Instability region in models of nonlinear reaction systems. The Stoichiometric Network Analysis [*]

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ABSTRACT

Stability analysis of reaction systems is described by the application of the Stoichiometric Network Analysis to the three-variable-autocatalator. Although simple, this model is complex enough to describe complex forms of nonlinear dynamics phenomena, like mixed-mode oscillations and chaos. Therefore, stability analysis of such model is not a trivial task. Using the Stoichiometric Network Analysis for this purpose makes the process clear and leads to the reliable result.

The method is described briefly in few general steps and all of them are further clarified through the application to the chosen example. First, the reaction rates in steady state are decomposed to contributions of independent pathways, called extreme currents. Then, linearized operator is constructed. Finally, through the analysis of the principal minors of the essential part of this operator, simple stability criterion is identified.

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1. Introduction

Reaction systems are wide but specific class of dynamical systems where state variables are usually concentrations of some reactive species. In these systems the contributions of the individual reaction rates to the overall rate of changes are governed by the stoichiometric relations between mentioned species. [1] The number of individual reaction rates (reaction steps) can be more or less large. In biochemical reaction systems it is generally very large. [2] Hence, the stability analysis of such systems is also specific and require use of adequate tools like the Stoichiometric Network Analysis (SNA). [3]

In models of reaction systems, various rate laws [4] may be used, but mass action principle is the most common. It is based on fundamental principle, that the rate of reaction is proportional to the concentrations of the reacting substances. As a result, rates of individual steps are power functions of concentrations as the state variables, and overall rates are obtained as linear combinations of such simple monomial terms. Nevertheless, final expressions are nonlinear as a rule. Moreover, the number of independent variables (the concentrations of independent species) and number of related equations that describe their evolution in time, may be very large.

Numerical simulations based on efficient algorithms for integration of systems of ordinary differential equations are often the best way to analyze dynamical states of the reaction systems. However, the main model parameters – rate constants of all individual reaction steps are generally unknown. Therefore, more general approach is required to evaluate possible dynamic states depending on unknown values of the rate constants. SNA is probably unique tool that may provide such general results on so complex objects as reaction systems are. Large number of reaction steps and reaction species may be limiting for application of the SNA, but several approximations, specific only for SNA, are available to attain some result on instability condition even for very large systems with dozens of reactions and reaction species.

Analytical expressions for the instability condition can be easily calculated as a function of the rate constants, and then tested by comparing them with the results of the numerical simulations obtained for selected parameter values. [5] For this purpose, bifurcation analysis may lead to crucial results. [6]

Simple model known as three variable autocatalator will be used to illustrate the method. [7]

2. The model

Our examinations are illustrated on a reaction model known as three-variable-autocatalator. [7] This model consisting of five reaction species (R, X, Y, Z and P) and six reactions having rate constants k_i where i = 0, 1, ... 5, is given in Table 1. The system may readily be reduced since P is only the product of the reaction which does not influence the rate of any reaction step. We will also assume that reactant R is in large excess so that changes in its concentration may be neglected and dynamical state of the system depends just on its initial value as a control parameter. Hence, only three variables remained (concentrations *x*, *y* and *z* of species X, Y and Z, respectively).

Table 1. The three-variable-autocatalator reaction network model [7]

$R \xrightarrow{k_0} X$	$v_0 = k_0\, r_0$	(M.0)
$X \xrightarrow{k_1} Y$	$v_1 = k_1\, x$	(M.1)
$X+2Y \xrightarrow{k_2} 3Y$	$v_2 = k_2\, x\, y^2$	(M.2)
$Y \xrightarrow{k_3} Z$	$v_3 = k_3\, y$	(M.3)
$Z \xrightarrow{k_4} P$	$v_4 = k_4\, z$	(M.4)
$R+Z \xrightarrow{k_5} X+Z$	$v_5 = k_5\, r_0\, z$	(M.5)

The dynamics of the model can be represented by set of ordinary differential equations:

$$\mathrm{d}x/\mathrm{d}t = v_0 - v_1 - v_2 + v_5 \tag{1}$$

$$\mathrm{d}y/\mathrm{d}t = v_1 + v_2 - v_3 \tag{2}$$

$$\mathrm{d}z/\mathrm{d}t = v_3 - v_4 \tag{3}$$

and if we use rates of reaction steps from Table 1 set of differential equations has the form:

$$\mathrm{d}x/\mathrm{d}t = k_0\, r_0 - k_1\, x - k_2\, x\, y^2 + k_5\, r_0 z \tag{4}$$

$$\mathrm{d}y/\mathrm{d}t = k_1\, x + k_2\, x\, y^2 - k_3\, y \tag{5}$$

$$\mathrm{d}z/\mathrm{d}t = k_3\, y - k_4 z \tag{6}$$

Species Z does not change the concentration in reaction (A.5) since it appears there both, as reactant and product.

From equations (4)-(6), we can calculate steady-state concentrations:

$$x_{\mathrm{SS}} = \frac{k_0 k_3^{\,2} k_4\, r_0\, (k_4 - k_5\, r_0)}{k_1 k_3^{\,2} (k_4 - k_5\, r_0)^2 + k_2 k_4^{\,2} (k_0\, r_0)^2} \tag{7}$$

$$y_{\mathrm{SS}} = \frac{k_4 k_0\, r_0}{k_3\, (k_4 - k_5\, r_0)} \tag{8}$$

$$z_{\mathrm{SS}} = \frac{k_0\, r_0}{k_4 - k_5\, r_0} \tag{9}$$

The stability analysis of three variable system can be performed by several methods. However, the stability analysis of a system with more than four variables can be done only by SNA. Nevertheless, we intend to present the stoichiometric network analysis with its advantages on three variable system for pedagogical purpose.

3. Stoichiometric network analysis of considered model

Stability analysis of complex nonlinear reaction mechanisms is very complicated task. For models that have large number of independent intermediate species, the classical tools for studying the stability conditions are quite ineffective. To avoid this problem it is necessary to use specialized methods. At present, the most powerful one is the stoichiometric network analysis (SNA). [3, 8]

In SNA, the kinetic equations of any stoichiometric model presented by a set of differential equations (such as (4), (5) and (6)) is written in the matrix form:

$$\dot{\boldsymbol{c}} = \mathbf{S} \times \boldsymbol{v} \tag{10}$$

where $\dot{c}$ is the time derivative of the $m \times 1$ concentration vector c comprising the change in concentrations of m independent intermediate species, known as internal ones in SNA. **S** is the stoichiometric matrix and $\boldsymbol{v}$ the so-called reaction or flux vector with reaction rates as components. The stoichiometric matrix **S** is an $m \times n$ matrix where n is the number of reactions in the reaction network (in the model considered $m = 3$ and $n = 6$.). The S_{ik} element of the stoichiometric matrix corresponds to the stoichiometric coefficient of reactive species i (i = 1,2, ..., m) in reaction (R_k) corresponding to column k and row i. The reaction vector v is $1 \times n$ vector whose elements describe the reaction rates.

Using the matrix representation given in equation (10), the model given in Table 1 corresponds to the following system of differential equations:

$$\dot{c} = \begin{matrix} \mathrm{M.0} & \mathrm{M.1} & \mathrm{M.2} & \mathrm{M.3} & \mathrm{M.4} & \mathrm{M.5} \end{matrix} \\ \begin{bmatrix} 1 & -1 & -1 & 0 & 0 & 1 \\ 0 & 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \end{bmatrix} \times \begin{bmatrix} v_0 \\ v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} \tag{11}$$

Row above the matrix **S** in equation (11) indicates correspondence between matrix columns and reactions in the model, and it is not part of the matrix.

Now, we want to obtain information about the interplay between the concentrations of independent intermediate species and the dynamics of the network as a whole. As a first step, we look for conditions where the network is in a quasi-steady-state. The rates at a steady state v_{ss} are solutions of the relation:

$$0 = \mathbf{S} \times \boldsymbol{v}_{ss} \tag{12}$$

Equation (12) represents system of homogenous equations, and we need to find all positive solutions. Method for finding all positive solutions of equation (12) depends on the size of examined model. For simpler

models equation (12) can be solved manually. However, if the number of reactions is large, solving equation (12) becomes much more complex, and only suitable way is to use computer programs based on algorithms developed for this purpose. There exist several algorithms. [9-13]

The solutions of (12), known as extreme currents [3, 8], are reaction pathways in steady state. They offer important information about the consistency of the model, and correlations between individual reactions like mutual exclusion or coupling. [14] The extreme currents E_i are usually presented as the columns (in any order) of a new extreme current matrix **E**. In the case considered, it is:

$$\mathbf{E} = \begin{array}{c} \begin{matrix} E_1 & E_2 & E_3 & E_4 \end{matrix} \\ \left[\begin{array}{cccc} 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{array}\right] \end{array} \begin{matrix} \text{M.0} \\ \text{M.1} \\ \text{M.2} \\ \text{M.3} \\ \text{M.4} \\ \text{M.5} \end{matrix} \tag{13}$$

As before, row above and column beside the matrix **E** in equation (13) indicate correspondence between matrix rows and reactions and between matrix columns and extreme currents, and they are not part of the matrix.

In any specific steady state, each extreme current contributes to reaction rates with its own, distinct, extent. The contributions of the extreme currents, denoted as the current rates j_i, are given as the components of the corresponding vector ***j***. Elements of vector ***j*** are nonnegative numbers. The basic equation of the SNA gives relation between rates at a steady state $v_{ss,k}$ and current rates j_k:

$$v_{ss} = \mathbf{E}\boldsymbol{j} \tag{14}$$

Using equation (14), the particular $v_{ss,k}$ can be written in the form:

$$\begin{aligned} v_{ss,0} &= k_0 r_0 = j_1 + j_2 \\ v_{ss,1} &= k_1 x_{SS} = j_1 + j_3 \end{aligned} \tag{15}$$

$$v_{ss,2} = k_2 x_{SS} y_{SS}^2 = j_2 + j_4$$
$$v_{ss,3} = k_3 y_{SS} = j_1 + j_2 + j_3 + j_4$$
$$v_{ss,4} = k_4 z_{SS} = j_1 + j_2 + j_3 + j_4$$
$$v_{ss,5} = k_5 r_0 z_{SS} = j_3 + j_4$$

The next step in our analysis is to examine stability of a steady state. In other words, we should like to find instability condition. The stability analysis of the particular steady state is usually performed on the linearized form of the general equation of motion of a system around the steady state. Namely, when the system is in a steady state little perturbation of the concentrations of intermediate species can be given as linear deviation from the steady state concentrations. [15]

$$c = c_{ss} + \Delta c \tag{16}$$

We can expand time derivative of concentration vector c in Taylor series near a steady state c_{ss} and keep leading terms only. Hence,

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{\mathrm{d}(c_{ss} + \Delta c)}{\mathrm{d}t} = \frac{\mathrm{d}\Delta c}{\mathrm{d}t} = \mathbf{M}\,\Delta c \ . \tag{17}$$

The leading term **M** is Jacobian matrix which in SNA has the form

$$\mathbf{M}(\boldsymbol{h}, \boldsymbol{v}_{ss}) = \mathbf{S}\,\mathrm{diag}(\boldsymbol{v}_{ss})\,\mathbf{K}^{\mathbf{T}}\mathrm{diag}(\boldsymbol{h}) \tag{18}$$

where diag(***h***) is a diagonal matrix whose elements h_i are the reciprocal of the steady state concentrations of the species *i*, for *i* = 1, 2, 3, and **K** is the matrix of the order of reactions with its transpose $\mathbf{K}^{\mathbf{T}}$. Hence, the stability is defined by the sign of the real part of the eigenvalues of the Jacobian matrix. A general derivation of Jacobian matrix **M** is given in references [8] and [15]. For the model under consideration, matrix **K** is:

$$\mathbf{K} = \begin{array}{c} \begin{matrix} \text{M.0} & \text{M.1} & \text{M.3} & \text{M.4} & \text{M.5} & \text{M.6} \end{matrix} \\ \begin{bmatrix} 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 2 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix} \end{array} \begin{matrix} \\ \text{X} \\ \text{Y} \\ \text{Z} \end{matrix} \tag{19}$$

As usual, row above and column beside the matrix **K** in equation (16) indicate correspondence between matrix rows and reaction species and between matrix columns and reaction steps, and they are not part of the matrix.

According to equation (14), the equation (18) can be transformed to

$$\mathbf{M}(\boldsymbol{h}, \boldsymbol{j}_{ss}) = \mathbf{S}\,\mathrm{diag}(\mathbf{E}\boldsymbol{j})\,\mathbf{K}^{\mathrm{T}}\mathrm{diag}(\boldsymbol{h}) \tag{20}$$

The matrix **M** written as a function of the SNA parameters j_i and h_i has particular advantages for the stability analysis since these parameters are non-negative and each element of **M** is linear function of ***j*** and ***h*** parameters, which is an essential feature of the SNA. The steady-state stability is determined by the sign of eigenvalues of **M**, which are the roots λ of the characteristic polynomial: [16]

$$\left|\lambda\mathbf{I} - \mathbf{M}\right| = \sum_{i=0}^{n} \alpha_i \lambda^{n-i} \tag{21}$$

where, for considered model, $n = 3$. If real parts of all eigenvalues are negative a steady state is stable. If one or more eigenvalues has positive real parts the steady state is unstable. The number of eigenvalues with positive real parts can be determined by Routh - Hurwitz criterion. According to this criterion the number of eigenvalues with positive real parts is equal to the number of the sign changes in the Routh array [16]

$$\mathrm{R} = \left(1, \Delta_1, \frac{\Delta_2}{\Delta_1}, \frac{\Delta_3}{\Delta_2}, \ldots, \frac{\Delta_n}{\Delta_{n-1}}\right) \tag{22}$$

where Δ_i, i = 1,…,*n*, is *i*-th Hurwitz determinant, defined as the determinant of the leading principal minor of the Hurwitz matrix **H**, where leading principal minor of dimension *i* is matrix constructed from the first *i* rows and columns of matrix **H**.

$$\mathbf{H}=\begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 & \alpha_7 & \dots & \alpha_{2n-1} \\ 1 & \alpha_2 & \alpha_4 & \alpha_6 & \dots & \alpha_{2n-2} \\ 0 & \alpha_1 & \alpha_3 & \alpha_5 & \dots & \alpha_{2n-3} \\ 0 & 1 & \alpha_2 & \alpha_4 & \dots & \alpha_{2n-4} \\ 0 & 0 & \alpha_1 & \alpha_3 & \dots & \alpha_{2n-5} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & \alpha_n \end{bmatrix} \tag{23}$$

Obviously, $\alpha_i = 0$ for $i > n$. Steady state is stable if all Hurwitz determinants are positive. If there is only one sign change in the Routh array (22), this indicates that only one eigenvalue has positive real part. Such instability occurs when the largest Hurwitz determinant changes its sign keeping all others positive, and this point presents saddle-node bifurcation. From Hurwitz matrix (23) we can see that the largest Hurwitz determinant Δ_n can be written as

$$\Delta_n = \alpha_n \times \Delta_{n-1} \tag{24}$$

Since the sign of the largest Hurwitz determinant is in this case determined by the sign of the largest coefficient of the characteristic polynomial α_n, the saddle-node bifurcation can be identified from [16]

$$\alpha_n = 0 \tag{25}$$

The Hurwitz matrix gives us also condition for appearance of Andronow-Hopf bifurcation which is of great importance, because it is source of oscillations in the system. The Andronow-Hopf bifurcation occurs when: [16, 17]

$$\Delta_{n-1} = 0 \tag{26}$$

For considered model where $n = 3$, the Hurwitz matrix is

$$\mathbf{H} = \begin{bmatrix} \alpha_1 & \alpha_3 & 0 \\ 1 & \alpha_2 & 0 \\ 0 & \alpha_1 & \alpha_3 \end{bmatrix} \tag{27}$$

and condition for appearance of Andronow-Hopf bifurcation given in equation (26) is

$$\Delta_2 = \begin{bmatrix} \alpha_1 & \alpha_3 \\ 1 & \alpha_2 \end{bmatrix} = \alpha_1\alpha_2 - \alpha_3 = 0 \tag{28}$$

Application of an instability condition obtained by this method becomes limited by the number of independent internal species and it is often very difficult to be determined by classical procedure, but this method is convenient for numerical evaluation of stability of steady state. Much simpler method to examine the steady-state stability is the use of the matrix of current rates **V**(***j***), where:

$$\mathbf{V}(\boldsymbol{j}) = \mathbf{S}\,\mathrm{diag}(\mathbf{E}\boldsymbol{j})\,\mathbf{K}^{\mathbf{T}} \tag{29}$$

The steady state is considered to be unstable if there is at least one negative diagonal minor of **V**(***j***). [8] Although it is an approximation, this criterion often gives satisfactory results. The matrix **V**(***j***) for the model considered is

$$\mathbf{V}(\boldsymbol{j}) = \begin{bmatrix} j_1 + j_2 + j_3 + j_4 & 2j_2 + 2j_4 & -(j_3 + j_4) \\ -(j_1 + j_2 + j_3 + j_4) & j_1 - j_2 + j_3 - j_4 & 0 \\ 0 & -(j_1 + j_2 + j_3 + j_4) & j_1 + j_2 + j_3 + j_4 \end{bmatrix} \tag{30}$$

We examined all diagonal minors and detected those with negative terms, since only these minors can be negative. They are negative when polynomial obtained from corresponding determinant is negative. The calculated polynomials have to be compared between one another, the core of instability must be recognized, and essential one ought to be selected. The aim is to find the polynomial with less possible order. Such obtained polynomials are expressed in function of j_i. In the case considered the

selected polynomial is coming from the minor corresponding to the second and third rows-columns:

$$2j_1j_3 - 2j_2j_4 + j_1^2 - j_2^2 + j_3^2 - j_4^2 < 0 \tag{31}$$

It may be transformed to

$$(j_1 + j_3)^2 < (j_2 + j_4)^2 \tag{32}$$

Since all j_i parameters are non-negative condition (32) can be rewritten as:

$$j_1 + j_3 < j_2 + j_4 \tag{33}$$

According to (15) instability condition (33) becomes

$$k_1x_{ss} < k_2x_{SS}y_{SS}^2 \tag{34}$$

which is equivalent to

$$y_{SS} > \sqrt{\frac{k_1}{k_2}} \tag{35}$$

Inserting (8) into (34) we obtain

$$\frac{k_4k_0\, r_0}{k_3\,(k_4 - k_5\, r_0)} > \sqrt{\frac{k_1}{k_2}} \tag{36}$$

which may be transformed to

$$r_0 > \frac{k_1^{1/2}k_3\, k_4}{k_4k_0\, k_2^{1/2} + k_1^{1/2}k_3k_5} \tag{37}$$

Equation (37) gives the critical condition, which need to be fulfilled for periodic temporal evolution of intermediate species that are involved in

dynamics of HPA system model, However, this result is only the approximation based on selection of the most significant minors of the matrix V(***j***), which are responsible for the sign of the corresponding coefficient in the characteristic polynomial (21). In large number of tested models this approximation works very well, even surprisingly well. However, in some cases it is not enough and complete condition for Andronov-Hopf bifurcation (28) must be used. It may be applicable only in the case of small models like the one used here. For the given model it is given by:

$$\begin{aligned}\Delta_2 = \begin{bmatrix} \alpha_1 & \alpha_3 \\ 1 & \alpha_2 \end{bmatrix} = \alpha_1\alpha_2 - \alpha_3 &= h_1^2 h_2 \left(j_1 + j_2 + j_3 + j_4\right)^3 + h_1^2 h_3 \left(j_1 + j_2 + j_3 + j_4\right)^3 \\ &+ h_1 h_2^2 \left(j_1 + j_2 + j_3 + j_4\right)^2 \left(j_1 - j_2 + j_3 - j_4\right) \\ &+ h_1 h_2 h_3 \left(j_1 + j_2 + j_3 + j_4\right)^2 \left(j_1 - j_2 + j_3 - j_4\right) \\ &+ h_2^2 h_3 \left(j_1 + j_2 + j_3 + j_4\right)\left(j_1 - j_2 + j_3 - j_4\right)^2 \\ &+ h_1 h_2 h_3 \left(j_1 + j_2 + j_3 + j_4\right)^3 + h_1 h_3^2 \left(j_1 + j_2 + j_3 + j_4\right)^3 \\ &+ h_2 h_3^2 \left(j_1 + j_2 + j_3 + j_4\right)^2 \left(j_1 - j_2 + j_3 - j_4\right) \\ &+ h_1 h_2 h_3 \left(j_1 + j_2 + j_3 + j_4\right)^2 \left(j_3 + j_4\right) = 0 \end{aligned} \tag{38}$$

Numerical simulations (Figure 1) were done for three values of the parameter r_0 and fixed values of rate constants.

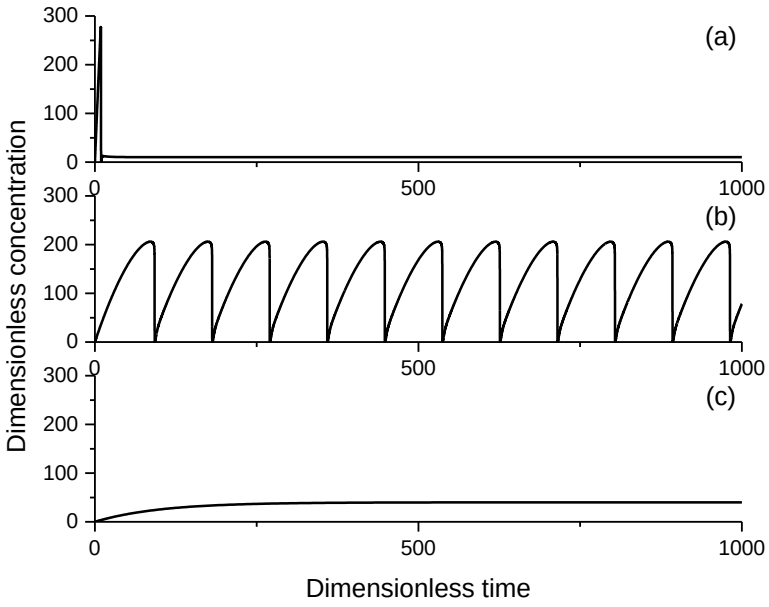

Figure 1. Numerical simulations of the three-variable-autocatalator model given in Table 1. Dimensionless rate constants: k_0=40; k_1=0.01; k_2= 2.439 10^{-3} ; k_3 = 2; k_4 = 0.5; k_5 = 0.5. Reactant dimensionless concentrations: (a) r_0 = 0.8; (b) r_0 = 0.1; (c) r_0 = 0.01.

In Figures 1(a) and 1(c) numerical simulation leads to the stable steady state, while in Figure 1(b) periodic oscillations are obtained. Accordingly, if Δ_2 given in (38) is evaluated with parameter values used in Figures 1(a) and 1(c), positive values are obtained and with parameter values used for Figure 1(b) negative value for Δ_2 is obtained. Hence, two bifurcation points of Andronov-Hopf type may be found between these extreme cases. However, approximate instability condition (37) predicts only one bifurcation value as a function of the r_0. This condition is fulfilled for both sets of parametar values, in Figure 1(a) and 1(b), and we can now say that used approximation was too large.

4. Conclusions

The three-variable-autocatalator was submitted to the Stoichiometric Network Analysis. Four elementary reaction pathways – extreme currents of the model were identified. Linearized operator of the model near the steady state was constructed and matrix of extreme current rates $\mathbf{V}(\boldsymbol{j})$ was extracted from it as the essential part. From the principal minors of the matrix $\mathbf{V}(\boldsymbol{j})$ the instability condition was identified which restricts the ratios between some reaction rates at the steady state, and consequently between the parameter values. Exact instability condition was identified from the Hurwitz matrix and it was validated by numerical simulations.

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