

Leveraging the Potential of Machine-Learning Interatomic Potentials for QM/MM Simulations

Antonia S. Kuhn[#], Igor Gordiy[#], Felix Pultar[#], and Sereina Riniker^{*}

Abstract: Machine-learning interatomic potentials (MLIPs) are increasingly used to replace computationally expensive quantum-mechanical (QM) calculations to obtain the energies and forces in *ab initio* or multiscale molecular dynamics (MD) simulations. While the computational cost of MLIPs lies between that of QM methods and classical force fields (molecular mechanics, MM), their accuracy is close to that of the chosen reference method (e.g. density functional theory, DFT) with sufficient training data. However, for large biological systems in solution, MLIPs are still too costly to perform long MD simulations, where the full system (*i.e.* including the solvent) is described by the MLIP. Instead, multiscale approaches analogous to QM/MM (*i.e.* ML/MM) offer a viable compromise between computational effort and accessible system size and time scales. In this review, we provide a brief overview of recent advances and current developments in this field.

Keywords: Machine learning · Molecular dynamics · Multiscale simulations · Neural network potentials · QM/MM

1. Introduction

A complete quantum-mechanical (QM) description of chemical systems in the condensed phase offers excellent descriptive power, but remains computationally expensive.^[1–7] Half a century ago, Levitt, Karplus, and Warshel proposed the QM/molecular mechanics (QM/MM) scheme (Fig. 1b) to preserve quantum-chemical accuracy for the essential part of the system (the QM zone), while the surrounding environment (the MM zone, *e.g.* solvent molecules and/or distant protein residues in enzymatic processes) is treated with cheaper and less accurate classical force fields.^[8,9] Different QM/MM variations have emerged, which can be grouped into two schemes based on the approach to compute the total energy. The first is the subtractive scheme introduced by Morokuma and coworkers,^[10,11] in which the MM energy of the QM zone is subtracted from the sum of the MM energy of the entire system and the QM energy of the QM zone. In additive QM/MM schemes,^[12–14] the total energy is expressed as the sum of the MM contribution (E_{MM}), the QM contribution (E_{QM}), and their interaction term $E_{\text{QM/MM}}$ (see Eqn. 1). In this review, we focus exclusively on the more popular additive scheme, whereas detailed discussions of subtractive schemes can be found in Refs. [10, 11, and 15].

$$E_{\text{tot}} = E_{\text{QM}} + E_{\text{QM/MM}} + E_{\text{MM}} \quad (1)$$

The term $E_{\text{QM/MM}}$ is usually decomposed into van der Waals and electrostatic contributions. While the van der Waals interactions between QM and MM particles are described classically with a Lennard-Jones potential in the different QM/MM schemes, the treatment of the electrostatic interactions varies. In mechanical embedding, the electrostatic interactions are described classically by the Coulomb potential of localized QM zone charges and MM zone point charges. In electrostatic embedding, electrostatic interactions are treated at the QM level by including the MM point charges in the Hamiltonian of the QM zone. Accordingly, the MM zone can polarize the QM zone. The polarizable-embedding scheme goes one step further by treating mutual polarization be-

tween the two zones.^[12] One major disadvantage of all QM/MM schemes is the poor scaling of QM methods to larger systems. Therefore, in enzymatic reactions, typically only the reactant and the few surrounding protein side chains are described with QM accuracy, while the rest of the enzyme is part of the MM zone. This limitation leads to truncation artifacts since the QM and MM zones are separated along chemical bonds.^[16,17] Fortunately, these problems can now be overcome with ML/MM approaches (see below), in which the expensive QM Hamiltonian is replaced by a computationally much cheaper machine-learning interatomic potential (MLIP). Most recently, this setup has allowed for much larger QM (ML) zones, which included the entire protein or enzymes.^[18]

Modern MLIPs rely on neural networks to predict energies and forces with near-reference accuracy methods (*e.g.* density functional theory, DFT). Increasingly, MLIPs are trained on large datasets and are thus global (also called foundational) models that can be applied to a large part of the chemical space. Unless specified otherwise, the models we discuss below fall into this category. As the training data consists of QM calculations, MLIPs are typically able to describe bond breaking and forming during simulation, which is not possible with non-reactive classical force fields. Compared to these force fields, the computational demands of MLIPs for time and memory are significantly higher (but still substantially smaller than for DFT methods). Nevertheless, the cost of MLIPs can be prohibitive for the simulation of large solvated systems over longer time scales (Fig. 1c). Thus, multiscale ML/MM schemes have emerged that use MLIPs to model the ML (QM-like) region, while a classical force field describes the MM region, analogous to QM/MM approaches.^[18–34]

2. Components of MLIPs

2.1 Advances in Deep Learning

In 2007, Behler *et al.*^[35–37] proposed the high-dimensional neural network potential (HDNNP) as an ML framework in which each atomic contribution is computed by an element-specific feed-forward neural network and the total electronic energy of the molecule can be expressed as their sum,

$$E_{\text{tot}} = \sum_i^{N_{\text{atoms}}} E_i. \quad (2)$$

^{*}Correspondence: Prof. S. Riniker, E-mail: sriniker@ethz.ch
Department of Chemistry and Applied Biosciences, ETH Zürich,
Vladimir-Prelog-Weg 2, 8093 Zürich, Switzerland.

[#]These authors contributed equally.

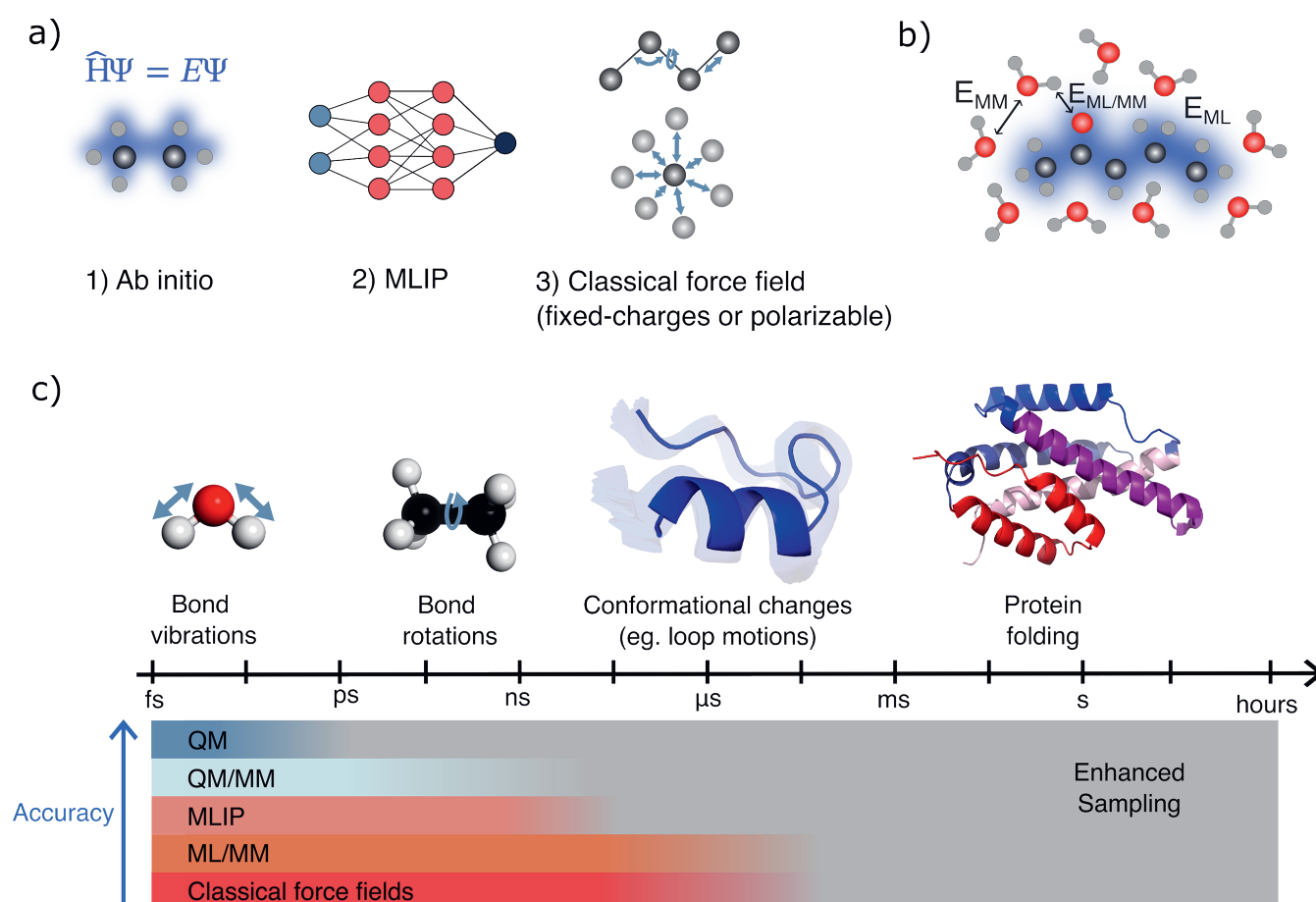


Fig. 1. Overview of single-scale methods for describing the Hamiltonian of a system (a) in comparison to multi-scale schemes (b) as well as accessible timescales with these methods (c). a) Choices for describing the Hamiltonian for single-scale simulations. b) Multi-scale scheme for ML/MM (analogous to QM/MM). c) Achievable timescales for QM (here for DFT), QM/MM, MLIP, ML/MM and classical force fields including an approximate range for observing molecular behavior of interest.

HDNNPs typically encode the environment of each atom with atomic environment vectors (AEVs), which scale quadratically with the number of element types.^[38] This can be problematic depending on the system of interest. One prominent example of the HDNNP architecture is the ANI-1 model^[38] published in 2017, with further developments to include more atom types, charges, open-shell and long-range treatment introduced with ANI-2x,^[39] and ANI-1xBB.^[40] Other model architectures that were used for MLIPs include kernel-based methods^[41] and Δ -learning schemes that learn the correction from a lower to a higher level of QM theory.^[22,23,42]

An alternative framework for MLIPs is the graph neural network (GNN), which operates on graph-structured data and produces predictions at the level of nodes, edges, or entire graphs. Graphs intuitively represent molecules, with nodes as atoms and edges as connections between them. In GNN-based MLIPs, edges are set not (only) between atoms sharing a covalent bond, but rather link nodes/atoms that are within a Euclidean distance cut-off of each other, allowing for a more general framework for 3D structures.^[43–46] As shown in Fig. 2, the graph is embedded with learnable layers to generate features, beginning, for example, with one-hot encoding of atom types. Other approaches utilize engineered features such as the atomic cluster expansion (ACE)^[47] framework, which has been utilized in MLIPs such as SNAP^[48] and Allegro.^[49] In all cases, the constructed features are mapped by a learnable function to construct a message that will be sent to all connected nodes (neighbors). The messages from the different edges are aggregated to iteratively update the node feature for each layer of the model. An important feature is the equivariance

to node permutations, meaning that the order of nodes processed by the GNN is respected in the output. The multi-ACE^[50] framework uses ACE to aggregate the messages at each step, and one of the most well-known models, MACE^[51] published in 2022, extended this architecture to high-order message passing, which leads to increased training efficiency and accuracy with fewer model layers. Finally, a learnable readout function predicts desired properties such as total energy and forces. The node-wise energies are summed to obtain the total electronic energy of a molecule, which is computed with reference QM methods and used to train the model.^[27,52–56]

Geometric deep learning systematically incorporates symmetry into neural-network architectures, resulting in models that are both more data-efficient and faster to train by inherently ensuring invariance (or equivariance) to rotations and translations without data augmentation. A pivotal example is the SchNet^[57] model from 2017, which used continuous-filter convolutions to be invariant to rotations and translations. Directional quantities, such as forces or multipole moments, must transform according to representations of the 3D rotation group $SO(3)$, *i.e.* satisfy rotational equivariance.^[58–60] In practice, $SO(3)$ -equivariant MLIPs construct features in vector spaces corresponding to the irreducible representations of the $SO(3)$ group, which can be expressed either in the spherical-harmonic basis used, for example, in Tensor Field Networks^[59] and NequIP,^[61] or equivalently as Cartesian symmetric traceless tensors.^[18,27,34,62–64] Regardless of the representation space of features, equivariant GNNs have become the gold standard for MLIPs and are now used for models like AMP,^[18,27,34] MACE,^[65,66] among many others. Another popular

design choice is directional message passing with angular information that was first included together with changes to the feature vector in DimeNet^[67,68] from 2020 which increased performance and has seen further developments.^[69,70]

There have been two major development directions of MLIPs over the last few years. The first focuses on improving computational efficiency through more lightweight models, such as GNNs with simplified message-passing schemes^[71] or the ANI framework, exemplified by the deep potential network,^[72] which benefits from an atom-wise model architecture that enhances computational speed and facilitates parallelization.^[32] The second trend involves the development of more complex GNN architectures that incorporate higher-order geometric information resulting in larger models (see Table 1 for a comparison of model size). A prominent example is the MACE model, which offers specialized versions for different applications such as MACE-OFF23 for small organic molecules,^[66] the MACE-MP family for bulky materials,^[73] and finally MACE-OMol-0 version^[51] trained on the largest dataset to date, OMol25.^[74] Together with OMol25, the universal models for atoms (UMAs)^[75] were published. Some models extend this approach further by including modules to predict additional physical properties beyond energies and forces, such as multipole moments.^[18] Although these models focus on accuracy, they are complex and have many parameters, making them computationally expensive and limiting their applications. In addition, the majority of the models have not been implemented with multi-graphics processing unit (GPU) support, and thus the application scope is limited by the accessible GPU memory.

2.2 Treating Physics

A quantum-chemical system is uniquely defined by the atom types, coordinates, charge, and spin multiplicity, where the latter two are not always treated by MLIPs. SpookyNet^[77] uses local and nonlocal interaction blocks that utilize mechanisms similar to attention^[78,79] to distribute the total charge and the number of unpaired electrons over the system, analogous to QM calculations. Another example is AIMNet2-NSE,^[80] which uses neural spin-charge equilibration to predict the spin-charges on every atom that are later incorporated in atomic feature vectors.

Dispersion interactions are poorly described by non-double-hybrid density functionals, motivating the routine use of *ad hoc* corrections to account for them. Widely adopted approaches include semi-classical DFT-D corrections by Grimme and coworkers^[81–86] and density-based methods.^[87–89] Since MLIPs are typically trained on dispersion-corrected reference data, some architectures incorporate explicit dispersion models. Notable examples are SpookyNet,^[77] which includes the D4 correction, AIMNet2 employing D3, and SO3LR, which relies on pairwise interatomic potentials derived from quantum Drude oscillators.^[90,91]

Table 1: Overview of the number of parameters for selected MLIPs (S: small, M: medium and L: large if available). For UMA, we report the active and total number of parameters.

Model	# params
AMPv3-EE-BMS25 ^[18]	412K
NepoIP ^[76]	426 K
MACE-OFF23-S ^[66]	694K
MACE-OFF23-M ^[66]	1.4M
MACE-OFF23-L ^[66]	4.7M
UMA-S ^[75]	6M (150M)
UMA-M ^[75]	50M (1.4B)

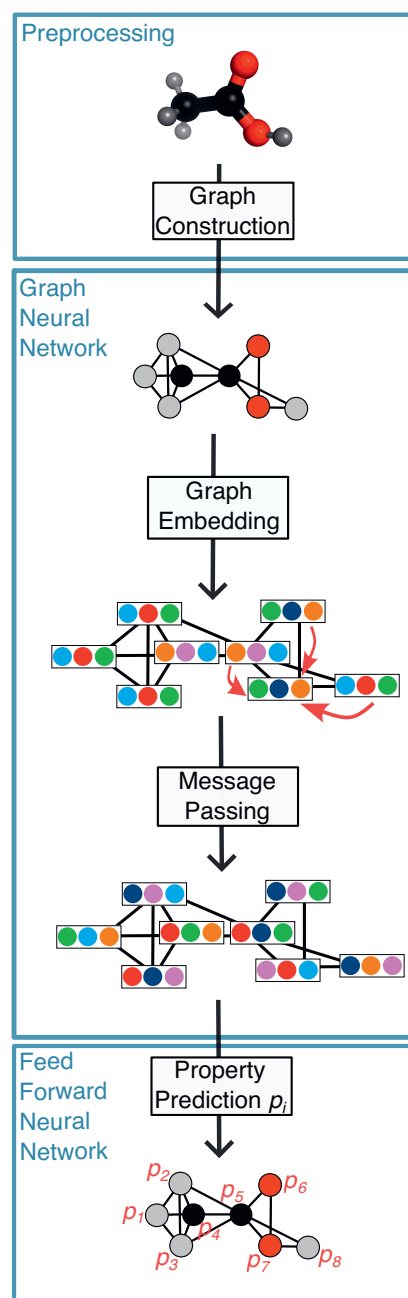


Fig. 2. Depiction of GNNs used for MLIPs with graph construction based on a 3D distance cutoff, embedding and message passing, and the final readout layer to predict atomic energies.

For improved regularization, the AMP model additionally predicts C^6 coefficients that are incorporated in the training loss.^[18] Other models such as FeNNix-Bio1^[92] are trained on dispersion-corrected data without an explicit functional form, instead learning the distance dependence *via* message-passing features based on dispersion-derived radial bases. The latter approach is closely related to the physics-inspired equivariant descriptors of Ceriotti and coworkers.^[93] Finally, some models trained on dispersion-corrected DFT data do not incorporate any explicit inductive bias for dispersion, *e.g.* MACE-OFF23.^[66]

Another challenge is the lack of description of long-range interactions in many MLIPs, which has been shown to be a limitation for the simulation of large systems with heterogeneous charge distributions.^[94–98] Some approaches predict properties in addition to energies to compute these interactions, such as in AIMNet2,^[99] PhysNet,^[100] So3krates,^[101] FeNNix,^[102] or BAMBOO.^[103] Another recent framework works as a univer-

sal correction to mimic long-range interactions for short-range MLIPs.^[104]

3. ML/MM Schemes

Since most MLIPs have been trained on molecules in vacuum, they are only compatible with a mechanical-embedding scheme in the ML/MM approach as the respective model cannot handle the surrounding environment.^[19,20,32,105] However, this representation neglects the polarization of the ML zone by the MM zone and is thus rather limited. To circumvent this issue and enable the use of the more accurate electrostatic-embedding scheme, two approaches have been proposed: (1) employ a scheme that adapts the electrostatic embedding to be compatible with any MLIP,^[29] and (2) train the MLIP directly within the electrostatic-embedding framework.^[18,23–25,27,34,76] The latter is more involved since the architecture needs to include interactions of the MM atoms with the ML zone and the ML atoms need to feel the electric field from a proxy of the MM environment in the training data.

3.1 ML/MM with Electrostatic Embedding

An early approach for ML/MM with electrostatic embedding was performed with the HDNNP architecture by adapting it to include polarization of the ML zone by the MM zone.^[23] We advanced this approach further, first with invariant GNNs^[106] and later with the $SO(3)$ -equivariant GNN AMP,^[27,34] where the message-passing steps are based on Cartesian symmetric traceless tensors and their ‘interactions’ are inspired by physics of multipole-multipole interactions.^[107] These features are especially valuable for the ML/MM simulations of condensed-phase systems as an electrostatic-embedding scheme can be employed at relatively low cost. During training, the loss is also computed for the molecular multipole moments against the quantum reference to improve the description.^[27,34] Note that the AMP models presented in these studies were system-specific. Recently, we extended the approach to a foundational MLIP designed for ML/MM simulation and trained on the multiscale BMS25 dataset,^[108] resulting in the AMPv3-EE-BMS25/MM model.^[118] This model is capable of simulating proteins for extended timescales (up to 100 ns), predicting melting curves of intrinsically disordered proteins, and qualitatively modeling enzymatic reactions.^[118]

In other recent work with NepoIP/MM,^[76] the NequIP architecture was adapted to learn the polarization effects from the MM zone on the ML zone. This model was trained on peptides in solution and was able to be used for stable MD simulations. Another recent publication uses a system-specific MLIP in an electrostatic embedding scheme with a polarizable force field to study free-energy profiles of charged systems.^[109]

3.2 Compatibility Between MLIPs and Classical Force Fields

In QM/MM calculations, achieving compatibility between classical force-field parameters and the QM Hamiltonian remains a well-recognized limitation,^[110–116] which likewise affects ML/MM frameworks.^[18,109,117] This limitation originates from the independent parametrization of force fields and QM methods, which does not guarantee automatic compatibility when combined in QM/MM setups. In particular, nonbonded force-field terms have typically been optimized to reproduce macroscopic thermodynamic properties,^[118] such as liquid density and enthalpy of vaporization, rather than microscopic QM-consistent quantities like energies or geometries.^[119,120] As a result, force-field parameters act as effective quantities compensating for missing interaction terms due to the restricted functional form. A representative example is TIP3P water,^[121,122] whose overpolarized partial charges compensate for neglected polarization effects.^[123] These overpolarized MM charges can, in turn, induce excessive polarization of the QM electron density, leading to unphysical charge ‘spill-out’ onto MM

atoms due to the absence of Pauli repulsion.^[124–127] Accordingly, ML-MM interactions may require *ad hoc* calibration, as in the AMPv3-EE-BMS25 model,^[118] or more general strategies for generating reference QM/MM data that partially reparametrize force fields to improve compatibility with a chosen density functional and basis set combination.^[112,116,128–131]

4. Datasets and Training Strategies

4.1 Datasets for Foundational Models

In recent years, generalizable foundational models have been developed for a variety of chemical systems. Their accuracy is primarily limited by the underlying level of QM theory, which must be adequate to describe the problem at hand. Numerous datasets exist,^[108,132–136] with OMol25^[74] being the largest one to date with 140 million data points for diverse types of compounds and clusters of molecules in the gas phase. For ML/MM approaches with electrostatic embedding, we recently introduced the BMS25 dataset,^[108] which provides 1.5 million QM/MM reference calculations of molecules in water. In addition to covering a diverse chemical space, training data should contain conformations beyond the low-energy regime, as models trained only on these can be unstable during simulations.^[133,135] In all cases, a thorough validation not just on QM energies and forces but also on simulation stability is essential to evaluate the predictive power.^[137] Additionally, comparison to experimental observables such as hydration free energies, bulk properties, and structural information of proteins is vital to determine viable applications of any MLIP.^[18,66,91,92,99]

4.2 Potential Pitfalls in Training MLIPs

MLIPs face known issues with training neural networks such as slow convergence and vanishing or exploding gradients,^[138–140] which can be mitigated with gradient clipping,^[141,142] dropout,^[143–145] batch^[146–149] and layer^[150,151] normalization. Another potential pitfall is using force predictions directly as the output of a GNN, which does not guarantee conservative forces.^[152] To ensure that the predicted forces are conservative, they should be computed as the negative gradient of the total potential energy predicted by the MLIP. This is typically straightforward using automatic differentiation, since MLIPs are designed to be continuously differentiable. Training solely on forces has been shown to provide similar performance to training on forces and energies simultaneously.^[153] Computing the gradient loss requires only one additional backward pass^[154] leading to the negligible drop in the training speed.

5. Conclusions and Outlook

Thanks to the rise of machine learning in recent years, much progress has been made in the field of MLIPs. Increasing computational resources have made the generation of large training sets possible, such as the OMol25 dataset, and thus the development of foundational MLIPs has become feasible. In addition, many attempts to explicitly include physics and long-range interactions have further advanced the field. However, there is a trade-off between the complexity of the model and the computational cost such that most models focus on one of the two aspects.

As MLIPs are computationally more expensive than classical force fields, multiscale ML/MM approaches provide a powerful strategy for the simulation of larger systems in the condensed phase – ideally with an electrostatic embedding scheme to include the polarization of the ML zone by the MM environment. Due to the reduced computational cost of ML/MM compared to QM/MM simulations, a much larger QM (or ML) zone can be treated at quantum accuracy (*e.g.* the entire enzyme in the study of enzymatic reactions), which removes the need to handle covalent

bonds between QM (ML) and MM particles and thus avoids the associated artifacts.

In the future, we expect to see improvements in the accuracy and general applicability of MLIPs in ML/MM simulations through advances in the training sets, architectural developments (e.g. physics-inspired or physics-augmented models, reduced complexity for increased speed), and/or going beyond electrostatic embedding. Polarizable-embedding schemes using polarizable force fields for the MM zone are known for QM/MM simulations, but to the best of our knowledge, no published ML/MM model has implemented for this scheme to-date. Overall, we anticipate that these developments will make ML/MM simulations of large systems and reactions in solution more accessible, providing a promising direction for the future.

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Conflict of Interest

There are no conflicts of interest to declare.

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