# Automated design of Li<sup>+</sup>-conducting polymer by quantum-inspired annealing

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#### Abstract

Automated molecule design by computers has been an essential topic in materials informatics. Still, generating practical structures is not easy because of the difficulty in treating material stability, synthetic difficulty, mechanical properties, and other miscellaneous parameters, often leading to the generation of junk molecules. We tackle the problem by introducing supervised/unsupervised machine learning and quantum-inspired annealing. Our autonomous molecular design system can help experimental researchers discover practical materials more efficiently. Like the human design process, new molecules are explored based on knowledge of existing compounds. A new solid-state polymer electrolyte for lithium-ion batteries is designed and synthesized, giving a promising room temperature conductivity of 10<sup>-5</sup> S/cm with reasonable thermal, chemical, and mechanical properties.

# 1. Introduction

The increasing demands of sustainable technology require the faster, more reliable design of functional materials, which are essential components of rechargeable batteries, solar cells, bioplastics, and drugs, and are used for other energy-, environment-, and health-related applications.<sup>[1, 2]</sup> Because there are massive chemical structures,<sup>3</sup> extracting candidate molecules from the search space is essential (Figure 1a).<sup>[1-3]</sup>

Recently, machine learning has been used to accelerate *in silico* material screening.<sup>[1, 2]</sup> The key idea of mimicking the structure-property relationship has enabled the rapid screening of candidate structures.<sup>[1, 2, 4]</sup> Recent deep learning models, such as deep reinforcement learning (DRL)<sup>[5, 6]</sup> and variational autoencoders (VAEs),<sup>[7, 8]</sup> help connect molecular geometry and numerical information (i.e., latent space) semi-reversibly, contributing to the automated design of materials with desirable properties.<sup>[9]</sup> The method is not just conceptual; it is also helping researchers develop high-conductivity electrolytes,<sup>[10]</sup> light emitters,<sup>[11]</sup> photovoltaics,<sup>[12]</sup> and other functional materials experimentally.<sup>[2, 13]</sup>

A major drawback of computational molecular screening has been the insufficient filterability of candidate materials. Usually, molecules are designed *de novo* only according to one or a small number of specific material parameters because of the high costs of preparing machine learning models and corresponding databases (Table S1).<sup>[1]</sup> However, materials must satisfy the diverse property standards for practical examinations. For instance, a solid-state polymer electrode should maintain sufficient ionic conductivity, electrochemical stability (e.g., potential window), thermal robustness, mechanical strength, crystallinity, and solubility in specific solvents during film preparation.<sup>[10, 14]</sup>

Methodically evaluating each factor by machine learning is usually infeasible because of the high cost of database preparation (i.e., one chemical experiment takes more than one day typically).<sup>[1, 2, 10]</sup> Apart from machine learning, there are few filtering methods. Synthetic accessibility score is a standard criterion for evaluating the synthetic difficulty of molecules.<sup>[15]</sup> However, the algorithm was designed only to roughly screen for drug-like compounds, meaning that the filtering is not sufficient for most other applications. Computational material simulations can predict various properties, but the accuracy is too low, especially for complex material systems (e.g., device response and polymer properties).<sup>[16]</sup> A breakthrough is needed in automated molecule design to filter out impractical materials.



Figure 1 Concept for our supervised/unsupervised machine learning system for automated molecule design. **a** Searching for candidate structures among over  $10^{60}$  structures. Candidates must be screened by a specific target property (e.g., conductivity) and other parameters, such as stability, preparation cost, and mechanical strength. **b** Designing molecules *de novo* by supervised/unsupervised learning, quantum-inspired annealing, and deep reinforcement learning (DRL). Chemical structures were converted into binaries by molecular fingerprint (MFP). Structures with a higher target parameter were explored based on the regression potential,  $E_{reg}$ , and user preference features,  $E_{RBM}$ , constructed by a restricted Boltzmann machine.

We developed a heuristic material exploration system of supervised/unsupervised learning and quantum-inspired annealing, which can suggest experimentally valid molecular structures (Figure 1b). In a similar way to ordinary materials informatics, a regression model predicting a specific parameter from structural information was constructed and yielded a search potential for a higher target parameter,  $E_{\rm reg}$  (steps 1–3 in Figure 1b). Simultaneously, a restricted Boltzmann machine (RBM)<sup>[17]</sup> was trained to build a potential,  $E_{\rm RBM}$ , so that the energy of the user-inputted structures decreased (steps 1'–3').

Crucially, users caninput existing compounds that had already been evaluated for the intended application, and thus the molecules usually satisfy applicable criteria. Structures designed *de novo* were examined with a linear sum of the potentials,  $E = c(rE_{reg} + 1/r \cdot E_{RBM})$  ( $c, r \in \mathbb{R}$ ). Chemicals with a higher target parameter and similar user preference structures maintained lower energy in the potential. A unique architecture, our digital annealing unit (DAU), was essential in discovering the solutions from the search space  $(2^n \text{ combinations}, n \ge 2048$ , steps 4–7).

A new lithium-ion-conducting polymer with a unique design and promising performance was experimentally examined to confirm our concept. The system paves the way for automated molecular design, which is expected to promote the more frequent finding of new materials.

# 2. Automated molecule generation system

## 2.1 Semi-reversible conversion of chemical structures to numbers

This section describes the idea of automated molecular design using quantum-inspired annealing. First, molecular information must be converted into numbers for machine learning (Figure 1b).<sup>[1]</sup> The 512-dimensional Avalon molecular fingerprint (MFP),<sup>[18]</sup> which is a traditional chemoinformatics algorithm, was used to express molecules with binary numbers (Figure 2a). This MFP was selected because of its compatibility with RBM and quantum-inspired annealing, discussed later.

Because MFPs indicate the specific fragments in a molecule, inverse conversion to molecular structures is not strictly accessible.<sup>[18]</sup> However, a carefully pretrained DRL model could reconstruct molecules from MFP with reasonable accuracy (Figure 2b, c, Supporting Data: Sheet 1).<sup>[5, 6]</sup> We rebuilt 150 random molecules with a DRL model<sup>[5]</sup> and calculated the Tanimoto similarity to check the reconstruction precision (Figure 2b). The average score was 93%, indicating that the inverse conversion was roughly accessible. This allowed the generation of molecules from ideal binaries sampled by quantum-inspired annealing (steps 6 and 7 in Figure 1b).



**Figure 2** Semi-reversible conversion of molecular structures into numerical information. **a** General scheme. The molecular fingerprint (MFP) algorithm encodes molecular structure information into binary data. DRL decodes molecular structures from binaries. The variational autoencoder (VAE) reversibly converts molecules into continuous vectors. **b** Results for molecule reconstruction. MFP/DRL or VAE were used to encode and decode 150 randomly selected molecules. The distribution of the Tanimoto similarities to the original structures is shown (a comparison using the cosine similarity of the molecular descriptors is shown in Figure S1). MFP and MFP' are the Avalon and Morgan MFPs, respectively. Average similarities were 0.93, 0.90, and 0.72 for MFP, MFP', and VAE, respectively. **c** Example original and reconstructed structures. Full results are given in Supporting Data: Sheet 1.

The 2048-dimensional Morgan fingerprint algorithm (MFP')<sup>[18]</sup> and a recent popular deep learning model, junction tree VAE,<sup>[8]</sup> were used as the controls for MFP/DRL. VAE converted chemical structures into 56-dimensional continuous vectors reversibly. The average Tanimoto similarities were 90% and 72% for MFP'/DRL and VAE, respectively. Reconstruction errors were more frequently detected (Figure 2b, c). The trend was the same for the cosine similarities of the molecular descriptors (Figure S1). A carefully designed Avalon MFP<sup>[18]</sup> expressed the molecules most accurately, and it could be decoded precisely by DRL.

#### 2.2. Preparation of regression potential E<sub>reg</sub>

The next task is preparing the regression potential,  $E_{reg}$ , which corresponded to a machine learning model,  $\hat{y} = f_{ML}(x)$ , for estimating a specific parameter, y, from structural data x (steps 1–3 in Figure 1b). The prediction model should follow quadratic equation (1) for the subsequent quantum annealing.<sup>[19]</sup>

$$E_{\text{reg}} = -\hat{y} = -f_{\text{ML}}(\boldsymbol{x}) = \sum_{i\neq j}^{N} J_{\text{reg,ij}} x_i x_j + \sum_{i=1}^{N} h_{\text{reg,i}} x_i$$
(1)  
$$J_{\text{reg,ij}}, h_{\text{reg,i}} = \text{constants}, N = \text{dimension of } \boldsymbol{x}, E_{\text{reg}} = -\hat{y} \text{ for compounds with higher } y$$

A regular chemical database, Bradley's dataset,<sup>[20]</sup> containing over 3000 experimental records, was used to train the model. The experimental melting point, y, was predicted successfully, even without quadratic terms ( $J_{\text{reg,ij}} = 0$ ,  $h_{\text{reg,i}} \neq 0$  Figure 3 and Figure S2). Partial least squares (PLS) regression yielded a mean absolute error (MAE) of around 40 °C for 10% of the test data that were randomly selected (Figure 3a). Similar results were observed with a sparse modeling algorithm, Lasso (Figure 3b).<sup>[3]</sup>



**Figure 3** Predicting experimental melting temperature by supervised learning. **a** Partial least squares (PLS), **b** Lasso, **c** factorization machine, and **d** random forest were used as the regression algorithms. Melting temperature in Bradley's dataset was predicted from the MFPs. The test data consisted of the top 10% of compounds in the dataset and 10% of randomly selected compounds. The other 80% of the records were inputted into the models for training. The full results are shown in Figures S2 and S3.

The introduction of higher-order interaction terms improved the prediction for the training data, but decreased the accuracy in extrapolating regions. The factorization machine is an algorithm yielding a quadratic formula for binaries ( $J_{\text{reg,ij}} \neq 0$ ,  $h_{\text{reg,i}} \neq 0$ ).<sup>[21]</sup> The quadratic term reduced MAE for the training data and randomly selected test data (Figure 3c and Figures S2 and S3). However, the quadratic term could not predict a test dataset as the top 10% of records in the original database (extrapolation regions, Figure 3a–c). Because pristine linear prediction models were compatible with extrapolation, the quadratic term was probably the main reason for overfitting the training data and for limiting  $\hat{y}$  up to the observed maximum. A similar result was obtained with the random forest decision tree model (Figure 3d).<sup>[3]</sup>

We selected the PLS algorithm with linear terms to construct  $E_{reg}$  because of its compatibility with the extrapolation region.<sup>[1]</sup> Regression potentials were similarly constructed with other properties, namely, the partition coefficient (MolLogP) and topological polar surface area (TPSA), for the subsequent compound exploration tasks. MolLogP and TPSA are known as facilely calculable molecular properties by computers. Their successful prediction supported the validity of the PLS model (see Supporting Discussion for details).

#### 2.3. Construction of user preference potential E<sub>RBM</sub> and exploration of minimum solutions

Methodically evaluating various criteria of candidate materials is not feasible. Instead of predicting each parameter, a more human approach was proposed in this study. Experimental researchers usually take inspiration for new materials from existing ones, which are already used in specific applications. New materials tend to satisfy the property criteria because of their structural similarity to existing materials. However, conventional computational molecule design has been done from scratch because of the difficulty of mimicking the heuristic approach (i.e., quantifying synthetic and practical feasibilities is difficult, as discussed in the introduction).<sup>[1]</sup> Our method can solve this problem by using unsupervised learning and quantum-inspired annealing.

RBM is crucial to obtaining new chemicals from the existing ones (Figure 1b). RBM is a probabilistic unsupervised learning model,<sup>[17]</sup> which constructed  $E_{\text{RBM}}$  for the MFP of the user-inputted structures (Figure 4a). The essential features of the inputted data (i.e., MFP) were learned by RBM. During unsupervised learning, the model weighed the bias ( $h_{\text{RBM,i}}$ ) and connection terms ( $J_{\text{RBM,ij}}$ ) for the visible and hidden layers (Figure S4 and S5, see Supporting discussion for hyperparameter optimization). RBM automatically constructed  $E_{\text{RBM}}$  so that the energies of the inputted chemicals decreased (step 3' in Figure 1b). RBM yielded quadratic equation (2) for  $E_{\text{RBM}}$ .  $E_{\text{RBM}} = \sum_{i \neq j}^{M} J_{\text{RBM,ij}} x_i x_j + \sum_{i=1}^{N} h_{\text{RBM,i}} x_i + \sum_{i=N+1}^{M} h_{\text{RBM,i}} x_i$ (2) M = total dimensions of RBM

To demonstrate the method, new chemical structures were generated from example starting compounds toluene, tetrafluoromethane, and acetic acid (Figure 4b–d). This was a mini task without using  $E_{reg}$  in the integrated system (steps 3'–7 in Figure 1b). First, the MFPs of the three compounds were inputted into RBM, which had 512- and 1488-dimensional visible and hidden layers, respectively. Then, the solutions that gave lower energies were explored by annealers. Finally, DRL decoded the chemical structures from the binaries.



**Figure 4** Generation of new chemicals by the restricted Boltzmann machine (RBM) and quantum-inspired annealing. **a** Configuration of RBM, consisting of visible and hidden layers. **b** Distribution of binary solutions obtained by DAU, D-Wave, and simulated annealing samplers. The sampling potential,  $E_{\text{RBM}}$ , was generated by inputting toluene, tetrafluoromethane, and acetic acid into RBM. Multiple solutions were obtained by DAU with the Boltzmann sampling mode and different values of sampling parameter *c*. Randomly selected records were used for the following decoding task by deep reinforcement learning (DRL; shown as larger blue points). DAU is compared with Markov chain Monte Carlo solvers in Figure S6. **c** Comparison of calculation time and energy for the sampling tasks. "DAU (min)" indicates the global minimum exploration mode. **d** Structures generated from the sampled solutions using DRL. Full results are shown in Figure S7 and Supporting Data: Sheets 2 and 3.

In informatics, a fundamental challenge in exploring chemical structures has been finding appropriate solutions in the astronomically huge chemical space, corresponding to  $2^M$  patterns in this case ( $M = 2048, 2^{2048} \approx 10^{600}$ ). Brute force exploration is impractical because there are too many combinations.

We introduced quantum-inspired annealing machines to acquire reasonable solutions from the enormous space. Annealers are emerging massively parallel computing hardware that can find minimums for the quadratic formulas.<sup>[19, 21-24]</sup> The superposition principle or its computational equivalent enables efficient solution exploration within a practical time range.<sup>[19, 21-24]</sup>

To acquire solutions, we examined quantum (developed by D-Wave),<sup>[22]</sup> quantum/digital hybrid (D-Wave),<sup>[22]</sup> our quantum-inspired DAU,<sup>[23, 25]</sup> simulated bifurcation machine (SBM; Toshiba),<sup>[24]</sup> standard CPU-based simulated annealing, and conventional Markov chain Monte Carlo (MCMC) solvers. Except for the D-Wave (quantum mode) and MCMC solvers, all the solvers provided solutions with an energy around -40 and the norm  $\sum x_i \approx 700$ . The results indicated that the solvers almost reached the global minimum (Figure 4b, Table S2, Supporting Data: Sheet 2). The calculation times for the methods (DAU: 0.3 s; D-Wave-hybrid: 5.2 s; SBM: around 1 s) were much shorter than that for CPU-based annealing (19 s). A genuine quantum solver for D-Wave was unavailable for the problem because of the limited qubit connections.<sup>[22]</sup>

An advantage of DAU is its ability to sample solutions quickly according to the Boltzmann distribution, in addition to finding global minimums. Local minimums were obtained from  $cE_{\text{RBM}}$ , where *c* was a scaling factor (c = 0.1, 1, 10, 100, Figure 4b). The solutions were similar to the regular MCMC for c = 0.1–10, indicating successful Boltzmann sampling by DAU (Figure S6). In contrast, the results differed significantly for sampling at c = 100. For DAU, the solution energy was around -38, whereas, for conventional MCMC, higher solution energy of -35 was obtained. The traditional approach could not reach the equilibrium solutions in a short time range ( $10^8$  iterations in 3.5 min). Only DAU quickly accessed both global and local minimums with a broad energy range (0.3 s). In contrast, D-Wave (hybrid mode) and SBM did not support the Boltzmann sampling (Figure 4c).

Using the local minimums found by Boltzmann sampling was critical to generating molecules with user preference. When the global minimum binary solutions were inputted into the DRL model, many perfluoroalkane derivatives were proposed (Figure 4d, Figure S7, Supporting Data: Sheet 3). The initial molecule tetrafluoromethane was emphasized too heavily when the global minimum was used. In contrast, mixtures of the three initial molecules (toluene, tetrafluoromethane, and acetic acid) were generated more frequently from the local minimums obtained by DAU with Boltzmann sampling. Local minimums with slightly higher energies than the global minimum were essential to reflect the user preferences.

#### 2.4. Generation of molecules from $E_{reg}$ and $E_{RBM}$

New molecules with a specific high target parameter were generated from multiple userinputted structures by integrating the potentials of regression  $E_{reg}$  and user preference  $E_{RBM}$ (Figure 1c). For example, we generated new structures with higher TPSA from toluene (TPSA = 0.0, Figure 5a).  $E_{reg}$  was considered by supervised learning of Bradley's dataset (Figure S2b).  $E_{RBM}$  was generated by RBM, trained with the MFP of toluene. Binary solutions were sampled from the potentials of  $E = c(rE_{reg} + 1/r \cdot E_{RBM})$ , with c = 0.1, 1, 10, and 100 and r = 1/16, 1/8, 1/4, 1/2, 1, 2, 4, 8, and 16, to generate diverse chemical structures (Figure S8, see Method section for details).

Larger r emphasized the effects of TPSA, promoting structures with higher performance but more challenging structures with respect to criteria including stability and synthetic accessibility. In contrast, smaller r generated more toluene-like structures that were feasible yet unremarkable. Most previous molecular design systems used  $r \rightarrow \infty$ , where only one target parameter was considered for molecule generation.<sup>[1, 22]</sup> Scaling factor c correlated with the randomness of the generated molecules, and structures that were more randomized were obtained with smaller c.

After DRL constructed new molecules, they were sorted according to their similarity to the original compound and predicted TPSA (Figure 5b, c). Representative records showing the highest predicted TPSA  $\hat{y}$  within the specific range of similarity were extracted as the final outputs (larger points in Figure 5b). The chemical structures are shown in Figure 5d and Figure S9. Toluene derivatives with higher TPSA (6–160) were generated. The regression model even predicted the TPSA of the newly generated molecules with high accuracy ( $R^2 = 0.92$ , Figure 5b, c, Table S3).



**Figure 5** *De novo* generation of molecules by our system. **a** A sample query for obtaining new chemical structures with higher topological polar surface area (TPSA) based on toluene. **b** Distribution of new chemical structures mapped by logarithmic similarity to the original molecule and TPSA (predicted and actual values are shown). Molecules with high predicted TPSA (larger points) were extracted as the final outputs, and the chemical structures are shown in **d**. **c** Relationship between the actual and predicted TPSA. **d** Example chemical structures generated by the system using deep reinforcement learning (DRL). Variational autoencoder (VAE) results are shown as the control. Full data are given in Figure S9.

The comparison with the conventional VAE approach highlights the advantages of the proposed system. A linear regression model for predicting TPSA was prepared using the continuous vectors encoded by VAE. A similar regression accuracy was observed with MFP, indicating the comparable capability of interpreting molecular structures as numbers (Figures S2 and S3). For VAE, toluene-like molecules with higher TPSA were constructed by decoding a vector,  $x_{new} = x_{toluene} + a\delta + \sigma$ , with VAE, where  $x_{toluene}$  was the vector for toluene, a was the slope of the regression model,  $\delta$  was a random constant, and  $\sigma$  was a random vector as noise (Figure S10).

Although new molecules were generated from toluene, most proposed structures were far from the original. Aromatic heterocycles were unexpectedly generated by VAE, whereas most molecules generated by the MFP/DRL system contained single benzene rings (Figure 5d, Figure S9). Statistically, 76% of the molecules obtained by DRL had single benzene rings, whereas only 20% of those obtained by VAE did (about 4-times improvement, Table S3 and S4).

Because there are significant differences in synthetic pathways and properties among aromatic rings, heterocyclic structures can disappoint experimental researchers. The automatically trained VAE model<sup>[8]</sup> could not distinguish the chemical features properly. In contrast, the carefully designed MFP algorithm and ideal solution sampling by DAU satisfied user expectations.

*De novo* molecule generation was also conducted with targets of TPSA or MolLogP, and with starting compounds of toluene, toluene and tetrafluoromethane, and toluene, tetrafluoromethane, and acetic acid (Figures S9 and S11). Although satisfying all requests was not easy, especially with the three-component input, DRL generated higher TPSA or MolLogP structures from the starting compounds. The extraction scores and manual criteria for checking user preference satisfaction were higher with DRL than VAE (Table S3 and S4). Higher R<sup>2</sup> values were also obtained with DRL than VAE during the property prediction tasks with the new molecules (Table S3).

An essential advantage of our system is its improved interpretation of multiple user preferences. Even with VAE, new molecules could be sampled by, for instance, decoding vector  $\mathbf{x}_{new} = \sum \lambda_i \mathbf{x}_i + \mathbf{a}\delta + \boldsymbol{\sigma}$ , where  $\mathbf{x}_i$  represents an original molecule and  $\lambda_i$  is a constant satisfying  $\sum \lambda_i = 1$  (Figure S10). However, most proposed structures were dissimilar to the originals (Figure S9). Because there was effective no restriction of  $\lambda_i$ , the constants were randomly taken from the ample search space, which resulted in junk structures being proposed. In contrast, our system interpreted multiple starting compounds to generate new ones using RBM. This should be the first human-inspired computational method of designing new compounds from versatile knowledge of conventional materials.

# 3. Synthesis of new polyelectrolytes from the suggested structures

This section examined a new polymer automatically designed by the system. Solid-state lithium-ion-conducting electrolytes, represented by the complex of polyethylene oxide (PEO) and a lithium salt, have been attracting attention as an essential component for next-generation secondary batteries. However, despite their facile processability and mechanical robustness, their solid-state ionic conductivity around room temperature (typically  $10^{-6}$  S/cm) is much lower than that of liquids (> $10^{-3}$  S/cm) without plasticizers.<sup>[14]</sup> New materials are being designed to overcome these limitations of polymer electrolytes.

A linear regression model for predicting logarithmic ionic conductivity from the electrolyte structures was constructed, and was also regarded as a regression potential,  $E_{reg}$ . Our original database, containing experimental records of solid-polymer and liquid lithium-ion-conducting electrolytes,<sup>[10, 26]</sup> was used for machine learning (>1000 cases at room temperature, Figure 6a). Most electrolytes consist of multiple components, including lithium salts, solvents, and other components. The MFPs of the two primary compounds, used as additives to lithium salts, were set as x. For simplicity, the lithium salt structure, weight ratio, and other component information were ignored. R<sup>2</sup> scores for the 80% trained and 20% untrained datasets were 0.65 and 0.57, respectively. Thus, the accuracy was sufficient for  $E_{reg}$ .



**Figure 6** Exploration of new lithium-ion-conducting polymer electrolytes. **a** Predicted and experimental logarithmic ionic conductivity. The conductivity was predicted from the MFP of the electrolyte components using a PLS model. **b** Query to generate molecules *de novo* from electron donor and acceptor molecules in the electrolyte database. All chemical structures are shown in Figures S12 and S13. A derivative of a phenothiazine polymer, enclosed by the red square, was selected for the subsequent chemical experiments. **c** Structures and photograph of the experimentally synthesized electrolyte. **d** Nyquist plot for the electrolyte. **e** Arrhenius plot for the electrolyte. As the control, the conductivity of a complex, polyethylene oxide (PEO)/lithium bis(trifluoromethanesulfonyl)imide (LiTFSI) (PEO/salt = 30), is shown, taken from a previous report.<sup>[27]</sup> The rapid increase in conductivity was attributed to the partial melting of the electrolyte, whereas the new electrolyte was solid, even at high temperatures.

User preference potential  $E_{\text{RBM}}$  was constructed by inputting electron donor and acceptor molecules from the database (Figure 6b, Figure S12). The charge-transfer complexes of the two species have been studied extensively as electron conductors, not ionic conductors.<sup>[28]</sup> However, our prior machine learning and experimental study indicated that their polarised structures could induce ion dissociation and even superionic properties.<sup>[10, 26]</sup> We focused on the de novo automated design of charge-transfer complex electrolytes in the present study.

New polymers and molecules for solid-state electrolytes were generated, followed by sampling solutions from  $E = c(rE_{reg} + 1/r \cdot E_{RBM})$ , and the structures were decoded by DRL. Most structures were electron donor or acceptor molecules (Figure 6b, Figure S13). In contrast, when molecules were sampled based on only their ionic conductivity, almost all candidates had poor chemical stability and synthetic accessibility.<sup>[29]</sup>

The system suggested an exciting structure was a phenothiazine polymer, where the donor molecules were attached to a PEO backbone (Figure 6b, marked red). The phenothiazine unit, an acceptor molecule, was not recorded in the initial user preference, but was proposed by the system. Introducing a PEO backbone is reasonable because it could enhance ion dissociation, migration, and mechanical properties.<sup>[14]</sup>

We experimentally examined a new phenothiazine polymer from the proposed structure (Figure 6c). The polymer was synthesized readily from polyepichlorohydrin and phenothiazine by a polymerization reaction. For more accessible synthesis, an extra halogen group in the original aromatic ring was removed. The introduction ratio *x* of phenothiazine was changed by tuning the synthetic conditions (Figure S14). A self-standing polymer electrolyte film was prepared by combining lithium bis(trifluoromethanesulfonyl)imide (LiTFSI), the donor polymer, and 7,7,8,8-tetracyanoquinodimethane (TCNQ) as a strong acceptor.<sup>[26, 28]</sup> Commercially available TCNQ was selected instead of the proposed chemicals for synthetic ease.

The new electrolyte exhibited promising ionic conductivity at room temperature during the impedance measurements (Figure 6d). The highest conductivity of around  $7 \times 10^{-6}$  S/cm was achieved when the density of the charge-transfer complex was maximized (x = 0.6, Figure S14). The conductivity was lower than the predicted value ( $1 \times 10^{-4}$  S/cm, using a model considering salt structures, Figure S15) partially because of the use of the simple regression model and the difference in the chemical structures (x = 1 for the predicted structure and 0.6

for the synthesized structure). The results indicated the importance of the polarized structure in the charge-transfer complex for ion conduction.

The conductivity was reasonably high considering that the polymer had a glass transition point (86 °C) above room temperature; the thermal motion of polymers was almost frozen during ion conduction. Although the mechanism is unknown, the polarisation in the polymer may have contributed to the dissociation and migration of ions.<sup>[10, 26]</sup> The conductivity was higher than a conventional PEO electrolyte around room temperature (Figure 6e). The PEO electrolyte exhibited higher conductivity at higher temperatures than the new electrolyte.

However, the increase was due to the partial melting of PEO,<sup>[27]</sup> whereas the phenothiazine electrolyte remained in the solid phase, at least 150 °C. The mechanically robust PEO backbone enabled the self-standing film property regardless of the high glass transition temperature. Our polymer was self-standing and moderately flexible, while previous glassy polymer conductors (transition temperatures of > 100 °C) were powdery and brittle.<sup>[10]</sup>

The new electrolyte's electrically insulating properties and electrochemical robustness allowed us to build and test a prototype solid-state lithium-ion battery, with lithium iron phosphate as a cathode and lithium titanate oxide as an anode (Figure S14). Reversible redox peaks appeared around the formal potential  $E^0 = 1.9$  V because the conductivity and stability of the electrolyte were sufficient.

The experimental conductivity was not so high as the state-of-art polymer electrolytes (10<sup>-3</sup> S/cm),<sup>[14]</sup> indicating that the heuristic potentials (i.e., regression model from the limited data and starting compounds of donors and acceptors in Figure 6b) were not best for conductivity. However, our method generated practically useful molecular structures without additional molecular filtering (i.e., satisfying conductivity, mechanical, thermal, chemical robustness, and synthetic accessibility): this has been difficult to achieve in materials informatics.<sup>[1, 2]</sup> We continue synthesizing and validating new functional polymers designed by the automated molecule generation system.

## 4. Conclusion

We developed a new automated functional molecule/polymer design system, which can generate structures *de novo* according to multiple user preference structures. Similar to how humans generate new structures, new designs were inspired by existing chemicals. Our approach could satisfy material screening criteria, such as stability and synthetic difficulty. Unsupervised machine learning and quantum-inspired annealing allowed complex search potential generation and quick solution sampling. A new solid polymer electrolyte for lithiumion batteries was experimentally demonstrated using the system. Our human-inspired molecule exploration system will help experimental researchers discover new and practically useful materials more frequently.

# 5. Experimental Section

#### General information

Calculations were conducted on an Ubuntu 18.04 workstation unless noted otherwise (CPU: Ryzen Threadripper 3990X, AMD; GPU: RTX 3090  $\times$  2; memory: 256 GB). A Python 3.7 environment was used to process the data. Molecular information was recorded by using a simplified molecular input line entry system (SMILES) and treated with open-source chemoinformatics software, RDKit 2019.09.3.

# Conversion of chemical structures into binary data and vice versa

For the reconstruction task, 150 randomly selected types of organic molecules recorded in an open database (Jean-Claude Bradley Open Melting Point Dataset)<sup>[20]</sup> were used (Figure 2, Supporting Data: Sheet 1). Chemical structures were converted into binary data by MFP algorithms, Avalon (512-dimensional, expressed as an MFP) or Morgan (2048-dimensional, defined as an MFP'), implemented in RDKit. An open-source molecular DRL program, REINVENT, was used for the inverse transformation.<sup>[5]</sup> The model was pretrained with our *in silico* molecule and polymer database. The model yielded new molecular structures displaying higher Tanimoto similarity to the target binary data. A molecule with the highest similarity and prior probability was selected as the final output.

#### VAE as the control for MFP/DRL

The conventional VAE algorithm was examined as a control for MFP/DRL and was used to convert chemical structures reversibly into continuous numeric vectors (Figure 2, Supporting Data: Sheet 1). A pretrained model for junction tree VAE,<sup>[8]</sup> implemented in an open-source library (dgllife 0.2.6), was used. The model encoded molecular structures into 56-dimensional vectors and decoded them into structures. The Tanimoto similarity of the MFP was used as the criterion for the reconstruction accuracy. If decoding failed, the score was set as 10<sup>-5</sup>. The original and reconstructed molecules were also evaluated by average cosine similarity for the 200 basic molecular descriptors generated by the RDKit module (Figure S1).

#### Preparation of regression models

Regression models that predicted a specific target parameter, y (melting point, TPSA, or MolLogP), from molecular structures were prepared using Bradley's dataset (Figure 3). Experimental melting points were recorded in the database. RDKit calculated TPSA and MolLogP. For machine learning, the structural information was converted into 512-dimensional MFPs or 56-dimensional continuous vectors by VAE (= x). The original database was split into training and test datasets. The test dataset contained the records for the molecules with the top 10% of target parameters and 10% of randomly selected cases in the database. The other 80% was training data, with which the regression models were trained. The random splitting and model evaluation were repeated five times to check the statistical significance (Figure S3).

An open-source machine learning library, scikit-learn 0.23.2,<sup>[30]</sup> was used to construct PLS (hyperparameter: n\_components = 30, others were default), Lasso (alpha = 0.01), Bayesian ridge, and random forest regression models. The factorization machine algorithm, yielding quadratic regression models, was implemented by pyFM 0.0.0. For the linear models (PLS, Lasso, and Bayesian ridge), x and y were inputted as *z*-scores, with means of 0 and standard deviations of 1. MAE or R<sup>2</sup> scores were calculated with scikit-learn to evaluate the models.

# Construction of user preference potentials $E_{RBM}$ and sampling with quantum-inspired annealing 1) Construction of potential

User preference potential  $E_{\text{RBM}}$  was constructed from the MFPs of toluene, tetrafluoromethane, and acetic acid (Figure 4). The fingerprints were inputted into an RBM with 512-dimensional visible and 1488-dimensional hidden layers. The total dimension was 2000 because of the input limit of the D-Wave device.<sup>[22]</sup> The model was implemented with a deep learning library, PyTorch 1.8.1 (GPU mode), and trained with a contrastive divergence (k = 3) algorithm with a minibatch size of 2. Hyperparameters (total dimension N + M, k, and minibatch) were preliminarily optimized by evaluating the reconstruction losses of the models, which were trained with 128 random molecules in Bradley's dataset ten times (Figure S4).

# 2) Quantum-inspired sampling

From the constructed potential,  $E_{\text{RBM}}$ , local minimums were sampled with different solvers. CPU-based simulated annealing was conducted with a module in the dwave-system 1.4.0 package. Quantum annealing was tested with a D-Wave machine (DW\_2000Q\_6). Quantum/classical hybrid-mode annealing was performed using the same D-Wave package (LeapHybridSampler). Toshiba SBM 1.2.2<sup>[24]</sup> was implemented via Amazon Elastic Compute Cloud (Amazon). DAU<sup>[23]</sup> operated on our private server. DAU found near-global minimums with a normal annealing mode and local minimums with a constant-temperature Boltzmann sampling mode. As the control, Boltzmann sampling was implemented using a conventional MCMC program (Metropolis–Hastings algorithm), compiled using the numba 0.53.1 package. The distribution of the solution was tuned by coefficient *c*. Larger *c* led to the global minimum, and smaller *c* offered random solutions.

# 3) Reconstruction of new molecules

Chemical structures were decoded by DRL from the first 512-dimensional data of the sampled 2000-dimensional binaries (Supporting Data: Sheet 3). DAU could yield 128 different solutions from one annealing query. Randomly selected solutions for each sampling condition were used for DRL (larger blue points in Figure 4b).

# Molecule generation from $E_{reg}$ and $E_{RBM}$

# 1) Construction of potential

Molecules were generated from  $E_{reg}$  and  $E_{RBM}$  (Figure 5).  $E_{reg}$  was constructed by preparing a PLS regression model to predict TPSA or MolLogP from MFP. Bradley's dataset was used for machine learning.  $E_{RBM}$  was generated by training RBM (512-dimensional visible and 1536-dimensional hidden layers). MFPs of toluene, toluene and tetrafluoromethane, or toluene, tetrafluoromethane, and acetic acid were inputted to train the model.

#### 2) Molecule generation

Local minimums were sampled from the potentials,  $E = c(rE_{reg} + 1/r \cdot E_{RBM})$ , where c = 0.1, 1, 10, and 100 (four conditions in total) and r = 1/16, 1/8, 1/4, 1/2, 1, 2, 4, 8, and 16 (nine conditions). Molecules with higher target parameters were more frequently obtained by larger r. The DAU with the Boltzmann sampling mode was used as the solver. Up to 20 solutions were extracted from the binary solutions ( $128 \times 4$ ) for the same r, namely, the minimum energy solution and 19 solutions with random energy. Here, lower energy solutions could be sampled more preferably with higher c, according to the Boltzmann distribution. Twenty independent DRL models generated five molecules from each solution (i.e.,  $20 \times 5 = 100$  molecules). Because r had nine variations, up to  $100 \times 9 = 900$  molecules, including duplicates, were generated.

# 3) Extraction of final candidates

The generated molecules were prefiltered to exclude excessively complex molecules. The synthetic accessibility score<sup>[15]</sup> was calculated with an open module available at https://github.com/rdkit/rdkit/tree/master/Contrib/SA\_Score (version Oct 31, 2019). The

candidate was excluded if the accessibility score was over four or the string length for its SMILES was over 30.

The trained regression model predicted TPSA or MolLogP of the generated molecules. Similarities to the user-inputted chemicals were calculated according to  $\log(\prod f_{sim} (x_{new}, x_i))$ , where  $f_{sim}$  was for cosine similarity of the vectors of the two chemicals,  $x_{new}$  was the MFP for the generated molecule, and  $x_i$  was for toluene, tetrafluoromethane, or acetic acid. The relationship between the predicted target parameter and similarity was plotted (Figure 5b). Molecules displaying the highest target parameters within specific similarity ranges were extracted as the final output (larger points in Figures 5b, c). R<sup>2</sup> scores for the predicted and actual target parameters were calculated with the generated molecules (Table S3). Extraction scores were calculated according to the criteria shown in Table S4.

#### 4) Molecule generation by VAE

VAE was also used to generate new molecules as the control for the annealing system. First, a 56-dimensional vector expression of the starting compounds,  $x_i$ , was generated by the VAE encoder. The vectors were converted to z-scores using the data distribution of Bradley's dataset. Then, a new vector,  $x_{new} = \sum \lambda_i x_i + a\delta + \sigma$ , was made, where  $\lambda_i$  was a random constant, satisfying  $\sum \lambda_i = 1$  and  $\lambda_i > 0$ , a was the slope for the regression model,  $\delta$  was a random scalar from the Gaussian distribution (mean = 0, standard deviation = 10), and  $\sigma$  was a random vector from the Gaussian distribution (mean = 0, standard deviation = 1). The vector was decoded to a molecular structure followed by inverse transformation. This random process generated 1000 new molecules. Final candidates were extracted according to the same procedure as the DRL approach.

#### Exploration of new polymer electrolytes with DAU and DRL

#### 1) Preparation of regression model

Our original lithium-ion-conducting molecular electrolytes database<sup>[10, 26]</sup> was used to construct potential  $E_{reg}$  and  $E_{RBM}$  (Figure 6). The database contained more than 1000 records of monomeric and polymeric lithium-ion-conducting electrolytes around room temperature. The basic algorithm for preparing the prediction model from our previous study was used.<sup>[26]</sup> The compounds in the electrolytes were sorted according to their types (salts appeared first and others later) and weight content ratio (higher to lower). For simplicity, up to the first three components in an electrolyte were considered. Weight ratio, molecular weight, and structural information for the polymers, and inorganic additives (e.g., SiO<sub>2</sub>) were ignored for **x** because quantum annealing systems can input only binary variables, not continuous numbers.<sup>[19]</sup> Experimental ionic conductivity around room temperature was predicted from the MFPs of the two additives to the salt, that is, a  $512 \times 2 = 1024$ -dimensional binary. The PLS algorithm was used to obtain a linear regression model. Logarithmic conductivity was converted into the *z*-score during machine learning and prediction. Only during the prediction of the synthesized electrolyte, the model was trained by considering the salt structures (i.e., salt and two main additives, Figure S15).

#### 2) Molecule generation

As the user preference structures, electron donor and acceptor molecules in the database were extracted systematically (Figure S12). The MFPs of donors and acceptors were set as the first and second information for the binary, respectively. The training RBM with the MFP yielded  $E_{\text{RBM}}$ . The model had a 1024-dimensional visible layer and a 3068-dimensional hidden layer (4096 dimensions in total). Local minimums were sampled by the DAU using potentials of  $E = c(rE_{\text{reg}} + 1/r \cdot E_{\text{RBM}})$ , where c = 0.1, 1, 10, and 100, and r = 1.5. Chemical structures were generated by DRL from the sampled solutions. For donor molecules, the DRL scoring function was tuned to predict polymer structures (higher scores were obtained when a generated molecule had two repeating unit atoms).

According to the following criteria, a final candidate polymer was selected from the generated molecules (Figure 6c, Figure S13). a) Has facilely synthetical polymeric backbones (e.g., vinyl, glycidyl, siloxane, and vinyl ether). b) Has more potent donor properties (e.g., hetero-aromatic rings and phenyl amines). c) Chemically stable (e.g., avoid carbocations, anions, and excessive allyl groups).

#### Chemical experiments for the new polymer electrolyte

#### 1) General information

Polyepichlorohydrin ( $M_n = 1.8 \times 10^4$ ,  $M_w = 2.8 \times 10^4$ ) was synthesized by anionic ring-opening polymerization according to a literature procedure.<sup>[29, 31]</sup> Phenothiazine, potassium *tert*-butoxide, and TCNQ were purchased from Tokyo Chemical Industry Co. LiTFSI was obtained from Kanto Chemical Co. Other solvents and chemicals were purchased from Tokyo Chemical Industry, Kanto Chemical, or Sigma-Aldrich. All reagents were used as received. The thermal properties of the materials were measured by differential scanning calorimetry using a calorimeter (Q200, TA Instruments).

## 2) Synthesis of the phenothiazine polymer

Syntheses were conducted under a nitrogen atmosphere. Polyepochlorohydrin (0.5 g, corresponding to 5.4 mmol monomer units) and phenothiazine (1.6 g, 8.1 mmol) were dissolved in dry N,N-dimethylformamide (DMF; 10 mL). Potassium tert-butoxide (0.91 g, 8.1 mmol) dissolved in DMF (15 mL) was injected into the solution, and the mixture was stirred at 80 °C for one week. After the reaction, the solution was precipitated in methanol, and the powder was collected by filtration and washed with methanol. A pale brown powder was obtained after removing the solvent in vacuo overnight (46% yield). The phenothiazine introduction ratio, x =0.6, was estimated by <sup>1</sup>H NMR. Polymers with different introduction ratios were synthesized by changing the molar ratio of phenothiazine and epichlorohydrin, and by stopping the reaction after one day. The introduction ratio, *x*. was 0.2. 0.3. and 0.4 for [phenothiazine]/[epichlorohydrin] preparation ratios of 0.6, 1.0, and 1.5, respectively. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.22–6.95 (br, 2.4H, phenothiazine), 6.95–6.57 (br, 2.4H,

phenothiazine), and 4.39–3.27 ppm (br, 5H, epichlorohydrin).

## 3) Preparation of solid-state electrolytes

Electrolytes were prepared in an argon-filled glove box to avoid water contamination (dew point of >-70 °C and O<sub>2</sub> concentration of >10 ppm). The polymer (50 mg, x = 0.6) and TCNQ (32 mg, equiv with respect to phenothiazine) powders were mixed and heated to 200 °C to form the black charge-transfer complex. LiTFSI (68 mg, 1.5 equiv with respect to phenothiazine) was added and heated at 250 °C. The molten mixture was mixed and cooled to room temperature to yield the electrolyte as the product.

### 4) Electrochemical measurements

Solid-state cell equipment (Hosen Co.) was filled with electrolytes. The typical thickness of the electrolyte layer was 100 mm. The ionic conductivity was evaluated by sandwiching the electrolyte with stainless disks with a diameter of 5 mm. Electrochemical impedance spectra were recorded with an impedance gain-phase analyzer (1260, Solartron; 10<sup>6</sup> to 1 Hz).

A conventional potentiostat (ALS 660D, BAS) was used for other electrochemical measurements. Electrical conductivity was evaluated by the Hebb-Wagner method. A prototype lithium-ion battery was fabricated using a LiFePO<sub>4</sub> cathode and a  $Li_4Ti_5O_{12}$  anode. The electrolyte was sandwiched between a stainless-steel disk and lithium foil. The as-prepared electrodes were purchased from Piotrek Co.

# Data and code availability

Source code and databases are available at https://github.com/KanHatakeyama/anneal\_project2. All related data supporting this study's findings are available from the corresponding authors upon reasonable request.

# **Data Source**

Original data for Figures 2 and 4 are provided as Supporting Data.

# **Competing Interests**

The authors declare no competing interests.

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Supporting Information

# **Supporting Tables**

Filtering criteria	Conventional	This work	This approach
Specific parameter <sup>a)</sup>	+	+	Supervised learning
Synthetic difficulty <sup>b)</sup>	(+)	+	Unsupervised learning <sup>c)</sup>
Stability (chemical, thermal, …)	-	+	Unsupervised learning <sup>c)</sup>
Other parameters	-	+	Unsupervised learning <sup>c)</sup>

Table S1 C	omparison	of the cu	arrent work	with cor	nventional	approaches.
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a) Molecules can be screened according to a specific target parameter predicted by a machine learning model.

b) Synthetic accessibility score is one of few practical approaches to screening chemicals.c) Molecules can be generated from user-inputted structures, satisfying the criteria of synthetic difficulty and other parameters.

Method	<b>Mode</b> <sup>a)</sup>	С	Time (s)	Energy
Simulated <sup>b)</sup>	Global minimum	-	18.7	-39.4
D-Wave (quantum) <sup>c)</sup>	Global minimum	-	n/a	n/a
D-Wave (hybrid) <sup>d)</sup>	Global minimum	-	5.2	-39.6
D-Wave (hybrid) <sup>d)</sup>	Boltzmann distribution	-	n/a	n/a
SBM <sup>e)</sup>	Global minimum	-	>1	-39.6
SBM <sup>e)</sup>	Boltzmann distribution	-	n/a	n/a
DAU <sup>f)</sup>	Global minimum	-	0.37	-39.4
DAU <sup>f)</sup>	Boltzmann distribution	100	0.37	-38.8
DAU <sup>f)</sup>	Boltzmann distribution	10	0.37	-8.3
DAU <sup>f)</sup>	Boltzmann distribution	1	0.38	74.7
MCMC <sup>g)</sup>	Boltzmann distribution	100	187	-36.0
MCMC <sup>g)</sup>	Boltzmann distribution	10	206	-8.0
MCMC <sup>g)</sup>	Boltzmann distribution	1	204	69.3

**Table S2** Comparison of sampling results from user preference potential  $E_{\text{RBM}}$ .

a) Global minimum was explored by the minimum mode. Solutions were also randomly sampled according to the Boltzmann distribution under another mode.

b) Simulated annealing by D-Wave API.

c) Quantum annealing. This mode was unavailable because of the limited data connection by D-Wave.

d) Quantum and digital hybrid annealing. Only global minimum sampling was available.

e) Toshiba simulated bifurcation machine (SBM). Only global minimum sampling was available. The minimum annealing time could be set as 1 s.

f) Fujitsu digital annealing unit (DAU). During the Boltzmann distribution mode, 128 samples were explored independently, using a potential of  $cE_{\text{RBM}}$ . Energy for a randomly selected solution is displayed.

g) Markov chain Monte Carlo (MCMC). A conventional Metropolis-Hastings algorithm was implemented. A single-thread process was conducted using a CPU.

	Method <sup>a</sup> )	TPSA -1	TPSA -2	TPSA -3	MolLogP -1	MolLogP -2	MolLogP -3
<b>D</b> 2 b)	DRL	0.92	0.82	0.74	0.21	0.13	0.48
<b>R</b> <sup>2</sup> <sup>3</sup>	VAE	-1.60	-0.91	-0.81	-1.53	-0.66	-1.30
Averag e Score	DRL	76	49	51	87	68	46
	VAE	20	22	39	43	45	44

Table S3 Generation of de novo molecules by the system.<sup>a)</sup>

a) New molecules were generated from 1–3 starting chemicals to exhibit higher TPSA or MolLogP. Starting chemicals and scoring criteria are described in Table S4.

b) R<sup>2</sup> scores for the predicted and actual TPSA or MolLogP of final proposed molecules. DRL: deep reinforcement learning; VAE: variational autoencoder; TPSA: topological polar surface area; MolLogP: partition coefficient.

Table	S4 Starting	g compounds ar	nd scoring	criteria for	molecule ge	eneration tasks.
			0		U	

	Starting compounds	Scoring criteria
Task 1	Toluene	+100: Contains one benzene ring
Task 2	Toluene, CF <sub>4</sub>	+50: Contains one benzene ring +50: Contains more than one F atom
Task 3	Toluene, CF4, CH3COOH	+33.3: Contains one benzene ring +33.3: Contains more than one F atom +33.3: Contains more than one O atom

# **Supporting Figures**



**Figure 1.** Distribution of cosine similarity between the reconstructed and original molecules. An RDKit module was used to calculate 200 basic molecular descriptors, and their similarities were compared. The average similarities for molecular fingerprint (MFP), MFP', and variational autoencoder (VAE) were 0.97, 0.96, and 0.90, respectively.





**Figure 2.** Prediction results for **a** melting temperature, **b** topological polar surface area (TPSA), and **c** partition coefficient (MolLogP). The target values were predicted from the molecular fingerprint. Molecules recorded in Bradley's dataset was used for machine learning. Related data are shown in Figure 3.



**Figure 3.** Mean absolute errors (MAEs) for the prediction of **a** melting temperature, **b** topological polar surface area (TPSA), and **c** partition coefficient (MolLogP). The target values were predicted from the molecular fingerprint or vectors encoded by variational autoencoder (VAE). MAEs for the test data of inner and extrapolating regions are displayed. The machine learning tasks were repeated five times along with the random train/test dataset splitting. Bayes: Bayesian ridge; RF: random forest; FM: factorization machine.



**Figure 4.** Training restricted Boltzmann machine with different learning conditions (*total dimension-k-minibatch size*). The molecular fingerprints of 128 randomly selected molecules in Bradley's dataset were trained. The logarithmic reconstruction errors with 10 independent learning tasks are shown. The size of the visible layer was always 512. The hidden layer size was *total dimension* minus 512.



**Figure 5.** Example images of original and reconstructed molecular fingerprints (MFPs). Reconstructed data were generated by the trained restricted Boltzmann machine (RBM) (total dimension = 2028, k = 3, minibatch = 1). The original MFP was randomly extracted from the training dataset.



**Figure 6.** Distribution of solutions sampled by the digital annealing unit (DAU) or Markov chain Monte Carlo (MCMC) according to the Boltzmann distribution from  $E_{\text{RBM}}$  (related data shown in Figure 4). An enlarged view of the distribution is shown in the bottom panel. DAU yielded 128 samples with a single annealing query. Solutions were sampled per 10<sup>5</sup> steps during the 10<sup>8</sup> iterations of MCMC.



Figure 7. Example molecules generated from binary solutions found with different annealing conditions (related data shown in Figure 4). Solutions with larger c converged to the global minimum. More randomized molecules were generated by Boltzmann sampling with smaller c. DAU: digital annealing unit.



**Figure 8.** Scheme for generating chemical structures by the digital annealing unit (DAU) and deep regression learning (DRL). DAU explored binary solutions with different c (= 100, 10, 1, and 0.1). The solution with the minimum energy and 19 solutions with random energies were extracted. The DRL model generated five molecules per solution.



102.9

a TPSA-1 (DRL)

106.7

116.0

159.8













68.3



70.2



78.0



90.3





64.0

71.7

101.2



77.2

66.0





98.5

**b** TPSA-1 (VAE)

124.1

128.8



c TPSA-2 (DRL)









61.2

74.4

82.6



46.9

52.0

52.0

61.2





71.8

78.0

104.3

125.7

0. N







78.0







84.2





98.2



100.8



101.3



104.3









109.1



109.9



121.3



н<sub>2</sub>N



134.0

d TPSA-2 (VAE)





44.1



55.0



58.0



61.2



63.9





71.8



72.2

61.1





75.3







78.3



81.4

75.0



90.3

92.7



93.6



98.1



99.4



105.9



136.7

Ĭ



118.4











135.6





141.6

<sup>141.6</sup> **f** TPSA-3 (VAE)



<sup>53</sup> **g** MolLogP-1 (DRL)



h MolLogP-1 (VAE)







k MolLogP-3 (DRL)

6.2

6.0



**Figure 9.** *De novo* molecules generated by deep regression learning (DRL) under the conditions in Table S4 (related data shown in Figure 5). Results for the variational autoencoder (VAE) are shown for comparison. Numbers under the structures show topological polar surface area (TPSA) or partition coefficient (MolLogP). **a** TPSA-1 (DRL), **b** TPSA-1 (VAE), **c** TPSA-2 (DRL), **d** TPSA-2 (VAE), **e** TPSA-3 (DRL), **f** TPSA-3 (VAE), **g** MolLogP-1 (DRL), **h** 

MolLogP-1 (VAE), i MolLogP-2 (DRL), j MolLogP-2 (VAE), k MolLogP-3 (DRL), and l MolLogP-3 (VAE)



Figure 10. Scheme for exploring new chemicals by the variational autoencoder. A new vector obtained from the linear combination of the vectors for the three starting compounds was studied.



**Figure 11.** Distributions of newly generated structures under conditions in Table S4 (related data shown in Figure 5). Larger plots in the graphs were selected as the final outputs, and their structures are shown in Figure S9. **a** topological polar surface area (TPSA)-2, **b** TPSA-3, **c** partition coefficient (MolLogP)-1, **d** MolLogP-2, and **e** MolLogP-3.



**Figure 12.** Donor and acceptor molecules, set as the user preference compounds during the electrolyte exploration task. The substances were automatically extracted from the recorded ones in the lithium-ion conducting electrolyte database. The symbol "Y" represents a polymer repeating unit.



a Donors



**b** Acceptors

Figure 13. Representative polymer and molecular structures proposed by the system. a Donors and b acceptors.





Figure 14. Experimental properties of electrolytes.

**a** <sup>1</sup>H NMR spectrum of phenothiazine-substituted polyepichlorohydrin (PPEH), measured in CDCl<sub>3</sub>.

**b** Differential scanning calorimetry curves for PEO, polyepichlorohydrin (PECH) and PPEH with different introduction ratios of phenothiazine x. Except for PEO, endothermic responses from the glass transition were detected. The scan rate was 10 °C/min.

**c** Room-temperature ionic conductivity as a function of x. The control electrolytes without 7,7,8,8-tetracyanoquinodimethane (TCNQ) were also examined. Higher conductivity by the charge-transfer complex electrolytes (PPEH/TCNQ/LiTFSI) indicated the importance of the polarised molecular structure induced by charge transfer.

**d** Electron-induced current of the charge-transfer complex electrolyte (x = 60%) measured by the Hebb-Wagner method. The estimated electronic conductivity from the slope was  $3.0 \times 10^{-9}$  S/cm, which was around 1000 times smaller than ionic conductivity.

e Cyclic voltammograms of a prototype lithium-ion battery scanned at 5 mV/s (50 °C). The redox peaks appeared around the formal voltage  $E^0 = 1.9$  V. Larger current density after repeated cycles indicated the formation of improved conduction pathways by ion migration.



**Figure 15. Conductivity prediction considering lithium salt structure.** In this graph, conductivity was predicted from salt and two main additives in the electrolytes. In Figure 6a, conductivity was predicted by ignoring salt structures.

# **Supporting Discussion**

# **Preparation of regression models**

Experimental melting point, topological polar surface area (TPSA), and partition coefficient (MolLogP) were predicted from the structural information for molecules recorded in Bradley's dataset (Figure S2, S3). The partial least squares (PLS), Lasso, Bayesian ridge, random forest, and factorization machine regression models were examined. The Avalon molecular fingerprint (MFP) algorithm generated 512-dimensional binary data as the structural information. Similarly, the variational autoencoder (VAE) generated a 56-dimensional continuous vector. The PLS, Lasso, and Bayesian ridge models assumed only linear terms  $\sum_{i=1}^{N} h_{\text{reg,i}} x_i x_j$ .

The prediction accuracy measured by mean absolute errors (MAEs) after repeated random regression tasks was examined (Figure S3). For melting temperature and TPSA, MFP exhibited smaller prediction errors than VAE, meaning that the molecular characteristics affecting the target parameters were described by MFP more precisely. Inner region prediction, where actual y existed in the range of the training dataset, was much easier than the extrapolation because smaller MAEs were obtained for the inner region; however, prediction for the unseen data region is challenging.

Models that were more complex, namely, the random forest and factorization machine models, offered higher prediction accuracy for the inner regions. However, they could not correctly predict the extrapolation cases. The decision tree-based prediction algorithm of random forest and quadratic terms in the factorization machine model capped  $\hat{y}$  up to the maximum of y in the training data.

A similar trend was observed with MolLogP, except for the reversed prediction accuracy for MFP and VAE in the extrapolation region. The MFP prediction models could not extract appropriate trends, contributing to higher MolLogP as successfully as VAE. The introduction of other MFP algorithms will solve this problem, which we intend to study in our future research.

# Hyperparameter exploration of the restricted Boltzmann machine

The hyperparameters of restricted Boltzmann machine (RBM), which were total dimension M, repeating count k during contrastive divergence learning, and minibatch size, were optimized using Bradley's dataset (Figure S4). Reconstruction tasks were repeated 10 times, using MFP for 128 randomly selected molecules in Bradley's dataset. The size of the visible layer, N, was always 512, corresponding to the MFP dimension. The total dimension, M = (N + hidden layer size), was 1024, 2048, and 4096, the minibatch size was 1, 2, 4, and 8, and k was 1, 3, and 5. The learning epoch was set to 300.

The logarithmic reconstruction error did not change drastically regardless of the training conditions (Figure S4). Considering the balance of expressiveness of the RBM model and calculation cost (including annealing), N was set as 2048 for single-molecule generation tasks

(N = 2000 in Figure 4 because of the input limit of D-Wave). We set *k* as 3 and minibatch size as 1 unless noted otherwise. The successful reconstruction is shown visually in Figure S5.