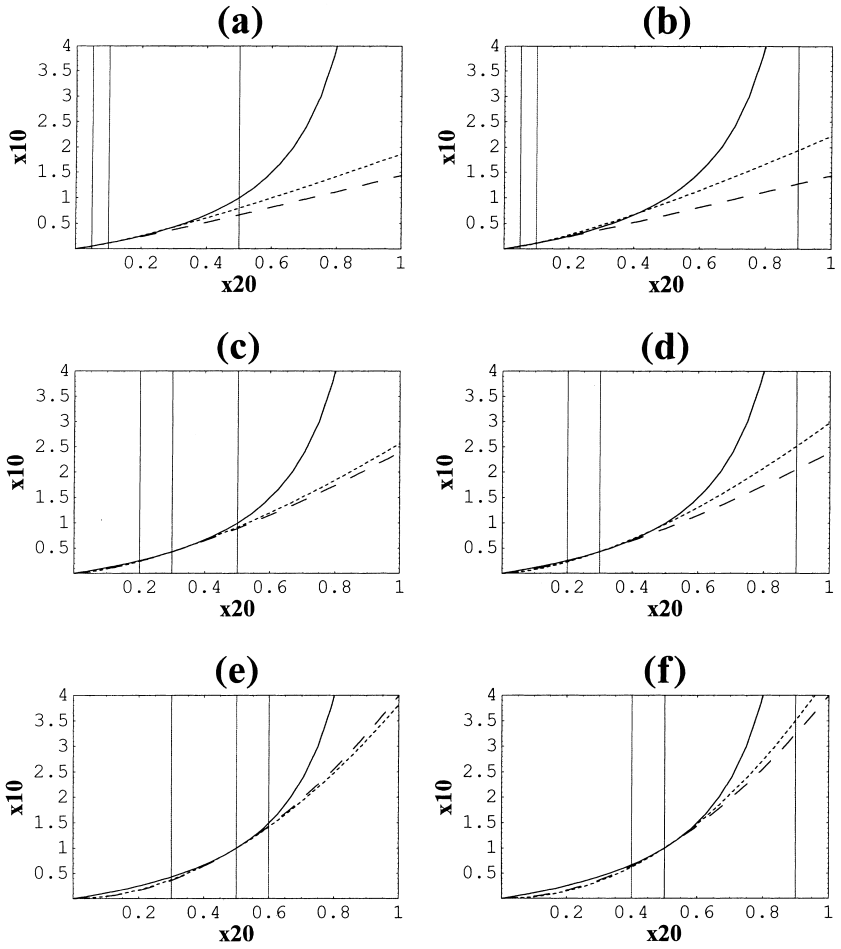

Fig. 3. Steady state prediction for system (8) for different operating points and minimization intervals. The exact solution (continuous line) is displayed together with the Taylor (– – –) and the least-squares (- - - - -) approximations. The vertical grid indicates the points $(X_{20}-L, X_{20}, X_{20}+U)$. (a) $(X_{20}, L, U) = (0.1, 0.05, 0.4)$; (b) $(X_{20}, L, U) = (0.1, 0.05, 0.8)$; (c) $(X_{20}, L, U) = (0.3, 0.1, 0.2)$; (d) $(X_{20}, L, U) = (0.3, 0.1, 0.6)$; (e) $(X_{20}, L, U) = (0.5, 0.2, 0.1)$; (f) $(X_{20}, L, U) = (0.5, 0.1, 0.4)$.

Application of this new procedure for deriving a power-law representation of a given system proceeds from the same kind of information than required in the traditional power-law approach [1–7,9,10,20,25]. Although the final numerical result is different, either the traditional or the least-squares methods for deriving a power-law approximation will produce the same kind of model, a GMA or an S-system model, in which the corresponding kinetic-orders and rate-constants, once evaluated, are considered constant quantities. System

characterization will proceed with exactly the same methodology [9,23], independently of the procedure we select for computing the parameters, yielding a complete steady-state characterization and providing a model for dynamical simulations. Although we have shown the improvement in the steady-state prediction in a very simple model, the least-squares power-law is expected to provide a similar increase in accuracy for large metabolic pathways while keeping intact all the analytical and conceptual framework of Biochemical Systems Theory. To develop in detail further implications of this new strategy for power-law modeling, either in data analysis or in the steady-state characterization and dynamic simulation of a system, shall be the aim of future research.

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