OPEN CHALLENGES TO UNLOCK DEEP EUTECTIC SOLVENT DISCOVERY

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ABSTRACT

Deep eutectic solvents (DESs) have attracted considerable attention as tunable, often low-toxicity alternatives to conventional organic solvents with a wide range of applications in synthetic chemistry, biomass processing, CO_2 capture, drug delivery, and electrochemistry. They can be described as multicomponent mixtures with a melting point significantly lower than that of the neat components due to complex hydrogen-bond network. The discovery of new DESs remains mostly empirical and is limited by the infinite number of combinations of suitable components. Existing computational approaches, from thermodynamic models and molecular dynamics (MD) to direct machine learning prediction of macroscopic properties, suffer from limited transferability, low accuracy of transport properties, and lack of mechanistic interpretability. Machine-learned interatomic potentials (MLIPs), which enable MD simulations at near *ab initio* accuracy and low computational cost, represent a largely untapped approach for DESs. Only a few dedicated studies have been published to date. We outline key scientific and methodological challenges, including long-range electrostatics, a complex hydrogen-bond network, slow convergence of transport properties, and chemical-space transferability, and discuss research directions to develop MLIPs that can accelerate the rational design of next-generation green solvents.

1 INTRODUCTION

Deep eutectic solvents (DESs) are binary or multicomponent mixtures of a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) exhibiting a melting point significantly lower than those of the neat components (Abbott et al., 2003; Hansen et al., 2021). This melting point depression is attributed to the formation of multiple hydrogen bonds between the DES components, the mechanism of which remains a subject of ongoing investigation (Abranches & Coutinho, 2023).

DESs often exhibit low vapor pressure, biodegradability, high selectivity, dissolving ability, and straightforward preparation from inexpensive precursors. Reported applications include CO_2 absorption with capacities up to $1.36\,\mathrm{mol\,CO_2/mol\,DES}$ (Zubeir et al., 2018), recovery of Li, Mn, Ni, and Co from spent lithium-ion batteries with extraction efficiencies greater than 96% (Hansen et al., 2021), and pretreatment of lignocellulosic feedstock to yield greater than 95% glucose by enzymatic digestion (Smith et al., 2014).

Despite this promise, the development of new DESs relies largely on experimental trial and error (Bonab et al., 2021; Song et al., 2021), which is highly limited by the infinite number of combinations of DES components and the wide ranges of pressures and temperatures that require iterative testing. Computational approaches that achieve sufficient accuracy while maintaining reasonable computational cost are therefore highly desirable.

2 CURRENT COMPUTATIONAL APPROACHES

Considerable effort has been made to develop computational approaches for predicting DES physicochemical properties. The modeling of phase diagrams, prediction of eutectic points, and solubility properties of DESs are particularly active areas of research, as these characteristics define the limits of DES applicability.

The state-of-the-art methodologies for modeling phase equilibria in DES are based on thermodynamic theories of solutions, realized in approaches such as COSMO-type models developed by Klamt et al. (Klamt, 1995). These models combine quantum-chemical calculations, electrostatic surface interactions, and statistical-thermodynamic treatments and are applicable to both individual compounds and liquid mixtures. COSMO-based models have been applied to calculate the relative solubility of active biological compounds in DESs (Palmelund et al., 2019) and binary DES phase diagrams (Song et al., 2021; Abranches et al., 2019; Mahanta et al., 2020) with reasonable success. However, the model insufficiently describes long-range electrostatic interactions and requires empirical corrections to hydrogen bond parameters, which are essential interactions present in DESs (Klamt et al., 2010; Silva et al., 2018; Lavrinenko et al., 2023; Abranches & Coutinho, 2023).

Alongside thermodynamic modeling, a growing approach is supervised machine learning (ML) for predicting macroscopic DES properties from quantum-chemical and molecular descriptors. Recent studies have employed random forests, support vector regression, gradient boosting, and neural networks to predict DES density ($R^2 \approx 0.89$), viscosity ($R^2 \approx 0.64$), melting point ($R^2 \approx 0.76$), and conductivity (Odegova et al., 2024; Mohan et al., 2024). COSMO-RS σ-profile features have been integrated with ML algorithms for surface tension, conductivity ($R^2 \approx 0.95$), melting points ($R^2 \approx 0.80$), and solid–liquid equilibrium diagram prediction (Lemaoui et al., 2020; Lavrinenko et al., 2023). Transformer-based ChemBERTa embeddings have also been applied to density and melting point estimation (Wu et al., 2025). Despite offering rapid screening, direct ML approaches are limited by low transferability, a lack of mechanistic insight into hydrogen-bond formation, and scarce training datasets containing only 1 000–2 000 experimental data points.

While these ML property prediction methods offer rapid screening, atomistic MD simulations provide physical interpretation and calculation of dynamic properties absent from descriptor-based ML. Polarizable force fields (OPLS-DES, CL&Pol) (Doherty & Acevedo, 2018; Goloviznina et al., 2022) provide structural insights and enable calculation of transport properties but face accuracy and transferability limitations (Tolmachev et al., 2022; Jeong et al., 2021; Velez & Acevedo, 2022). Fixed-charge models cannot capture the dynamic charge redistribution within hydrogen bond networks and tend to overestimate transport properties (Velez & Acevedo, 2022). Empirical charge scaling is commonly applied to improve modelling accuracy, but this approach lacks physical interpretation and must be adjusted for each system.

Machine-learned interatomic potentials (MLIPs) address the accuracy–cost trade-off by learning the potential energy surface from reference quantum-chemical calculations and reproducing energies and forces at near *ab initio* accuracy while requiring orders-of-magnitude lower computational cost (Batzner et al., 2022; Batatia et al., 2022). This enables nanosecond-scale simulations of systems containing thousands of atoms, providing the required timescales and system sizes to converge DES transport properties. Rapid development in the field has produced several MLIP architectures, including equivariant message-passing networks (NequIP, MACE, Allegro), deep potential methods (DeePMD), and universal foundation models (MACE-MP-0, CHGNet, M3GNet) offering the possibility of transfer learning to new chemical systems with reduced training data requirements (Batzner et al., 2022; Batatia et al., 2022; 2025; Deng et al., 2023; Chen & Ong, 2022). Application of MLIPs has been demonstrated for systems with challenging ionic interactions (e.g., ionic liquids) (Montes-Campos et al., 2022) and for molecular liquid mixtures (Magdău et al., 2023). Yet application to DES remains sparse. To our knowledge, only a few published studies have reported the development of a dedicated MLIP for a DES system. Shayestehpour and Zahn (Shayestehpour & Zahn, 2023) trained a DeePMD potential for reline using iterative active learning, achieving energy RMSEs of 1.0-5.5 meV/atom and force RMSEs of 50 meV/Å on held-out configurations. The resulting model enabled nanosecond-scale MD trajectories for systems of 2500 atoms, reproducing experimental liquid densities within 3-3.5% and radial distribution functions in excellent agreement with reference *ab initio* MD. Self-diffusion coefficients were underestimated by a factor of 3–4 relative to experiment, which the authors attributed to limitations of the reference DFT method (BLYP-D3/TZVP) rather than the MLIP architecture, suggesting that training data quality is currently the primary bottleneck. Nevertheless, recent studies on ionic liquids and electrolyte mixtures showed that MLIP architectures can also significantly affect transport property accuracy (Niblett et al., 2025; Park et al., 2025), indicating that both training data quality and model architecture require careful consideration in future DES

MLIP development. A follow-up study extended this approach to LiTFSI-based DES electrolytes using an Allegro equivariant neural network architecture (Shayestehpour & Zahn, 2024). These few studies, covering a handful of DES compositions, underscore the scarcity of published MLIPs for DESs and define the open challenge addressed here.

3 OPEN CHALLENGES AND RESEARCH DIRECTIONS

MLIPs for DESs are an under-developed yet high-leverage approach to accelerating materials discovery and sustainable solvent design. Unlike descriptor-based ML, MLIPs provide atomistic trajectories to directly extract structure-property relationships, investigate mechanisms of hydrogen bond formation and melting temperature depression, and calculate transport and thermodynamic properties such as density, viscosity, ionic diffusivity, and gas solubility. Providing the physical understanding needed to guide experimental validation, this information is essential for rational solvent design but is inaccessible to current screening approaches.

The development of accurate and transferable MLIPs for DES requires addressing several interconnected challenges (Figure 1).

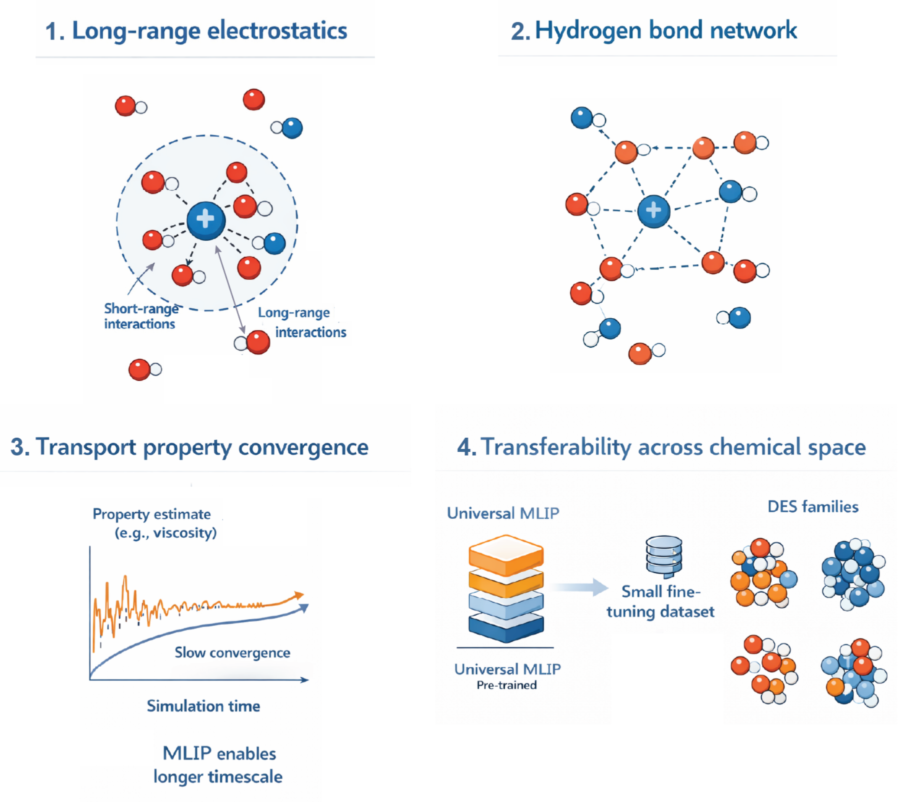

Figure 1: Open challenges in MLIP development for DESs.

Long-range electrostatic interactions. DESs components often contain charged species that exhibit long-range Coulomb interactions. Message-passing MLIP architectures often underestimate the interaction energies by considering only short-range electrostatic contributions within 5–6 Å cutoff radii and result in incorrect liquid densities. This problem is especially relevant for DESs because of their mixed ionic-molecular nature, which distinguishes them from similar liquid mixtures where these challenges have been more extensively studied. Unlike ionic liquids, DESs contain neutral organic molecules that typically function as hydrogen bond donors, creating a hybrid environment where both long-range Coulomb interactions and short-range directional hydrogen bonding must be captured simultaneously. Unlike dilute electrolyte solutions, DESs are concentrated stoichiometric mixtures where the distinction between solute and solvent breaks down. Unlike neutral molecular liquid mixtures, DESs involve ionic species and significant charge transfer between components, preventing the use of the fixed-charge approximations that perform adequately for organic solvent mixtures.

Several methods have been proposed to incorporate long-range electrostatic interactions and charge transfer into MLIPs, including fourth-generation high-dimensional neural network potentials (4G-HDNNP) with environment-dependent electronegativities to determine the global charge distribution (Ko et al., 2021), latent Ewald summation method, which learns long-range interactions from local atomic features without requiring explicit atomic charges (King et al., 2025), and equivariant architectures that incorporate long-range Coulomb interactions using predicted electronegativities (Maruf et al., 2025). However, none of these approaches have been applied to DES, where the combination of diverse chemistries, variable stoichiometry, and complex hydrogen and ionic bonding presents both a unique test case and an opportunity for methodological development.

Hydrogen bond network. The formation of eutectic mixtures and the significant melting point depression that defines DES arise from multiple hydrogen bonds upon mixing. Different mechanisms of hydrogen bond network formation have been observed in DESs, depending sensitively on composition and temperature (Hansen et al., 2021; Vázquez-González et al., 2020; Stefanovic et al., 2017; Perkins et al., 2014). For example, in choline chloride–based systems, the chloride anion acts as a central HBA interacting with the donor network, whereas in hydrophobic DES based on terpenes the network is governed by weaker, non-ionic interactions with fundamentally different nature. An MLIP must accurately reproduce inter- and intra-component hydrogen-bond interactions, their spatial and temporal correlations, and their response to changes in molar ratio and composition. This places stringent demands on the reference DFT method requiring dispersion-corrected hybrid functionals (ωB97X-D3BJ, revPBE0-D3). However, their cost limits the size of the training set. A collective effort to curate a standardized openly accessible DFT dataset across the major DES families would facilitate the development of general MLIPs for these systems.

Transport property convergence. The transport properties of greatest practical interest, such as viscosity, ionic conductivity, and self-diffusion coefficients, converge slowly due to sluggish dynamics of DES under ambient conditions. Reliable viscosity estimation requires trajectory lengths of several nanoseconds, which is far beyond what *ab initio* MD can provide. MLIPs enable these timescales but require carefully curated training data that include rare transition events and compositional variability (e.g., water content and changes in molar ratios). The water content has been shown to have a significant effect on the transport properties of DES. For example, viscosity studies reported water content to enable accurate prediction (Shi et al., 2022). Without such context, ML models can learn dataset-specific artifacts rather than physical trends. Active learning with ensemble uncertainty, as implemented in DP-GEN (Shayestehpour & Zahn, 2023), provides a systematic approach but has been applied to only a few DES systems to date. Notably, no established benchmark currently exists for evaluating MLIP-predicted transport properties of DES against experiment. Such benchmarks have driven improvements in development of classical DES force fields (Velez & Acevedo, 2022).

Transferability across the DES chemical space. Developing a separate MLIP for each DES mixture is timely and computationally expensive. The complexity is increased by the fact that DES families involve qualitatively different interactions. They are strong electrostatic interactions in metal salt systems (types I, II, IV), asymmetric hydrogen bonds in mixtures of organic salts and HBD (type III), and weak, dispersion-driven interactions in hydrophobic DESs (type V). Universal MLIPs such as MACE-MP-0 and MACE-OFF23 (Batatia et al., 2025; Kovács et al., 2025) provide starting points for DES MLIP development, but their training data, dominated by inorganic crystals and small organic molecules, respectively, do not correctly represent the liquid phase of DES with ionic and hydrogen bond interactions. Fine-tuning via transfer learning by freezing core layers and retraining final interaction layers can achieve near-DFT accuracy with 10-20% of new training data (Batatia et al., 2025). This approach is yet to be evaluated for DES.

While the four challenges identified above are interconnected, we recommend prioritizing training data curation as the first focus, specifically the sampling of rare configurations and the use of hybrid-functional DFT reference calculations. This direction simultaneously addresses the challenges of hydrogen bond network description and transport property accuracy. Existing MLIP studies for reline achieved accurate prediction of liquid structure and density while underestimating self-diffusion coefficients, a discrepancy the authors attributed to limitations of the DFT reference data (Shayestehpour & Zahn, 2023). However, these studies cover only a few of Type III DES compositions. Therefore, the subsequent priority should be transferability across different HBA:HBD ratios, DES types, and water content. While explicit treatment of long-range electrostatic interactions was not required for adequate MLIP performance in the studied bulk DESs, recent investigations have demonstrated improvements in transport and structural property accuracy upon inclusion of long-range electrostatics (Gao et al., 2025; Kim & Cheng, 2026), suggesting this as a subsequent focus. Ionic DES or interfacial systems involving significant charge transfer, such as DES interactions with electrode surfaces, dissolved species, or extraction substrates, will likely require explicit long-range electrostatic treatment.

4 CONCLUSION

Deep eutectic solvents (DESs) combine significant application potential across sustainable chemistry with a vast, tunable chemical space that remains largely unexplored by computational methods. The rational DES design, which is still largely empirical, requires prior knowledge of structure, thermodynamics, and transport properties. However, existing tools provide only part of this information, often lack the physical interpretation required for mechanistic understanding, and demand high computational cost. Machine-learned interatomic potential (MLIP) is a promising approach to address this bottleneck. The existing MLIP studies on reline and LiTFSI-based DESs have demonstrated the ability to enable molecular dynamics at near–first-principles accuracy on the time and length scales needed for structure–property prediction and screening. Extending this capability beyond individual compositions to the broader DES chemical space would enable rational design of new materials.

The challenges outlined in this work are specific to the chemical nature of DESs. The mixture of ionic and molecular species requires an accurate description of long-range electrostatic interactions and charge transfer. The complex and diverse hydrogen-bond networks across DES families impose stringent demands on the quality of the DFT training dataset. Reliable transport-property prediction requires long timescales and carefully curated training data that include rare configurations and transition events. The vast chemical space requires broad transferability to avoid impractical system-specific model development. These challenges are interconnected and should be addressed together in the context of DES for reliable MLIP development. As a first priority, we recommend focusing on curation of the training data and the use of hybrid-functional DFT reference calculations to improve the hydrogen bond network description and transport property accuracy. The next priority should be extending MLIP applicability across broader DES types and compositions to establish transferability beyond the few Type III systems studied to date. Finally, explicit treatment of long-range electrostatic contributions will improve charge transfer description for investigations of ionic DES and for research on interfacial phenomena involving electrode surfaces, dissolved substrates, or extraction processes.

Realizing this potential requires efforts in three directions: (i) curation of standardized, openly accessible DFT benchmark datasets at hybrid-functional accuracy across representative DES families, (ii) evaluation of MLIP architectures with transport properties as the primary validation metric, and (iii) development of transfer-learning workflows from universal foundation models to enable high-throughput compositional screening. Unlike established MLIP benchmarks such as Rowan (Scientific) or Matbench (Dunn et al., 2020), which primarily evaluate models against energy and force reference data or static DFT-calculated properties, a DES benchmark requires trajectory-based assessment, since transport properties are the values of practical interest where current methods perform worst. Existing MLIPs reproduce liquid structure while underestimating transport properties, making viscosity, diffusivity, and ionic conductivity the essential validation metrics against experimental data or production AIMD trajectories. Dataset requirements include dispersion-corrected hybrid-functional DFT reference calculations, compositional diversity across HBA:HBD molar ratios and water content, elevated-temperature sampling via active learning to access rare hydrogen-bonding configurations and transition events, and coverage of DES types I–V for transferability assessment. Establishing such workflows would shift DES design from empirical trial and error to physics-guided discovery of new materials and development of sustainable chemical processes.

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