Poisson-Boltzmann Equation Boundary Conditions for Biological Applications

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Abstract—Poisson-Boltzmann equation (PBE) is widely used in the context of deriving the electrostatic energy of macromolecular systems and assemblies in solution. Its numerical solution is briefly described together with some aspects that limit its applicability, especially to large systems. In this work, new sets of boundary conditions are described, that take into account the impenetrability of the molecule to the solvent. This choice promises to be particularly useful in the context of biological applications, where the solvation energy, arising from medium polarization, has a prime role. © 2005 Elsevier Ltd. All rights reserved.

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1. INTRODUCTION

Electrostatics is believed to play a pivotal role in regulating interactions between biological macromolecules, such as proteins and nucleic acids [1,2]. Specifically, the solvation contribution, that is the energy arising from the dielectric response to the electric field generated by the charge present on the molecule, has particular importance in many biological phenomena. In this framework, Poisson-Boltzmann equation (PBE) proved to be extremely useful in providing a tool that quantitatively estimates electrostatic interaction energy [3]. PBE is a second order nonlinear partial differential equation derived in the context of the Debye-Huckel continuum electrostatic theory [4]. It has the following form

$$
\nabla [\varepsilon(x) \nabla \Phi(x)] = -\frac{e}{\varepsilon_0 k_B T} [\rho^{\text{fixed}}(x) + \rho^{\text{solv}}(x)],
$$

(1)

where $\phi(x)$ is the dimensionless electrostatic potential corresponding to $(e/(k_B T))\varphi(x)$, $e$ is the unit charge, $k_B$ and $T$ are Boltzmann constant and absolute temperature, respectively. Fixed and solvent charge densities correspond to the partial charges located on the molecular body and the ionic charge located in solution. They can be expressed as follows

$$
\rho^{\text{fixed}}(x) = \sum_{i=1}^{N_f} q_i \delta(x - x_i),
$$

(2)

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where $i$ spans over the $N_f$ fixed charges, and

$$\rho^{\text{solv}}(x) = e \sum_{j=1}^{N_s} C_j^b z_j e^{-z_j \Phi(x)},$$

(3)

where $j$ spans over the $N_s$ ionic species and $C_j^b$ is the bulk concentration of the $j^{\text{th}}$ ionic species.

For this equation fast and accurate numerical solution is usually difficult to accomplish, due to presence of discontinuous coefficients, delta functions, three spatial dimensions, unbounded domain, and rapid, exponential, nonlinearity. In biological applications, when low charged molecules are concerned, PBE is linearized whereas the full nonlinear equation is used for highly charged molecules such as nucleic acids. However, once the solution has been obtained, following a suitable energy partitioning scheme, described in [5,6], one can also distinguish among the different electrostatic energy contributions and figure out which the most relevant physical phenomena occurring at a specific site of interest are. In this work, a particular attention is given to the estimation of the so-called direct ionic contribution, described in Section 4. The usual approach taken when using PBE for the cited applications, is to solve it in its weak form adopting a finite-difference or a finite-element scheme [3,7,8]. Now, two demands arising from the computational biology community are faced: the need to deal with always bigger system dimensions and the need to have a tool that can be run extensively on databases, consenting a rapid data processing. Among other applications, this could help studying receptors for adhesion molecules, growth factors, hormones, and cytokines, that are important regulators of many critical cell biological functions, including proliferation, migration, and apoptosis. The main intention of this paper is to initiate the development of improved sets of boundary conditions for both linearized and nonlinear PBE that allow to deal with bigger systems or to increase the resolution without increasing the grid dimension where the equation is solved.

2. PBE SOLVING TECHNIQUE

When PBE is used to calculate the electrostatic energy of a system constituted by one or more macromolecules the first task to be accomplished is to map the system onto the grid where the finite-difference solution is to be performed. A thorough description of how this can be done is given in [9,10]. This phase consists in assigning every fixed partial charge to the grid points and the dielectric constant value to each middle point between two adjacent grid points. If $N$ is the side dimension of the cubic grid, then there are $3N^2(N - 1)$ points to be assigned with their own dielectric constant value. A proper assignment requires a suitable definition of the boundary between inside and outside of a given molecule because this is the region where the dielectric constant changes from its internal value to the higher value inherent in many solvents, especially water. Although there is some uncertainty as to where to define this boundary, in most applications it is taken to correspond to the molecular surface defined as the contact surface between the van der Waals surface of a molecule and the surface of a spherical probe representing the solvent [11–13]. The process leads to the definition of two regions, $\Omega_1$ and $\Omega_2$. The region inside the molecular system $\Omega_1$ contains the fixed charge density and therein is solved the Poisson equation. The outer region $\Omega_2$, which contains only the solvent charge density, is where the PBE is solved. In the case of a solution containing a monovalent salt, equation (1) in region $\Omega_2$ becomes

$$\nabla^2 \Phi(x) = \frac{1}{\lambda^2} \sinh[\Phi(x)].$$

(4)

In equation (4), $\lambda$ is the so-called Debye length, a parameter that represents the screening effect of the ionic cloud around the molecule and that is inversely proportional to the square root of the ionic strength [14].
It is worth pointing out that equation (1) on $\Omega = \Omega_1 \cup \Omega_2$ cannot be interpreted classically due to the form (2) of the fixed charge density and to the presence of the discontinuous function $\varepsilon(x)$. How to deal with this issue has been extensively discussed elsewhere [7]; what is presently concerned is the solution of equation (4) in $\Omega_2$.

PBE is solved numerically on a cubic grid contained in $\Omega$, which necessarily is a truncation of $\mathbb{R}^3$. The resulting $\Phi(x)$ is obtained imposing its continuity at the interface between $\Omega_1$ and $\Omega_2$ and imposing suitable boundary conditions on $\partial\Omega$, which coincides with the external frontier of $\Omega_2$.

The boundary conditions are usually taken to be induced by a known analytical solution to one of several possible approximations of the linearized PBE. Far from the molecule, such analytical solutions provide a quite accurate boundary condition approximation for the PBE solved on the truncation $\Omega$ of $\mathbb{R}^3$. It is easy to understand that, the bigger is grid dimension with respect to molecule dimension, the more accurate the boundary conditions turn out to be. All of them must respect the condition

$$\lim_{|x| \to \infty} \Phi(x) = 0. \tag{5}$$

The most commonly BCs used are

$$\Phi(x) = \frac{e}{4\pi\varepsilon_0\varepsilon_s k_BT} \sum_{i=1}^{N_f} q_i e^{-|x-x_i|/\lambda}, \quad x \in \partial\Omega. \tag{6}$$

The physical situation represented by BCs (6), where $\varepsilon_s$ is the dielectric constant of the solvent, corresponds to $N_f$ point charges directly immersed in a solvent, let's call it the full penetrating solvent approximation. The differences from the real situation reside both in the different dielectric constant of the physical medium constituting the molecule and in the ionic cloud that is nonphysically penetrating the molecule. The accuracy of these boundary conditions depends on the mutual dimension of $\Omega$ with respect to that of $\Omega_1$ and on the Debye length. The parameter describing the reciprocal dimension is the percent filling, i.e., the ratio of the maximum linear dimension of the molecule in a coordinate direction to the grid cube side.

As it will be shown in Section 5, large molecular systems, high resolution and a filling parameter that consents conditions (6) to be accurate, lead to tasks which are hugely time and memory consuming. Since the vast majority of interesting phenomena in this scope occurs at molecule-water interface, rather than in vicinity of $\partial\Omega$, often the practical approach is to adopt conditions (6) even in cases where a lower filling would be advisable. Evidently, this affects primarily the potential values close to the boundaries of the box where the PBE is solved; nonetheless, the deviation of the electrical quantities from their correct value propagates throughout the system. The need of new strategies aimed to derive boundary conditions suitable for higher filling values arises from these considerations.

3. BOUNDARY CONDITIONS DESIGN

As it has been already noted, the boundary conditions (6) correspond to the asymptotic behavior of the penetrating solvent case, for which the analytical solution is known. The boundary conditions proposed here correspond to the analytical solution for the spherical symmetry case. Linearized PBE solution is known in this case whereas nonlinear PBE needs to be suitably approximated, so that it is possible to get an analytical solution without entirely neglecting the nonlinearity. The procedure then consists in finding the best sphere, centered in the center of charge, that approximates the molecular system. From the numerical point of view this does not bring any additional computational cost, due to the fact that the molecular boundaries are anyway calculated and mapped onto the grid through an optimized routine [9]. Then, the sphere radius $r_1$ is simply the average of the distances from the external boundary grid points to the
center. \( \Omega_1 \) and \( \Omega_2 \) correspond to the two intervals \([0, r_1]\) and \([r_1, r_2]\), respectively. The full problem consists in solving Poisson equation in \( \Omega_1 \), and then PBE in \([r_1, \infty)\) imposing null potential for \( r \to \infty \), continuity for \( \Phi(r) \) and for the radial component of the displacement vector \( \vec{D}(r) \) at \( r = r_1 \). The procedure leads to new expressions for the constant \( C \) ruling the asymptotic behavior of the solution, that is the behavior for large values of the independent variable

\[
\Phi(\rho) = C e^{-\rho/\rho},
\]

where \( \rho = |x|/\lambda \) is the new, dimensionless, independent variable. The physical situation represented by this approximation envisions a sphere of radius \( \rho_1 \) and relative dielectric constant \( \varepsilon_{\text{in}} \) centered in the coordinate origin. A symmetrically distributed charge \( Q \) is smeared on a spherical surface of radius \( \rho_0 < \rho_1 \); the first sphere is then immersed in an electrolytic solution characterized by the Debye length \( \lambda \). The constant \( C \) corresponding to the full penetrating solvent limit in spherical symmetry is

\[
C_{\text{pen}} = \frac{Q e}{4\pi \varepsilon_0 \varepsilon_s \lambda k_B T}.
\]

In contrast, the constant corresponding to the spherically symmetric solution of the linearized PBE is the following [7]

\[
C_{\text{lin}} = \frac{Q e}{4\pi \varepsilon_0 \varepsilon_s \lambda k_B T} \frac{e^{\rho_1}}{1 + \rho_1}.
\]

### 3.1. Nonlinear PBE Boundary Conditions

As far as the nonlinear PBE is concerned, more extended considerations need to be done. First of all, it is worth noting that the boundary conditions (6) do not correspond to the asymptotic behavior of the solution of (4), even in the full penetrating solvent limit. In fact, it is true that the null asymptotic condition (5) for the potential requires that, for \( |x| \) sufficiently high, the set of solutions of equation (4) tends to coincide with the one of its linearized version

\[
\nabla^2 \Phi(x) = \Phi(x)/\lambda^2.
\]

However, among all the solutions, only one has to be chosen, namely the one that makes the solution compatible with the conditions at fixed charge location and of continuity at \( \partial \Omega_1 \). The influence of these conditions onto the solution strongly depends on the form of the equation in proximity of \( \partial \Omega_1 \), where the solutions of (4) and (10) can have a completely different behavior. The situation is made clearer in the case where both linear and nonlinear PBE are analytically solvable: the one dimensional planar case [14,15]. Then, the solution of the full nonlinear PBE is

\[
\Phi(x) = 4 \arctan \left[ \tanh \left( \frac{\Phi_0}{4} \right) e^{-x/\lambda} \right],
\]

whereas the solution of its linearized version with the same initial condition \( \Phi_0 \) is

\[
\Phi(x) = \Phi_0 e^{-x/\lambda}.
\]

The behavior of the solutions for different initial conditions is shown in Figure 1. If one considers the asymptotic expression of the actual solution (11), one obtains

\[
\Phi(x) = 4 \tanh \left( \frac{\Phi_0}{4} \right) e^{-x/\lambda}.
\]

If this equation would have been solved numerically using the boundary conditions induced by (12), then an error as relevant as \( \Phi_0 \) is high would have been committed. As far as the computational biology applications are concerned, the full nonlinear PBE is solved in the cases where
the molecule is highly charged, this usually means that the potential at molecule/solvent interface is also high and therefore, one should expect also the asymptotic behavior of the potential to differ from the one of the linearized PBE. Henceforth, it will be attempted to approach the problem of improving boundary condition for equation (4) by finding a finer than linear approximation that is also analytically solvable at least in the spherical case. Then, its asymptotic behavior will provide the new boundary condition set.

The nonlinear PBE in spherical symmetry takes the form

$$\frac{d^2 \Phi (r)}{dr^2} + 2 \frac{d\Phi (r)}{dr} \sinh (\Phi (r)) = 0.$$  \hfill (14)

Initially, a general approximated solution of equation (14) in $[r_1, \infty)$ depending on the initial value $\Phi (r_1) = \Phi_1$ is found. It is known that, for any given $\Phi_1$ the solution is unique [16]. From what has been said previously, that solution is asymptotically proportional to the solutions of the linearized equation. The present aim is to find a good estimate of the constant $C$ characterizing its asymptotic behavior. In order to do that, an auxiliary function is defined, $g(r) = \Phi (r)e^{\rho r}$. The exact equation for $g(r)$, together with the approximation chosen, follows

$$\frac{d^2 g(r)}{dr^2} - 2 \frac{d g(r)}{dr} = \sinh \left[ g(r) \frac{e^{-\rho r}}{\rho} \right] \frac{\rho}{e^{-\rho r}} - g(r) \approx \left[ g(r) \right]^3 \frac{e^{-2\rho}}{6 \rho^2}.$$ \hfill (15)

This equation is solved with the conditions $g(r_1) = g_1 = \Phi (r_1)\rho_1 e^{\rho_1}$ and $\lim_{r \to \infty} g(r) = C_{nl} \in (0; +\infty)$.

The detailed analytical derivation of the constant is given in the Appendix. The asymptotic behavior for the potential turns out to be

$$\Phi (r) \to \frac{2\rho_1 \Phi_1}{1 + \sqrt{1 + (\Phi_1^2/12)}} \frac{e^{-(\rho - \rho_1)}}{\rho}.$$ \hfill (16)

The complete solution requires that the PBE outside the sphere is joined smoothly with the solution of Poisson equation within the sphere. This procedure is quite standard in electrostatics.
and here it will only be sketched. The real axis spanned by $\rho$ is divided into three parts. The $[0; \rho_0]$ interval corresponds to the region internal to the spherical surface where the charge $Q$ is smeared; inside that sphere the potential is constant. The $(\rho_0; \rho_1)$ interval corresponds to a dielectric sphere where the solvent cannot penetrate, in this region the potential has the form $\xi + (\eta/\rho)$, $\xi$ and $\eta$ being constants with respect to $\rho$. The last interval, namely $(\rho_1; +\infty)$, corresponds to the solvent filled region where the Poisson-Boltzmann equation is to be solved. It can be shown that for the nonlinear approximated equation (15), the resulting $\Phi_1 = \Phi(\rho_1)$ is such that $z = (\varepsilon_{in}\eta \rho_1 \Phi_1)/(\lambda \varepsilon_s)$ is solution of the following algebraic equation

$$z^4 + (\rho_1^2 - 1)z^2 + 2z - 1 = 0.$$  \hspace{1cm} (17)

The series expression for $C_{nl}$ in this case therefore is

$$C_{nl} = C_{lin} - \frac{e^{\rho_1}(3\rho_1 + 1)}{48\rho_1^2(1 + \rho_1)^4}\eta^3 + \frac{e^{\rho_1}(11\rho_1^2 + 6\rho_1 + 1)}{1152\rho_1^4(1 + \rho_1)^7}\eta^5 + O(\eta^7).$$  \hspace{1cm} (18)
In Figure 2 the relations between asymptotic constant $C_{\text{lin}}$ and $C_{\text{pen}}$ versus the parameter $\eta$ at various sphere dimensions are shown.

In Figure 3 the $C_{\text{lin}}/C_{\text{pen}}$ ratio versus $\eta$ is shown, again at various sphere dimensions.

These graphs show that the proposed boundary conditions predict a potential value substantially higher than the usually assumed one. On the other side, as expected, the nonlinear asymptotic behavior considers a higher screening effect, and thus, a lowered potential with respect to its linear counterpart.

4. IONIC DIRECT CONTRIBUTION

The direct ionic contribution is that part of the electrostatic energy due to the direct electric interaction between the charge in solution and the fixed charges onto the molecular system. A way to calculate it consists in running the numerical solver twice, first with zero ionic strength and then with the actual ionic strength value. The difference between the total energy in the two runs is due to the presence of the ions. However, in [6] a quite different method giving similar insights within a single run is described. The ionic direct contribution takes the following form

$$
E_{\text{ion}} = \frac{1}{2} \sum_{t=1}^{N_f} \sum_k q_{i} \sum_k e_{i} \frac{e_{k}^{\text{ion}}}{4\pi \varepsilon_{0} \varepsilon_{s} |r_{k} - r_{i}|},
$$

where $k$ spans over all the grid cubes in solution and $e_{k}^{\text{ion}}$ is the ionic charge in each of them.

In order to consider the complete ionic contribution, $\Omega$ should extend all over the region of the solvent where the electrostatic potential is appreciably different from zero. However, under the same kind of assumptions made in the first order spherical approximation that led to the BCs (3), one can hypothesize the potential behavior from the boundary box element to infinity, and then derive the charge distribution, which depends only on the potential, outside the grid box. This can be done analytically once and for all. The final step is to sum the interactions over the fixed charges. The estimation of the contribution due to the ions located out of the lattice where the PBE is solved is obviously very sensitive to the potential value at the box boundaries, that is to the BCs.

5. SIMULATIONS AND RESULTS

To assess convenience and appropriateness of the newly introduced boundary conditions in the context of electrostatic potential and energy calculation for biological macromolecules two systems have been analyzed using the widely used numerical PBE solver DelPhi (Columbia University) suitably adapted.

The first was a control system, a charge of $+6e$ centered in sphere of radius 10.0 Å. In this case, the BCs (9) are exact. Physiological ionic strength $I = 0.145$ M and normally assumed values for electronic polarizability of a protein, corresponding to a dielectric constant $\varepsilon_{\text{lin}} = 2$, and for water dielectric constant $\varepsilon_{s} = 80$ were used. On grid box boundaries, when a filling of 90% was taken, the disagreement between penetrating solvent BCs and (9) was around 40% of the actual potential value. The second system was the Nerve Growth Factor, shown in Figure 4, whose structure has been kindly provided by the Statistical and Biological Physics Group at the International School for Advanced Studies in Trieste, Italy. It is a molecule of 3554 atoms whose largest dimension is around 70 Å. The net charge on it is around $+6e$, the best approximating radius turns out to be 22.8 Å with a root mean square (RMS) difference from the actual molecular surface shape equal to 7.4 Å. The problem of assessing the new method in terms of accuracy for a system where the exact solution is not known rises some obvious difficulties. The strategy implemented here is to make the BC choice irrelevant by solving the PBE with the lowest filling allowed by the computational facilities available, a SGI workstation with 16250 MHz IP27 MIPS R10000 processors and main memory size of 16 Gb. The filling was 27.3% with a grid spacing of $h = 0.5$ Å. This resolution
consents to represent possible cavities and invaginations on molecule surface. With this filling, both BCs differ from zero with a RMS difference less than $4.0 \times 10^{-8} (k_B T)/e$. Now, as a reference value, the potential on a fictitious box at 90\% filling is taken and compared to the BCs. It has to be said that, solving the system on a very large grid can increase the inaccuracy of the solution. In order, to estimate this inaccuracy, the same method has been applied on the above-mentioned spherical system. To summarize the results, both BCs coincide within the inaccuracy induced by the numerical method so, from this viewpoint the simulation is not conclusive. However, the CPU time needed to assign BCs with the new technique is diminished of roughly two orders of magnitude. As a further figure of merit for the proposed BCs, the calculation of the ionic direct contribution has been done in the NGF system. The direct contribution calculated in the 90\% filling run accounted for the 85\% of the same contribution calculated in a 45\% run. The contribution arising from the outside ions estimated as described brought the total amount to the 92\% of the total.

6. SUMMARY AND CONCLUSIONS

In this work, new boundary conditions for the Poisson-Boltzmann equation have been proposed to be applied in the context of potential and electrostatic energy calculation for biological macro-
molecules. Moreover, a methodology to exploit boundary conditions to estimate the direct ionic contribution outside the finite-difference grid is described. The new BCs are derived from the analytical solution of two different approximations of the PBE in the case of spherical symmetry. One conclusion that can be drawn from this study is that, keeping fixed all other physical quantities, the potential calculated through the nonlinear PBE is lower than the one obtained solving the linearized PBE. A quantitative expression of this fact is taken into account in the suggested BCs. Everything would let suppose that, the solution to the full nonlinear PBE would prescribe even more damped asymptotic behavior. As it is expected, nonlinear and linearized behaviors tend to coincide for low net charge on the system. The approach taken has two limits; first, only the first term of the multipole expansion of the fixed charge distribution is kept. Secondly, the potential at the boundaries results having spherical symmetry. On the other side, the location of both polarization and ionic charge is taken into account in more detail, making impossible the full penetration of the solvent inside the molecule. Given the presence of a low/high dielectric interface and due to the ionic screening, the net result is beneficial, at least for globular systems. Analytical solutions to more complex geometries are presently under study; however, they should not entail too heavy computation or the advantages of the technique will vanish.

**APPENDIX

NONLINEAR EQUATION SOLUTION**

Let us consider the following differential problem

\[
\frac{d^2g(\rho)}{d\rho^2} - 2 \frac{dg(\rho)}{d\rho} \left[ g(\rho) \right]^3 e^{-2\rho} \frac{2}{6\rho_1^2} = 0,
\]

\[
g(\rho_1) = g_1, \quad \lim_{\rho \to +\infty} g(\rho) = \text{const.}
\]

After the two substitutions \( z(\rho) = g(\rho)e^{-\rho} \) and \( p(z) = \frac{dz}{d\rho} \), the problem (20) becomes

\[
\frac{d^2z(\rho)}{d\rho^2} - \frac{dz(\rho)}{d\rho} \frac{1}{6\rho_1^2} [z(\rho)]^3 = 0,
\]

\[
z(\rho_1) = z_1 = \Phi_1 \rho_1, \quad \lim_{\rho \to +\infty} z(\rho) = 0,
\]

and

\[
p(z) \frac{dp(z)}{dz} - z - \frac{1}{6\rho_1^2} z^3 = 0,
\]

\[
p(z_1) = p_1.
\]

The boundary conditions on \( g(\rho) \) expressed in (20) require that \( z(\rho) \) tends to zero with exponential order for \( \rho \to \infty \). The assumptions \( \rho_1 > 0 \) and \( \Phi_1 \geq 0 \) can be made with no loss of generality.

Problem (22) leads to a variable separable differential equation for \( p(z) \) admitting the following family of solutions

\[
p(z) = \pm \sqrt{\frac{z^4 - z_1^4}{12\rho_1^2} + z^2 - z_1^2 + p_1^2}.
\]

The only solutions compatible with the conditions on \( z(\rho) \) correspond to the negative sign for \( p(z) \) and, therefore, for \( p_1 \). The implicit expression for \( z(\rho) \) thus becomes

\[
\rho - \rho_1 = - \int_{z_1}^z \frac{1}{\sqrt{(z^4 - z_1^4)/12\rho_1^2 + z^2 - z_1^2 + p_1^2}} dz.
\]
Now, the first term of the asymptotic expression of \( z(p) \) for \( p \to \infty \) is

\[
z(p) \approx \sqrt{\frac{p^4}{z^2} - \frac{z^4}{12p^2}}(\rho - \rho_1).
\]  

(25)

Therefore, the condition of exponential infinitesimal order for \( z \) requires that

\[
p^2 - z^2 - \frac{z^4}{12p^2} = 0,
\]

(26)

Under this condition, the implicit solution for \( z(p) \) becomes

\[
\rho - \rho_1 = \arctanh\left(\frac{1}{\sqrt{1 + z^2/12\rho_1^2}}\right) - \arctanh\left(\frac{1}{\sqrt{1 + \Phi_1^2/12}}\right).
\]

(27)

However, equation (27) can be made explicit

\[
z(p) = \frac{\rho_1 \Phi_1}{\sqrt{1 + (\Phi_1^2/12) \sinh(\rho - \rho_1) + \cosh(\rho - \rho_1)}}.
\]

(28)

The expressions for \( g(p) \) and \( \Phi(p) \) descend directly from the previous one, but what is of interest is the constant \( C_{nl} \) which is the limit of \( g(p) \) for \( p \to \infty \). One can verify that

\[
C_{nl} = \frac{2\rho_1 \Phi_1 e^{\rho_1}}{1 + \sqrt{1 + \Phi_1^2/12}}.
\]

(29)

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