THE JOURNAL OF CHEMICAL PHYSICS **131**, 171101 (2009)

A least-constraint principle for population dynamics and reaction kinetics: Modeling entropy-controlled chemical hypercycles

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(Received 31 July 2009; accepted 2 October 2009; published online 2 November 2009)

In this paper, we investigate the treatment of constraints in rate equations describing the temporal evolution of biological populations or chemical reactions. We present a formulation for arbitrary holonomic and linear nonholonomic constraints which ensures the positivity of the dynamical variables and which is an analog of Gauss' principle of least constraint in classical mechanics. The approach is illustrated for the replication of molecular species in the Schuster–Eigen hypercycle model, imposing the conservation of the total number of molecules and the entropy production as constraints. The latter is used to model the behavior of an isolated system tending toward equilibrium and, for comparison, a stationary nonequilibrium state of an open system, which is characterized by undamped oscillations. © *2009 American Institute of Physics*.
[doi:10.1063/1.3253688]

A large class of problems in chemistry and biology can be treated by dynamical models for a set of chemical or biological species in which the time evolution of the latter is described by a system of ordinary differential equations. Well-known examples are the kinetics of chemical reactions[1,2] and the dynamics of biological species,[3] in particular the Lotka–Volterra model for the population dynamics of prey and predator fishes in the Mediterranean Sea.[4] The interactions between the species can be either explicitly described by the parameters and the structure of the equations of motion, or by modeling them implicitly in terms of constraints describing their resulting effect. A simple example for such a constraint is a fixed total number of individuals, as a result of limited resources.

In classical mechanics, the treatment of constraints has a long history and goes back to D'Alembert, Lagrange and Gauss.[5,6] Gauss achieved in particular a formulation of constrained classical mechanics in form of a least-squares problem for the particle displacements.[7] The treatment of constraints in mechanical systems from a unifying mathematical point of view has been recently discussed in Refs. 8 and 9, where the equations of motion of a constrained mechanical system are interpreted as a system of linear equations for the components of two orthogonal vectors - the vector comprising the constraint forces and the vector comprising the unrestricted components of particle accelerations. In the theory of electrical networks, the solution of linear equations for mutually orthogonal vector variables has been discussed in the 1950s by Bott and Duffin.[10] Following the lines of Refs. 8 and 9, we show here how constraints can be treated in the equations of motion describing the time evolution of non-negative dynamical variables, $c_1(t),\dots,c_n(t)$, which represent molecular concentrations or biological populations.

We suppose that the unconstrained equations of motion have the general form

$$\dot{c}_i=\Psi_i(\mathbf{c})+c_i\phi_i(\mathbf{c}),\quad i=1,\dots,n, \tag{1}$$

where $\mathbf{c}=(c_1,\dots,c_n)^T$ is an n-dimensional column vector comprising the dynamical variables, $\lim_{c_i\to 0^+}|\phi_i(\mathbf{c})|<\infty$, and $0\le\lim_{c_i\to 0^+}\Psi_i(\mathbf{c})<\infty$ $(i=1,\dots,n)$. The superscript T denotes a transposition. Since $\dot{c}_i\ge 0$ for $c_i\to 0^+$, no continuous trajectory $\mathbf{c}(t)$ exists in which one or more concentrations cross or even reach the line of zero concentration, given that the initial values, $c_1(0),\dots,c_n(0)$, are all positive. The dynamical system under consideration may be subject to m_h holonomic and m_v nonholonomic (differential) constraints of the form

$$\sigma_i(\mathbf{c},t)=\sigma_i^{(0)},\quad i=1,\dots,m_h, \tag{2}$$

$$\sum_{j=1}^{n}A_{ij}^{(v)}(\mathbf{c},t)\dot{c}_j=b_i^{(v)}(\mathbf{c},t),\quad i=1,\dots,m_v, \tag{3}$$

respectively, where $m_h+m_v<n$, the $\sigma_i^{(0)}$ are constants and the σ_i are supposed to be differentiable with respect to all arguments. Differentiating the holonomic constraints [Eq. (2)] with respect to time leads to m_h linear rate constraints which may be combined with those defined through Eq. (3),

$$\mathbf{A}\dot{\mathbf{c}}=\mathbf{b}. \tag{4}$$

Here, $\mathbf{A}$ is an $m\times n$ matrix, with $m=m_h+m_v$, and $\mathbf{b}$ is an m-dimensional column vector. The elements of $\mathbf{A}$ and $\mathbf{b}$ read explicitly (the arguments are omitted)

$$A_{ij}=\begin{cases}\partial\sigma_i/\partial c_j & \text{if } i=1,\dots,m_h,\ j=1,\dots,n\\ A_{i-m_h,j}^{(v)} & \text{if } i=m_h+1,\dots,m,\ j=1,\dots,n,\end{cases} \tag{5}$$

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$$b_i = \begin{cases} -\partial\sigma_i/\partial t & \text{if } i = 1, \ldots, m_h \\ b^{(v)}_{i-m_h} & \text{if } i = m_h + 1, \ldots, m. \end{cases} \tag{6}$$

In the following, we suppose that $\text{rank}(\mathbf{A}) = m$, i.e., we consider only *independent* constraints.

Equation (4) can be viewed as an underdetermined system of m equations for the n components of the rate vector $\dot{\mathbf{c}} = (\dot{c}_1, \ldots, \dot{c}_n)^T$. The latter may be decomposed into two orthogonal components, $\dot{\mathbf{c}}_\parallel$ and $\dot{\mathbf{c}}_\perp$, the first of which is in the null space of $\mathbf{A}$, i.e., $\mathbf{A}\dot{\mathbf{c}}_\parallel = \mathbf{0}$, and the second of which is in its orthogonal complement. In the following, these two vector spaces are denoted by $\mathcal{V}_\parallel$ and $\mathcal{V}_\perp$, respectively. Their dimensions are $\dim(\mathcal{V}_\parallel) = n - m$ and $\dim(\mathcal{V}_\perp) = m$. By definition, the rows of $\mathbf{A}$ are a basis of $\mathcal{V}_\perp$, such that $\dot{\mathbf{c}}_\perp = \mathbf{A}^T\boldsymbol{\nu}$ where $\boldsymbol{\nu} = (\nu_1, \ldots, \nu_m)^T$ contains the m coordinates of $\dot{\mathbf{c}}_\perp$ in that basis. Inserting $\dot{\mathbf{c}} = \dot{\mathbf{c}}_\parallel + \mathbf{A}^T\boldsymbol{\nu}$ into Eq. (4) shows that $\mathbf{A}\mathbf{A}^T\boldsymbol{\nu} = \mathbf{b}$. The vector of all possible rates $\dot{\mathbf{c}}$ which is compatible with the imposed constraints [Eqs. (2) and (3)] is thus given by

$$\dot{\mathbf{c}} = \dot{\mathbf{c}}_\parallel + \mathbf{A}^+\mathbf{b}, \tag{7}$$

where the matrix

$$\mathbf{A}^+ = \mathbf{A}^T(\mathbf{A}\mathbf{A}^T)^{-1} \tag{8}$$

is the Moore–Penrose inverse of $\mathbf{A}$ if the latter has full rank, m.[11–14]

In order to ensure that the imposed Eqs. (2) and (3) are verified we introduce n new *constraint fields*, $z_i(\mathbf{c})$ $(i = 1, \ldots, n)$, and write Eq. (1) in the form

$$\dot{c}_i = \Psi_i(\mathbf{c}) + c_i[\phi_i(\mathbf{c}) + z_i(\mathbf{c})], \quad i = 1, \ldots, n. \tag{9}$$

The substitution $\phi_i(\mathbf{c}) \to \phi_i(\mathbf{c}) + z_i(\mathbf{c})$ leaves the general form [Eq. (1)] of the equations of motion unchanged, guaranteeing thus the positivity of the resulting solutions for finite constraint fields. To compute the latter we introduce the matrix

$$\mathbf{G} = \text{diag}(c_1, \ldots, c_n) \tag{10}$$

and write Eq. (9) in matrix form,

$$\dot{\mathbf{c}} = \boldsymbol{\Psi}(\mathbf{c}) + \mathbf{G}[\boldsymbol{\phi}(\mathbf{c}) + \mathbf{z}(\mathbf{c})], \tag{11}$$

where $\boldsymbol{\Psi} = (\Psi_1, \ldots, \Psi_n)^T$ and $\boldsymbol{\phi} = (\phi_1, \ldots, \phi_n)^T$. Inserting here Eq. (7) leads to a system of n linear equations for the vector variables $\dot{c}_\parallel$ and z, which are *both* unknown, $\dot{\mathbf{c}}_\parallel + \mathbf{A}^+\mathbf{b} = \boldsymbol{\Psi}(\mathbf{c}) + \mathbf{G}[\boldsymbol{\phi}(\mathbf{c}) + z(\mathbf{c})]$. Introducing

$$\mathbf{h} = \mathbf{A}^+\mathbf{b} - \boldsymbol{\Psi} - \mathbf{G}\boldsymbol{\phi}, \tag{12}$$

we may write this system in the compact form

$$\mathbf{G}\mathbf{z} - \dot{\mathbf{c}}_\parallel = \mathbf{h}. \tag{13}$$

If one requires that $\mathbf{z}$ be orthogonal to $\dot{\mathbf{c}}_\parallel$,

$$\mathbf{z}^T\dot{\mathbf{c}}_\parallel = 0, \tag{14}$$

Equation (13) defines a Bott–Duffin problem,[10] which has a *unique* solution for $\dot{\mathbf{c}}_\parallel$ and $\mathbf{z}$. It follows from Eq. (14) that $\mathbf{z} \in \mathcal{V}_\perp$, i.e., $\mathbf{z}$ can be expressed as a linear combination of the rows of $\mathbf{A}$, $\mathbf{z} = \mathbf{A}^T\boldsymbol{\lambda}$. A system of linear equations for the components of the column vector $\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_m)^T$ can be established by inserting $\mathbf{z} = \mathbf{A}^T\boldsymbol{\lambda}$ into Eq. (13) and by multiplying with $\mathbf{A}$ from the left. On account of $\mathbf{A}\dot{\mathbf{c}}_\parallel = \mathbf{0}$ and $\mathbf{A}\mathbf{A}^+\mathbf{b} = \mathbf{b}$ it follows that $\mathbf{A}\mathbf{G}\mathbf{A}^T\boldsymbol{\lambda} = \mathbf{A}\mathbf{h} = \mathbf{b} - \mathbf{A}(\boldsymbol{\Psi} + \mathbf{G}\boldsymbol{\phi})$. The condition $\det(\mathbf{A}\mathbf{G}\mathbf{A}^T) \neq 0$ for the existence of a solution $\boldsymbol{\lambda}$ does not necessarily imply that $\mathbf{G}$ has full rank n. One or more concentrations c_i may be zero, as long as $\text{rank}(\mathbf{A}\mathbf{G}\mathbf{A}^T) = m$. Solving the above system of linear equations for $\boldsymbol{\lambda}$ leads to

$$\mathbf{z} = \mathbf{G}_\perp^{(-1)}\mathbf{h}, \tag{15}$$

where the matrix

$$\mathbf{G}_\perp^{(-1)} = \mathbf{A}^T(\mathbf{A}\mathbf{G}\mathbf{A}^T)^{-1}\mathbf{A} \tag{16}$$

is the *Bott–Duffin inverse* of $\mathbf{G}$ with respect to the vector space $\mathcal{V}_\perp$.[8,10]

Equation (14) can be given a more intuitive interpretation, noting that the variations of the concentrations at time $t + dt$ are determined by the possible variations of the rates at time t and that the latter are restricted due to the imposed constraints,

$$\boldsymbol{\delta}\mathbf{c}(t + dt) = \boldsymbol{\delta}\dot{\mathbf{c}}(t)dt = \boldsymbol{\delta}\dot{\mathbf{c}}_\parallel(t)dt. \tag{17}$$

Equation (14) is thus equivalent to

$$\mathbf{z}^T(t)\boldsymbol{\delta}\mathbf{c}(t + dt) = \sum_{i=1}^{n} z_i(t)\,\delta c_i(t + dt) = 0, \tag{18}$$

which recalls D'Alembert's principle of virtual displacements in classical mechanics.[5,6,9,15,16] In the same way as D'Alembert's principle was reformulated by Gauss as a minimum principle (the principle of least constraint), Eq. (18) can be formulated as a "least constraint problem for rate equations." For this purpose we introduce the function

$$f(\dot{\mathbf{c}}) = \sum_{i=1}^{n} \frac{1}{2c_i}[\dot{c}_i - c_i\phi_i(\mathbf{c}) - \Psi_i(\mathbf{c})]^2, \tag{19}$$

and we claim that the system evolves in time such that f takes its minimum with respect to $\dot{c}_1, \ldots, \dot{c}_n$ under the imposed constraints. This condition leads to

$$\sum_{i=1}^{n} \frac{\partial f}{\partial \dot{c}_i}\delta\dot{c}_i = \sum_{i=1}^{n} \frac{1}{c_i}[\dot{c}_i - c_i\phi_i(\mathbf{c}) - \Psi_i(\mathbf{c})]\delta\dot{c}_i = \sum_{i=1}^{n} z_i\delta\dot{c}_i = 0. \tag{20}$$

If no constraints are imposed the variations $\delta\dot{c}_i$ are arbitrary and Eq. (20) implies that the constraint fields vanish, $z_i = 0$ $(i = 1, \ldots, n)$, which leads again to the free equations of motion [Eq. (1)]. If constraints are imposed, the rate variations must fulfill the condition $\boldsymbol{\delta}\dot{\mathbf{c}} = \boldsymbol{\delta}\dot{\mathbf{c}}_\parallel \in \mathcal{V}_\parallel$, on account of Eq. (7). In this case, the necessary condition for a minimum of f leads thus to $\mathbf{G}^{-1}[\dot{\mathbf{c}} - \mathbf{G}\boldsymbol{\phi}(\mathbf{c}) - \boldsymbol{\Psi}(\mathbf{c})] = \mathbf{z} \in \mathcal{V}_\perp$. This corresponds exactly to the general form [Eq. (11)] for the equations of motion, supplemented by Eq. (14) for the constraint forces. It must, however, be observed the least constraint formulation implies that all concentrations are nonzero.

We apply now the method presented above to study the impact of two particular constraints on the dynamics of a cyclic network of autocatalytic reactions which has been introduced by Eigen and Schuster as a model for prebiotic evolution.[17] We confine our study to a variant of the replication scheme, which is referred to as elementary hypercycle. The dynamics of a group of n species is then described by the equations of motion

$$\dot{c}_i = k_{\mathrm{h}} c_i c_{i+1}, \quad c_{n+1} = c_1. \tag{21}$$

Using the notation introduced above, we have here $\phi_i = k_{\mathrm{h}} c_{i+1}$ and $\Psi_i = 0$. The rate is controlled by the kinetic constant $k_{\mathrm{h}} > 0$.

In absence of any additional conditions, the dynamics described by Eq. (21) leads to unlimited, exponential growth of the individual species. Such a behavior is certainly not realistic in view of limited resources of energy and molecules. A simple and crucial constraint to consider is therefore the *constant population* constraint,[18,19] which we formulate in the most simple form as

$$\sum_{i=1}^{n} c_i = 1. \tag{22}$$

Here, we define $c_i = N_i/N$, where N_i is the number of molecules of species i and $N = \Sigma_{i=1}^{n} N_i$ is the total number of molecules. Experimentally, such a constraint is realized by a so-called chemostat in which the total number of molecules is kept constant, but which allows for variations in the decomposition $\{N_1, \ldots, N_n\}$. These variations may be due to a chemical reaction in the reaction vessel or due to an exchange with the exterior.

The second constraint we impose concerns entropy production and has not been considered so far. It is motivated by the fact that molecular replication must be considered in nonequilibrium conditions, since chemical reactions evolve irreversibly.[1,19] The entropy change in the system may be decomposed as $dS = dS_{\mathrm{int}} + dS_{\mathrm{ext}}$, where the indices "int" and "ext" stand for "internal" and "external" with respect to the reaction vessel, respectively. From a thermodynamic point of view, the latter is *a priori* an open system, allowing for exchange of matter across the boundaries. The internal entropy change is due to the irreversible process of entropy production by the chemical reaction, $dS_{\mathrm{int}} > 0$, whereas dS_{ext} is due to reversible exchanges with the exterior. Here, we suppose that the system is close to equilibrium, such that the expressions for the thermodynamic potentials from equilibrium thermodynamics can still be used.[1] Introducing the entropy per molecule, $s = S/N$, we have then $T ds_{\mathrm{int}} = -\Sigma_{i=1}^{n} \mu_i dc_i^{\mathrm{int}}$, where dc_i^{int} is the change of c_i due to the chemical reaction in the vessel, μ_i the corresponding chemical potential, and T is the temperature. If the reaction vessel is isolated, we must have $\dot{s} = \dot{s}_{\mathrm{int}} > 0$ and $\dot{c}_i = \dot{c}_i^{\mathrm{int}}$. In order to construct an explicit constraint for the evolution of the entropy, we impose

$$s(t) = s_0 + (s_{\mathrm{eq}} - s_0)[1 - \exp(-t/\tau_{\mathrm{s}})], \tag{23}$$

where $s_0 = s(0)$ and $s_{\mathrm{eq}} > s_0$. The parameter τ_{s} sets the time constant of the exponential relaxation process. Since $s_{\mathrm{eq}} > s_0$, we get a positive entropy production, $\dot{s}(t) > 0$, and $s(t)$ exhibits a concave form, in agreement with general assumptions concerning reactions in nonequilibrium conditions (see for example Ref. 20). Using the time derivative of Eq. (23) as entropy production rate, we obtain a linear constraint for the velocities $\dot{c}_1, \ldots, \dot{c}_n$,

$$\sum_{i=1}^{n} \mu_i \dot{c}_i = -\frac{T(s_{\mathrm{eq}} - s_0)}{\tau_{\mathrm{s}}} \exp[-t/\tau_{\mathrm{s}}]. \tag{24}$$

For the chemical potentials, we suggest the form $\mu_i = \mu_i^{(0)} + k_{\mathrm{B}} T \ln(c_i / \Sigma_{l=1}^{n} c_l)$, which is suitable for mixtures.[21] Here, k_{B} is the Boltzmann constant and $k_{\mathrm{B}} T$ sets the scale for the chemical potentials. The differences in $\mu_i^{(0)}$ may be attributed to the differences in states of the polyfunctional molecules[22,23] that form hypercyclic catalytic chains or reaction networks. The equilibrium entropy is expressed in the form $s_{\mathrm{eq}} = -k_{\mathrm{B}} \Sigma_{i=1}^{n} c_i^{\mathrm{eq}} \ln c_i^{\mathrm{eq}}$. The equilibrium concentrations fulfill $c_i^{\mathrm{eq}} \propto \exp[-\mu_i^{(0)}/(k_{\mathrm{B}} T)]$ and can be obtained by minimizing the Gibbs free energy $F_G = \Sigma_{i=1}^{n} \mu_i c_i$ subject to the CP constraints.

Alternatively, we can consider an open system, where the entropy production in the reaction vessel is compensated by a negative entropy flow into the vessel, such that $\dot{s} = \dot{s}_{\mathrm{int}} + \dot{s}_{\mathrm{ext}} = 0$. Assuming that external entropy changes are only due to particle flow, we have $T\dot{s} = -\Sigma_{i=1}^{n} \mu_i (\dot{c}_i^{\mathrm{int}} + \dot{c}_i^{\mathrm{ext}})$, where $\dot{c}_i^{\mathrm{ext}}$ denotes the change of concentration of species i due to an exchange of matter across the boundaries of the system. With $\dot{c}_i = \dot{c}_i^{\mathrm{int}} + \dot{c}_i^{\mathrm{ext}}$ one obtains instead of Eq. (24)

$$\sum_{i=1}^{n} \mu_i \dot{c}_i = 0. \tag{25}$$

The constraints introduced above lead to matrix elements $A_{ij} = \delta_{i1} + \mu_j \delta_{i2}$, where δ_{ij} is the Kronecker symbol. The elements of $\mathbf{b} = (b_1, b_2)^{\mathrm{T}}$ are $b_1 = 0$, $b_2 = -T(s_{\mathrm{eq}} - s_0)\exp[-t/\tau_{\mathrm{s}}]/\tau_{\mathrm{s}}$ for the Eqs. (22) and (24) and $b_1 = 0$, $b_2 = 0$ for the Eq. (22) and (25). Straightforwardly, we obtain

$$[\mathbf{G}_{\perp}^{(-1)}]_{i,j} = \eta_{\mathrm{M}}[\mu_i \mu_j - \mathcal{M}_1(\mu_i + \mu_j) + \mathcal{M}_2], \tag{26}$$

where the "moments" $\mathcal{M}_q$ are given by $\mathcal{M}_q = \Sigma_{l=1}^{n} \mu_l^q c_l$, $q = 1, 2$ and $\eta_{\mathrm{M}} = 1/(\mathcal{M}_2 - \mathcal{M}_1^2)$, and the vector of constraint fields is found to be

$$z_i = \eta_{\mathrm{M}}[(\eta_1 + \eta_0 \mathcal{M}_1)\mu_i - (\eta_1 \mathcal{M}_1 + \eta_0 \mathcal{M}_2)] \tag{27}$$

where $\eta_0 = k_{\mathrm{h}} \Sigma_{i=1}^{n} c_i c_{i+1}$, $\eta_1 = b_2 - k_{\mathrm{h}} \Sigma_{i=1}^{n} c_i c_{i+1} \mu_i$, and $c_{n+1} = c_1$.

Figure 1 shows a numerical solution of the equations of motion for $n = 5$ species in the hypercycle. The corresponding model parameters are given in the figure caption. The dotted black lines show the effect of the constant population constraint alone, which leads to undamped phase-shifted nonlinear oscillations in the five concentrations, $c_1, \ldots, c_5$. The same observation has been reported some time ago[19] and a similar behavior is found for the well-known Lotka–Volterra model,[4] although in this case the conserved quantity is not the total number of individuals. Imposing in addition the entropy production constraint [Eq. (24)] corresponding to an isolated system leads to a damping of the oscillations in the individual concentrations, which approach each its respective equilibrium value (solid black lines). Imposing instead zero entropy production, which corresponds to an open system, leads again to undamped oscillating populations (solid gray lines). We note here that the development of oscillations depends on the choice of the $\mu_i^{(0)}$ $(i = 1, \ldots, n)$, which determine the equilibrium concentrations. If the vector $\mathbf{c}_{\mathrm{eq}}$

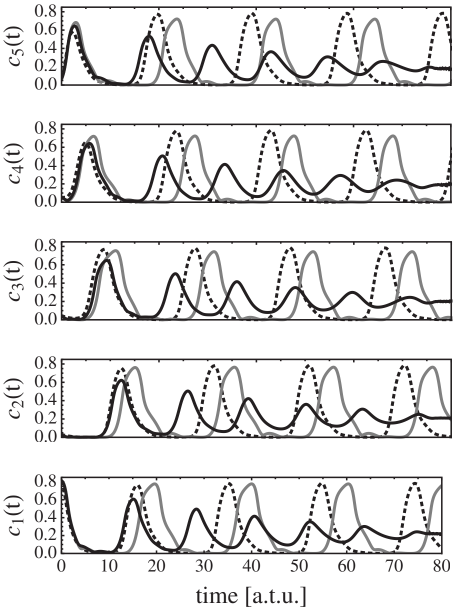

FIG. 1. Dynamics of a hypercycle with $n=5$ populations for different types of constraints: (a) constant total population (dotted black line), (b) constant total population and entropy production (solid black line), (c) constant total population and zero entropy production (solid gray line). The calculations have been performed for $\tau_s=30$ a.t.u. (arbitrary time units), a rate constant $k_h=3/\text{a.t.u.}$, and $\mu_l^{(0)}=(0.1+0.05l)k_BT$ $(l=1,\ldots,5)$.

$=(c_1^{eq},\ldots,c_n^{eq})^T$ is close to the boundaries of the simplex described by $\sum_{i=1}^n c_i=1$, oscillations are unlikely to develop.

The above example illustrates that the combination of holonomic and nonholonomic constraints in the dynamics of chemical reactions and biological populations can be elegantly handled by using the same mathematical tools as for the treatment of constraints in mechanical systems. One can, in particular, formulate a principle of least constraint, in analogy with Gauss' principle in classical mechanics. The possibility to treat also nonholonomic constraints opens a route to introduce concepts of nonequilibrium thermodynamics into reaction kinetics, leading to meaningful results, such as damping effects though entropy production.

ACKNOWLEDGMENTS

D.H. acknowledges financial support as a visiting scientist provided by *Le Studium*, Research Agency of the Région Centre, France, and support of VEGA, Slovak Republic (Grants No. 1/4021/07 and 1/0300/09).

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