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## Molecular generation targeting desired electronic properties *via* deep generative models†

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As we seek to discover new functional materials, we need ways to explore the vast chemical space of precursor building blocks, not only generating large numbers of possible building blocks to investigate, but trying to find non-obvious options, that we might not suggest by chemical experience alone. Artificial intelligence techniques provide a possible avenue to generate large numbers of organic building blocks for functional materials, and can even do so from very small initial libraries of known building blocks. Specifically, we demonstrate the application of deep recurrent neural networks for the exploration of the chemical space of building blocks for a test case of donor–acceptor oligomers with specific electronic properties. The recurrent neural network learned how to produce novel donor–acceptor oligomers by trading off between selected atomic substitutions, such as halogenation or methylation, and molecular features such as the oligomer's size. The electronic and structural properties of the generated oligomers can be tuned by sampling from different subsets of the training database, which enabled us to enrich the library of donor–acceptors towards desired properties. We generated approximately 1700 new donor–acceptor oligomers with a recurrent neural network tuned to target oligomers with a HOMO–LUMO gap <2 eV and a dipole moment <2 Debye, which could have potential application in organic photovoltaics.

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## Introduction

The successful development of new functional molecules remains one of the most important challenges to be addressed, not only due to the vastness of the chemical space to be explored, but also given the level of specificity required in the targeted properties for each application. In many cases, serendipity has played a fundamental role in the discovery and production of new materials and molecules. Recently, there is growing interest in applying artificial intelligence (AI) to the discovery of novel functional molecules, particularly in the field of drug discovery, with the aim of both exploring larger chemical space and saving the time and cost involved in the experimental synthesis and characterisation of such molecules.<sup>1–4</sup>

The use of AI in material discovery generally falls into two categories. Firstly, predictive AI models, based upon supervised machine learning, are becoming more common in the use for

the computation of material properties, calculating the properties of interest at reasonable accuracy, but a fraction of the computational cost compared to widely used electronic structure calculations. Predictive AI models have been applied widely for material discovery tasks, including organic photovoltaics,<sup>5–8</sup> bioinspired hierarchical composites<sup>9</sup> and supercompressible polymers.<sup>10</sup> Secondly, there are generative models, which use unsupervised machine learning such that a model learns from a dataset and can then produce data of a similar format. This can be applied in chemistry to produce novel molecules from libraries of known molecules. Generative models have been reported mainly for drug or drug-like molecules,<sup>11</sup> with only limited application for other types of functional molecules, for example non-fullerene electron acceptors<sup>12</sup> and thermally conductive polymers.<sup>13</sup> Our study here focuses on developing deep generative AI models for the discovery of novel donor–acceptor oligomers with desired electronic properties with potential application as organic semiconductors.

Development of a deep generative model for material discovery can be divided into several tasks. The first task is to represent the molecules of interest in a way that is easy to be read and written by a computer. A standard representation of molecules is the simplified molecular-input line-entry system (SMILES), which encodes molecular graphs compactly as human-readable strings. The SMILES representations of molecules highly resemble that of natural language, where long

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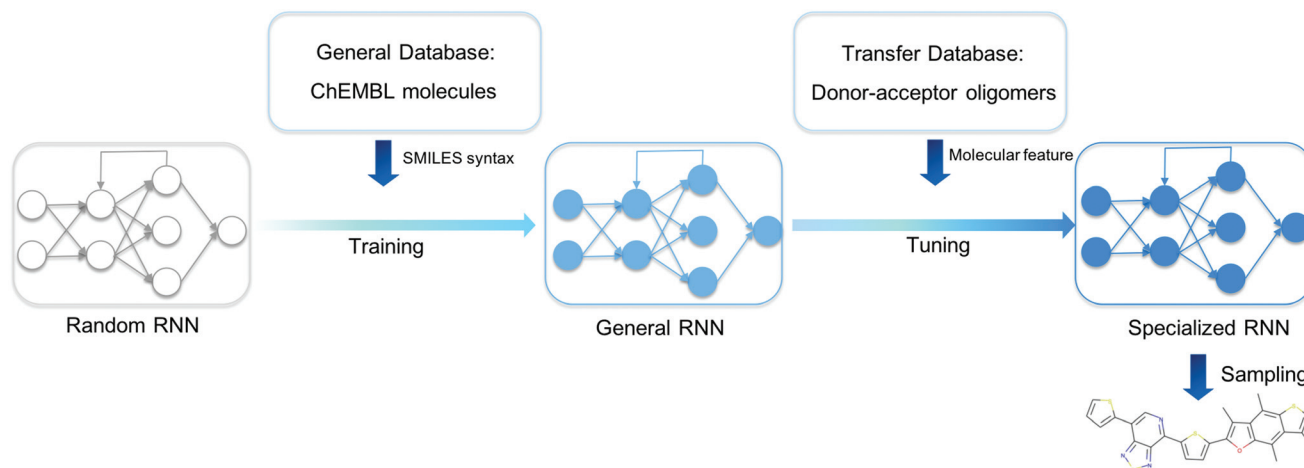
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Recent development and design of electronic donor-acceptors has attracted significant attention due to their application in organic light emitting diodes (OLEDs),<sup>21</sup> organic photovoltaics (OPVs),<sup>22</sup> and non-linear optical (NLO) materials.<sup>23</sup> The donor-acceptor oligomers need to be modified in order to obtain desired electronic properties.<sup>24,25</sup> For example, the optical gap of donor-acceptor oligomers usually needs to be

In this work, we have developed deep generative models for the generation of molecular libraries of donor-acceptor oligomers with preferred electronic properties using an RNN combined with TL. TL was required as the libraries of existent donor-acceptor oligomers are not of sufficient magnitude for training a robust RNN model. We explore whether the structural and electronic properties of the donor-acceptors can be learned *via* TL, and whether the chemical space of the training sets can be fully explored with the TL models. As a proof of concept, we targeted the chemical space of donor-acceptor oligomers with an optical gap, as approximated by the HOMO-LUMO gap, close to 2 eV and a dipole moment smaller than 2 Debye. These oligomers can potentially form organic semiconductor crystals offering alternatives to the traditional families of molecular candidates such as oligoacenes or benzothieno[3,2-*b*][1] benzothiophene derivatives. A low HOMO-LUMO gap, and by extension a low optical gap, ensures the generated oligomers are promising materials for organic photovoltaics, and a low dipole moment in the ground state is desired as it has been shown that this can help with directing self-assembly towards supramolecular arrangements that promote macroscopic properties such as charge-carrier mobility.<sup>33</sup> Our approach would be equally applicable to a focus on a different region of property space and we would note that for optoelectronic device applications such as OPVs and OLEDs, it is typical for there to be multiple material properties and device characteristics contributing to high performance, and these would need to be considered and appropriately weighted on a case-by-case basis. We discuss the challenges for further extension of the method in the discussion.

We present an overview of our approach for generating novel donor–acceptor oligomers with targeted electronic properties in Fig. 1. In the following sections, we will describe the origin



**Fig. 1** Our workflow for the discovery of novel donor–acceptor oligomers. An RNN with randomized parameters was built, and the General RNN was obtained by training the random RNN with the General Database of the ChEMBL library. The specialized RNN was developed by tuning the General RNN using the Transfer Database that only contains donor–acceptor oligomers, and then used to generate novel donor–acceptor oligomers.

of our datasets, how we first trained a general RNN and then used unsupervised cluster detection to uncover different clusters of molecules in a database of donor–acceptor oligomers. Next, we compared the performance of transfer learning models built from different transfer databases and finally validated the performance of the newly generated oligomers.

## Datasets

The task for molecular discovery using deep generative models can be divided into two parts; (i) learning the correct representation of molecules, for instance the valid SMILES representation, and (ii) learning the required structural property relationship of the molecules in order to generate novel functional molecules. To successfully carry out the first stage of the task, it is necessary to train the model on an extensive and varied database from which the syntax of valid SMILES can be learned. For the training of such an RNN model, which will hereafter be referred to as the ‘General RNN’, we used the GuacaMol Training SMILES database<sup>34</sup> as published by Brown *et al.*,<sup>35</sup> which contains 1.2 million SMILES strings from the ChEMBL database. And we refer to the training set for the General RNN hereafter as the ‘General Database’. For the TL model, the ‘Database of organic donor–acceptor molecules’ from the Computational Materials Repository<sup>31</sup> was used and is referred to hereafter as the ‘Transfer Database’. The Transfer Database originally contained 5419 molecules, but after removing candidates that contained characters not present in the General Database and those for which density functional theory (DFT) calculations we carried out to characterise the molecular properties (see below) failed to converge, we were left with a final Transfer Database of 5024 molecules. The average length of the SMILES in the General Database is 47.6, while the average length of SMILES strings in the Transfer Database is 103.3, so it is of interest how well the General RNN

will be able to be applied to the more complex molecules in the Transfer Database.

The values of the Kohn–Sham HOMO–LUMO gaps, which we use to approximate the optical gaps, and dipole moments in the database of organic donor–acceptor molecules were previously calculated using the B3LYP functional.<sup>36–38</sup> However, due to the exponentially decaying nature displayed by this exchange–correlation, instead of the correct  $r^{-1}$  behaviour at long distances, the excitation energies can be expected to be underestimated and the polarizability overestimated.<sup>39,40</sup> We therefore performed additional calculations to evaluate the electronic properties of the oligomers in the Transfer Database with a long-range corrected DFT functional that does not suffer from this issue. Firstly, we generated 100 conformers of each oligomer using the RDKit ETKDG method<sup>41</sup> and evaluated the conformers’ energies using UFF.<sup>42</sup> The lowest energy conformation was then geometry optimised by using the GFN-xTB2 method as implemented in xTB.<sup>43</sup> The optimisation was considered complete when a threshold of  $8 \times 10^{-4}$  Hartrees per atomic unit length in forces and  $1 \times 10^{-6}$  Hartree in energies was reached, all conformations were confirmed to be true minima. We opted to optimise the geometry of the molecules using GFN-xTB2 rather than with DFT calculations due to the large number of molecules in the Transfer Database. A benchmark between geometries optimised using GFN-xTB2 and DFT ( $\omega$ B97X-D3/def2-TZVP) is reported in section 5 of the ESI,<sup>†</sup> showing that GFN-xTB2 provides reasonable geometries at a much reduced computational cost. The optical and electronic features such as the HOMO–LUMO gap and polarizabilities were then computed by employing the long-range corrected  $\omega$ B97X-D3 functional<sup>44</sup> as implemented in ORCA.<sup>45</sup> The ground and excited state properties were computed using the def2-TZVP basis set and by employing the simplified Tamm–Dancoff approach (sTDA).<sup>46–49</sup> Excited states with an excitation energy of lower than 10.0 eV were computed, corresponding to



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access to massively parallel computer architectures, was not viable. Instead, to assess the properties of the generated molecules at acceptable computational cost, the HOMO–LUMO gaps and dipole moments were calculated using supervised gradient boosted decision tree (GBDT) models trained on the Transfer Database. The GBDT algorithm uses a weighted ensemble of decision trees to fulfill regression or classification tasks. The GBDT model was trained on the Transfer Database, with the database randomly divided into training (80%, 4019 molecules) and test (20%, 1005 molecules) sets, and the Morgan fingerprints calculated using RDKit as the molecular input feature. Morgan fingerprints with varied length (512, 1024, 2048) and radius (2, 4, 6) were used for the molecular fingerprinting. The GBDT models were optimised so as to minimise the mean squared error between the predicted values and the true values in the training set. The GBDT models were then used upon the generated unique and novel molecules from TL to predict their HOMO–LUMO gaps and dipole moments. Those molecules with a HOMO–LUMO gap less than 2 eV and dipole moment less than 2 Debye were deemed ‘promising’, as they were the target of our study. In order to validate the ‘promising’ molecules identified using the GBDT models, 90 ‘promising’ molecules were randomly sampled from the ‘promising’ generations and their HOMO–LUMO gaps and dipole moments were calculated using DFT calculations with the  $\omega$ B97X-D3 functional, using the setup as described above.<sup>44</sup>

## Results and discussion

### Supervised machine learning model of electronic properties

Supervised GBDT models were developed to evaluate the donor–acceptor oligomers generated from the generative RNNs. It was found in this study that a GBDT model using Morgan fingerprint with length 1024 and radius 2 had the lowest error in terms of predicting the properties of the oligomers in the test set. The comparison between the  $\omega$ B97X-D3-

calculated electronic properties and those predicted using the GBDT models on the test set (20% of the Transfer Database, 1005 molecules) is shown in Fig. 2. The mean absolute error of the GBDT prediction for HOMO–LUMO gaps is 0.09 eV and for dipole moments is 1.31 Debye. While the GBDT model is therefore reasonably accurately predicting the HOMO–LUMO gap of the molecules, the accuracy of the prediction for the dipole moments was significantly lower. Previously, graph neural network models using molecular graphs as feature vector inputs, such as the SchNet,<sup>55</sup> MEGNet<sup>56</sup> were trained to predict the dipole moments of functional molecules with good accuracy. However, when we tested these models for our study, the mean absolute error of the dipole moment predictions was exceptionally large (over 10 Debye). The poor performance of the graph neural networks on the Transfer Database was probably due to the fact that such models were trained and tested against the QM9 dataset,<sup>57</sup> which contains only molecules with no more than 9 heavy atoms. However, the number of heavy atoms in molecules in our Transfer Database ranges from 20 to 180, and application of such graph convolution networks was therefore inadequate due to the complexity of molecules in the Transfer Database. We trialled other models, such as random forest, and other fingerprints, such as Molecular ACCess System (MACCS) keys,<sup>58</sup> but these performed less well than our selected model.

Here, we aim to discover as many ‘promising’ oligomers as possible for further validation, thus recall (identifying ‘promising’ oligomers) was pursued at the sacrifice of precision (labelling ‘promising’ oligomers correctly). The mean error of GBDT prediction for dipole moment was 0 Debye, with a standard deviation of 1.83 Debye. The molecules generated *via* TL were fed into the GBDT models to predict their electronic properties. Molecules with a GBDT-predicted dipole moment of lower than 3.66 Debye (corresponding to 0.9 standard deviation above the mean error of 0 Debye) and a HOMO–LUMO gap lower than 2.0 eV were considered as potential ‘promising’ oligomers. The choice of 3.66 Debye as cutoff for ‘promising’ oligomers implies a higher false positive rate and lower false

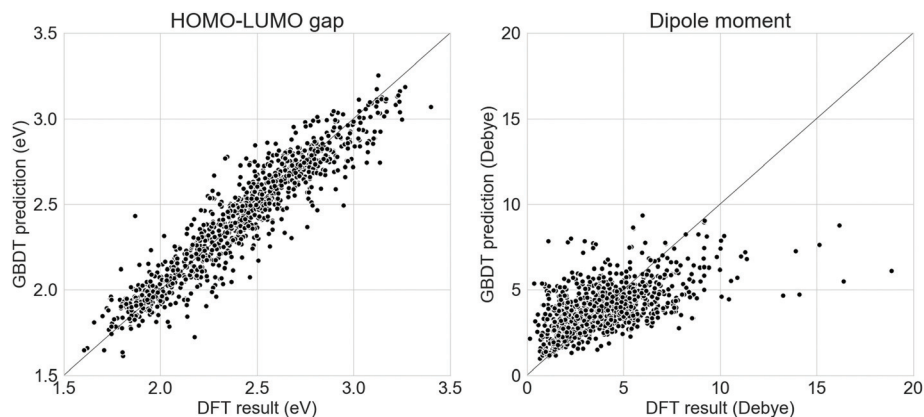
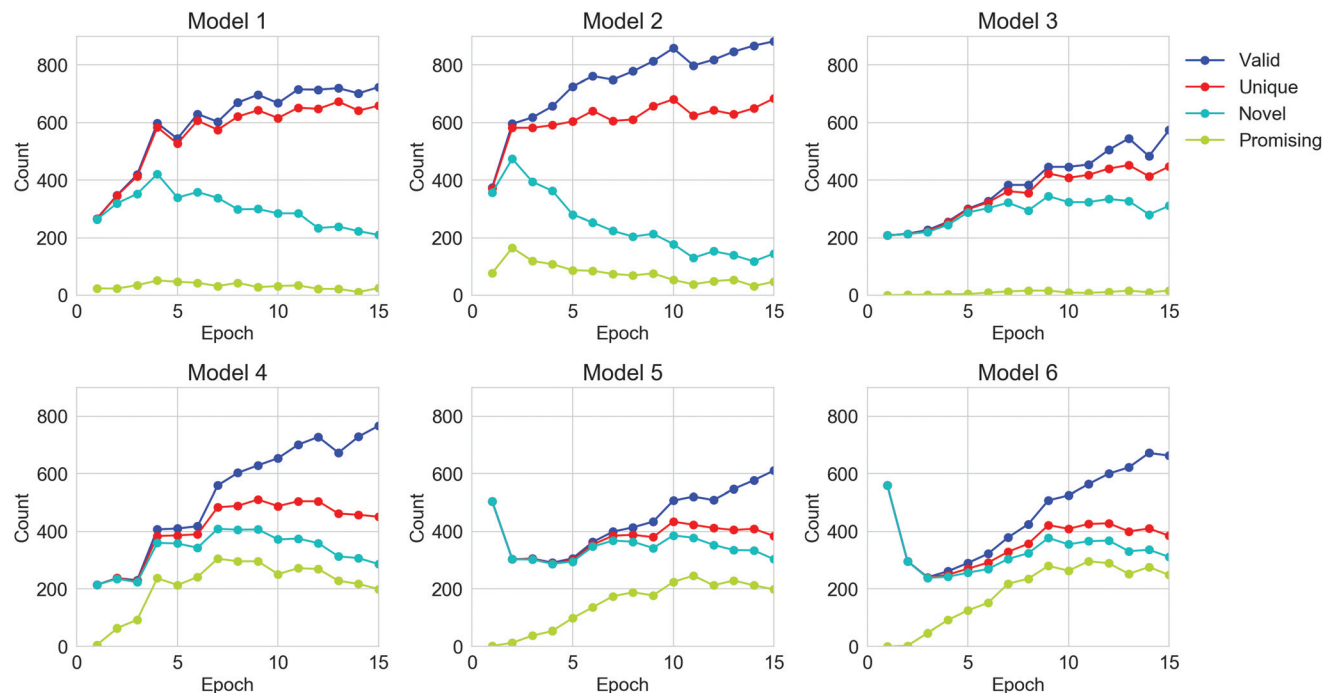


Fig. 2 Relationship between the DFT calculated electronic properties and GBDT predictions on the test set of the Transfer Database for (left) the HOMO–LUMO gap and (right) the dipole moment. The line of  $y = x$  is shown in both plots.



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**Fig. 4** The number of valid, unique, novel and ‘promising’ oligomers generated for the six TL models along the epochs of TL. An epoch of transfer learning for a model here refers to passing the corresponding training set through the TL model once.

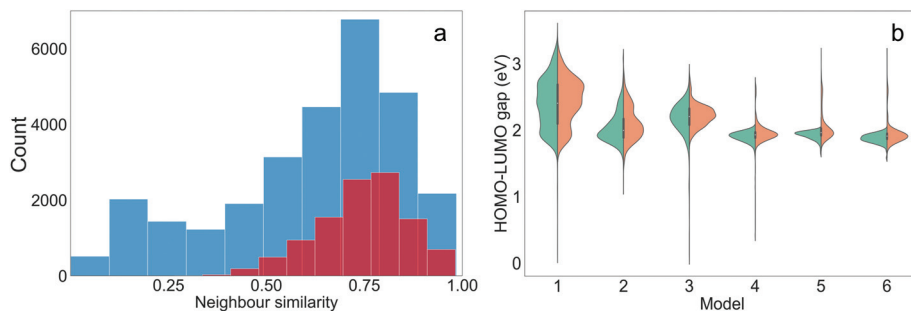
For Models 1, 2 and 4, the number of novel SMILES dropped in the later epochs of TL. The fact that the uniqueness and novelty do not increase despite the increasing validity indicates that the TL models were trying to ‘remember’ certain valid SMILES strings in the training sets rather than learning the general rule of the SMILES format, which can be referred to as overfitting of the training set. This can be rationalised in terms of the nature of the molecules in the Transfer Database, which are considerably different from the ones observed in the ChEMBL database. Therefore, all the parameters in the General RNN had to be refined during the TL to ‘learn’ the features of the SMILES strings in the Transfer Database. Due to the limited size of the training sets for TL, a certain extent of overfitting could not be avoided. It can also be observed that Models 4, 5 and 6, which only used molecules with the target properties for the TL, were more powerful in generating ‘promising’ oligomers compared to Models 1, 2 and 3. This is an indication that the electronic properties of the training sets were ‘learned’ *via* TL, which will be discussed in the following section. According to the trends of performance of the models in Fig. 4, epochs beyond epoch 10 have not improved the models in generating more unique novel ‘promising’ oligomers, thus the parameters in the TL RNNs should be frozen beyond epoch 10 so that the sampling of ‘promising’ SMILES is more efficient.

## Learning structural and electronic properties

It is interesting to assess to what extent the structural properties of the different training sets were ‘learned’ through TL. The training molecules with the highest Tanimoto similarities

to the generated molecules were defined as the nearest neighbours of the generated molecules. The distribution of the neighbour similarities of all generated molecules and the ‘promising’ molecules from the six TL models (those with target properties) is shown in Fig. 5(a). The mean neighbour similarity of all the generated ‘oligomers’ and the ‘promising’ oligomers are 0.62 and 0.74, respectively. Examples of pairs of generated molecules and molecules in the Transfer Database with different levels of similarities of 0.62 and 0.74 are shown in Fig. S5,<sup>†</sup> to allow the reader to visualise what these values correspond to chemically. It can be seen that the novel oligomers with 0.62 and 0.74 neighbour similarity were generated by different levels of atom replacement on the corresponding neighbours, indicating that the molecular structural property of the training sets were ‘learned’ from the TL process, especially by the ‘promising’ oligomers. The similarities of the generated molecules and their neighbours increased as TL proceeded (Fig. S6<sup>†</sup>), and the median of the neighbour similarities at epoch 10 were larger than 0.6 for all models (Fig. 5(b)).

In addition to learning the structural properties of the training sets, another task for the TL was to learn the electronic properties of the training molecules. Since the properties of the generated molecules were evaluated using the GBDT model and accurate prediction of dipole moment was not achieved in this study, only the HOMO–LUMO gaps were examined. The distributions of the HOMO–LUMO gaps of the molecules generated from the TL models at the 10th epoch are shown in Fig. 5(b) and shown for each epoch in Fig. S7.† For Models 4, 5 and 6, the HOMO–LUMO gaps of the vast majority



**Fig. 5** (a) Distribution of the neighbour similarities of all the generated oligomers (blue) and the 'promising' oligomers (maroon); (b) distribution of the HOMO–LUMO gaps of the molecules generated from the six TL models on the 10th epoch (red) compared to the corresponding training sets (green).

of generated molecules are lower than 2.0 eV, and therefore the chance of obtaining 'promising' oligomers increased. Models 1 through 6 had varied distributions of HOMO–LUMO gaps and all of these specific distributions were 'learned' by the corresponding TL models. Therefore, the HOMO–LUMO gaps of the generated molecules can be tuned by sampling different subsets of the training database of interest.

### Chemical space exploration

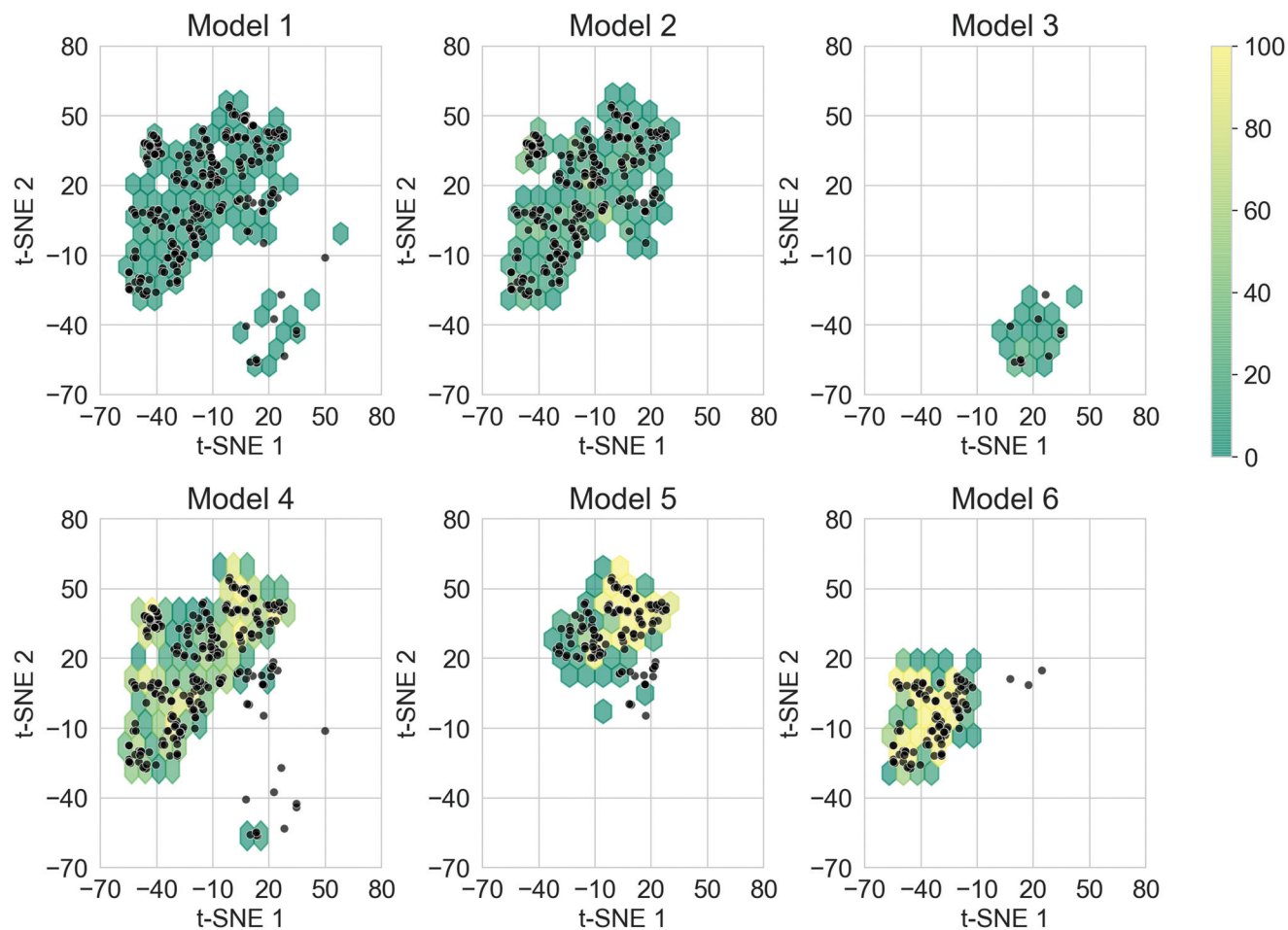
The ability for deep generative models to sample larger chemical space while obtaining oligomers with desirable properties is also important. This is a particular goal of the study here – to see whether our approach can move beyond traditional substitution strategies well established in the material chemistry community, to uncover 'wild cards' that might suggest alternative molecular replacements or a series of fragment alterations. The training sets of the TL models covered different regions of the chemical space, and it was expected that each of the models would cover the corresponding chemical space. In addition, covering chemical space beyond the training sets could lead to the discovery of novel donor–acceptor oligomers that had not been considered. To create a qualitative visualisation of the chemical space covered by the molecules in this study, the t-SNE projections of the fingerprints of the molecules generated from the six TL models, together with the fingerprints of the molecules in the corresponding training sets are shown in Fig. S8.† The chemical space of each training set has been thoroughly explored by the corresponding TL model, as well as unexpected regions of the chemical space of the training sets having also been covered, especially for Models 4, 5, and 6. It was thus possible to generate donor–acceptor oligomers that are not directly related to those in the Transfer Database from the TL models.

Merely covering more chemical space does not ensure the discovery of novel 'promising' donor–acceptor oligomers; it is possible that oligomers in the newly explored regions do not exhibit the preferred electronic properties. To compare the chemical space covered by the 'promising' oligomers, the t-SNE projections of only the 'promising' training and generated oligomers are shown in Fig. 6. Representative molecules were sampled from the 'promising' oligomers generated from

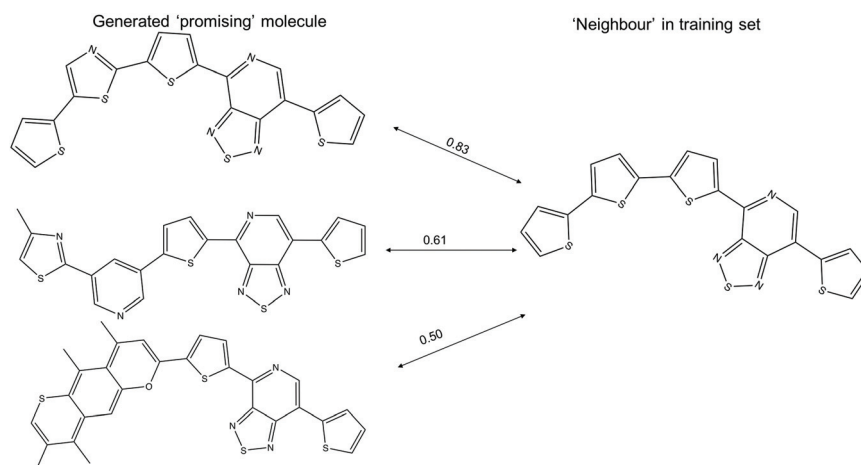
each TL model, and the structure of such molecules and their t-SNE projection values are shown in Fig. S9.† It can be seen from Fig. 6 that 'promising' oligomers generated from the TL explored well the corresponding chemical spaces of their respective training sets. As demonstrated in Fig. 6 and S9,† the 'promising' oligomers generated from Model 3 occupy a different region of chemical space compared to the other five models. In addition, oligomers generated from Models 5 and 6 occupied different sub-parts of the chemical space than Model 4. It is thus possible to explore particular regions of interest in chemical space by tuning the training sets for TL with the assistance of unsupervised cluster detection. However, the chemical spaces covered by the 'promising' oligomers were more conservative than that covered by all the generated molecules, as seen by higher neighbour similarity in Fig. 5a. The distribution of the neighbour similarities of generated molecules with their corresponding training sets for each of the TL models are shown in Fig. S10,† and the trend of 'promising' oligomers having higher neighbour similarities was found for all six models. Such results indicate that the excessive regions of chemical space explored by the TL models had limited contributions in terms of providing 'promising' oligomers, and the trade-off between exploring unseen regions of the chemical spaces and generating a greater percentage of more 'promising' oligomers is something to bear in mind.

The t-SNE projections in this study are the two-dimensional projection of the 1024-bit molecular fingerprints, allowing one to visualise the distribution of the high dimensional fingerprints. The computed neighbours in the t-SNE plots could result from either structural similarity (as intended) or from a crowding effect of the low dimensional representation of high dimensional data. Examples of 'promising' generated molecules with high and low similarity with their nearest neighbour in the training sets are shown in Fig. 7. A 'promising' oligomer with high similarity to a neighbour could be generated by simple atom replacement, while a 'promising' oligomer with a low similarity to a neighbour less than 0.6 involves multiple alterations on the neighbour molecule, which would be difficult to suggest by using traditional experimental functionalisation strategies. We obtained about 1300 'promising' oligomers with similarity to a neighbour lower than 0.6 with the





**Fig. 6** Hexagonal binning plot of the t-SNE projection of the fingerprints of the 'promising' molecules generated from the TL models. Colours of the hexagons represent the density of generated 'promising' oligomers in each hexagon according to the colour bar. The 'promising' molecules in the corresponding training sets are shown as black points. t-SNE 1 and t-SNE 2 correspond to the first and second dimensions of the 2-D projection of the molecular fingerprints.



**Fig. 7** Example of three 'promising' oligomers generated from the TL and their nearest neighbour in the training set, as calculated using the Tanimoto similarity criterion. The Tanimoto similarities between the donor-acceptor oligomers are shown above the arrows. It should be noted that these 2-dimensional structures do not show the exact 3-dimensional conformation of the molecule used in the calculations.



Within the predicted structures, one can find known units, such as thiophene and furan, which have been previously used in the construction of donor-acceptor oligomers. The deep generative model also performed interesting substitutions such as fluorination or methylation. These strategies are commonly found in the literature and can be categorised as traditional substitutions in donor-acceptor oligomers. Similarly, completely changed small units such as selenophene (e.g. Fig. 8o) can be found within the set of suggested molecular transformations executed by the deep generative model. Analogously, one can observe frequently employed units for donor-acceptor molecules such as benzo[1,2-*b*:4,5-*b'*]dithiophene (BDT)<sup>62</sup> or pyridal[2,1,3]thiadiazole(PyT).<sup>63</sup> However, the original composition of the molecule is not preserved in all cases, with the molecules displaying interesting atomic substitutions in the core such as BDT selenium (Fig. 8i) or oxygen substituted (Fig. 8v). Similar molecules have been experimentally synthesised and characterised as organic semiconductor with enhanced charge-carrier mobility as a consequence of such replacements.<sup>64</sup> These previous findings provide an argument in favour of the capability of the deep generative model not only to offer an effective procedure to

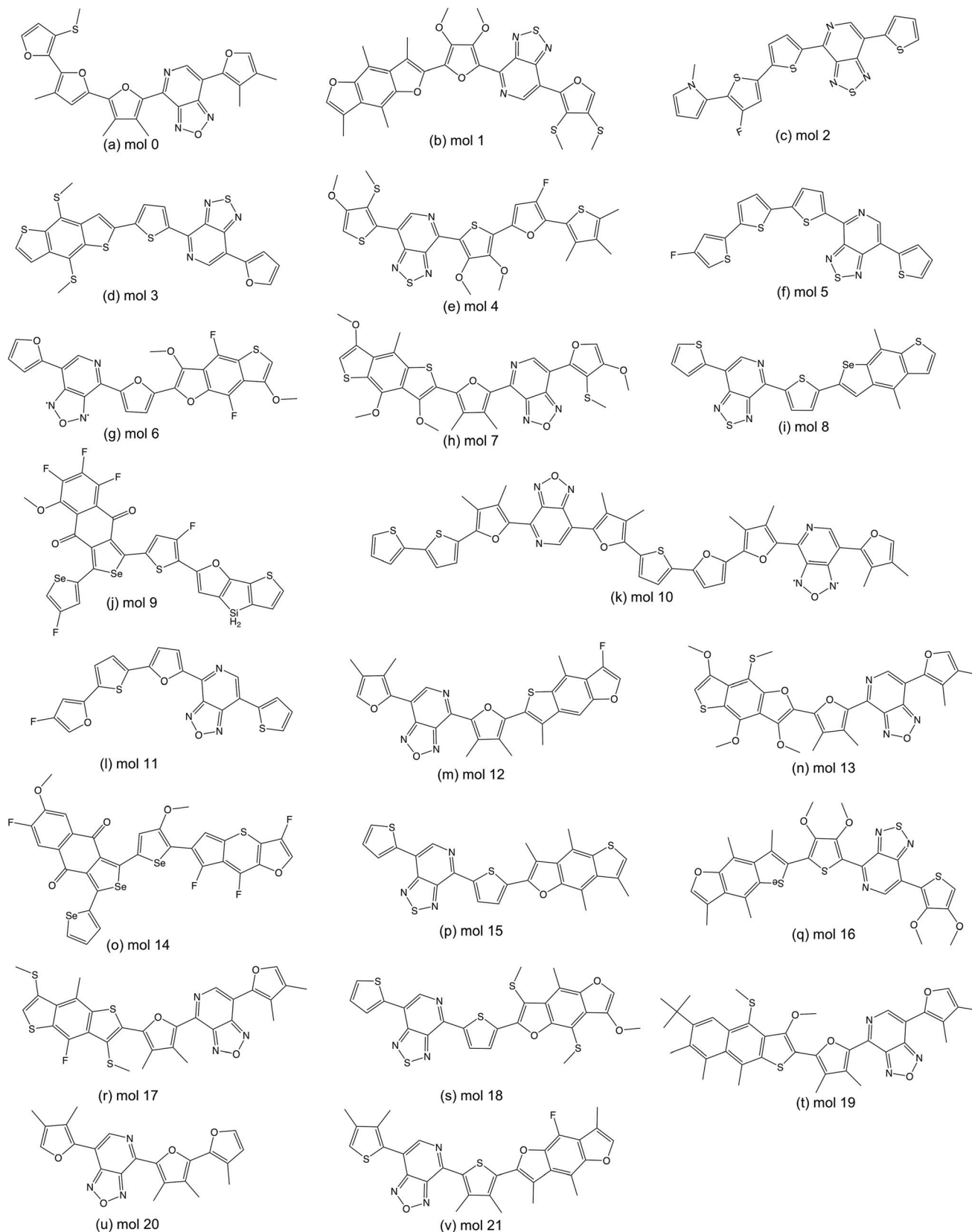
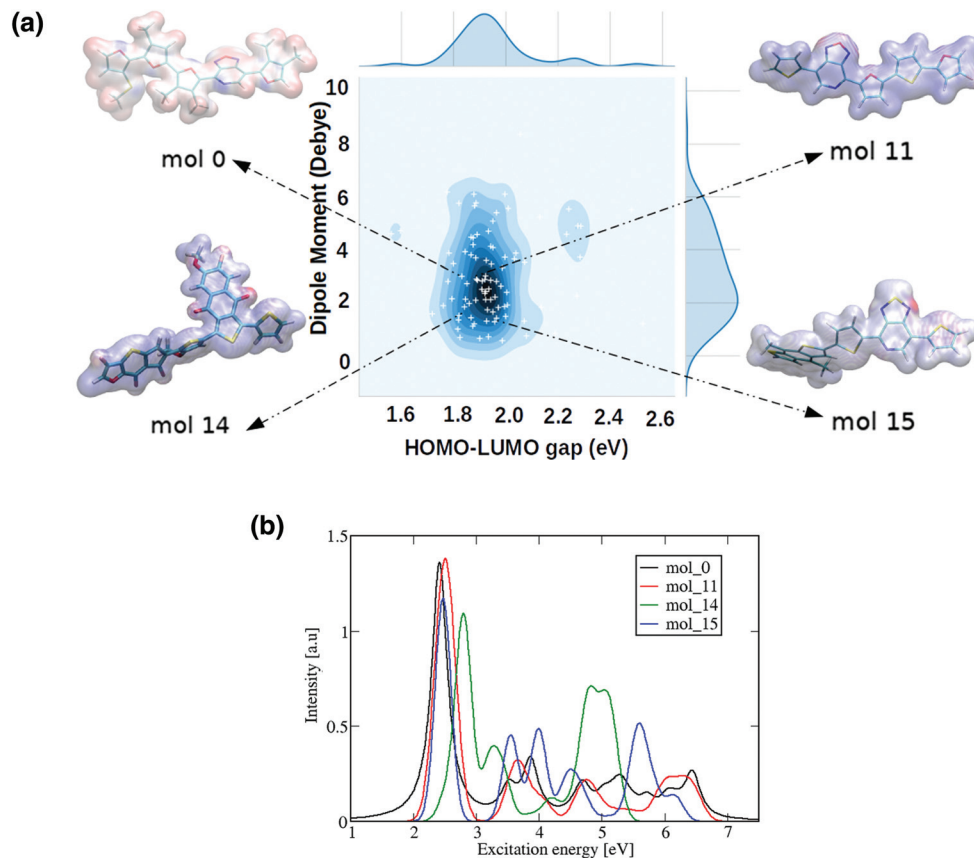


Fig. 8 The subset of 'promising' oligomers validated by DFT calculations.





**Fig. 9** (a) Distribution of the  $\omega$ B97X-D3 calculated HOMO–LUMO gaps and dipole moments of 90 randomly selected ‘promising’ oligomers generated from our trained deep generative model. Each newly produced donor–acceptor oligomer is represented as a white cross in the 2-D distribution, where darker regions represent a greater density of molecules found. The example molecules are shown with their molecular electrostatic potential, red represents more electron-rich regions and blue more electron-poor. (b) Computed UV-Vis spectra for the 4 selected oligomers.

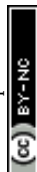
explore the chemical space, but also as a tool to provide new ideas and paths for novel atomic substitutions.

The TL model in this work is not limited to the generation of novel donor–acceptor oligomers as organic semiconductors; with proper tuning of the training sets for TL, electronic materials for other applications could be obtained. For example, the power conversion efficiency of organic solar cells is qualitatively related to HOMO energy of the donor, LUMO energy of the acceptor, and bandgap of the donor according to the Scharber model;<sup>65</sup> OLED materials require low singlet–triplet gap and minimized spatial overlap of HOMO and LUMO.<sup>66,67</sup> If such properties can be described with a supervised learning model from molecular information contained in the SMILES representation, the TL models can ‘learn’ the relevant properties with corresponding tuning of the training sets. In addition, when multiple electronic properties need to be optimized to improve device performance, the optimization can be assisted with a sampling approach such as an evolutionary algorithm (EA). In this fashion, we believe that the low precision and high recall model in discovering novel donor–acceptor oligomers can be used as a new methodology to discover and enhance selected families of new materials.

There are challenges in applying this type of approach to more complex properties beyond simple single molecule properties, particularly for applications based on combinations of properties. The first bottleneck to focus on to test expanding the approach is the generation of further training data for organic materials, such as to include excited state properties or, even more challenging, properties or behaviours beyond the single molecule level. While calculation of these properties *ab initio* for the requisite large number of systems is computationally demanding, it is pleasing to note recent additions to open-source databases in this area, which will open up new opportunities.<sup>32</sup> Of course, device characteristics that are not predominantly linked to molecular features, such as preparation conditions and sample history that influence the device microstructure, are beyond the scope of what could be screened for by this approach. However, identification of promising molecules is still an important starting point.

## Conclusions

In attempting to discover new molecular building blocks with promising properties for materials, a limitation can come



An ideal generative model for molecular discovery would enable exploration of wider chemical space while retaining desired properties. However, it was found in this study that there is some degree of trade-off between exploration of chemical space and the optimisation of electronic properties. ‘Wild’ modifications to the training molecules were observed, likely modifications that would not be proposed by chemists, but such molecules did not generally exhibit satisfactory electronic properties. The generated ‘promising’ oligomers, with target properties, were more ‘conservative’ neighbours of the oligomers in the training set. The two factors need to be balanced in future molecular discovery tasks, although there is always the possibility that we are seeking a ‘needle in a hay stack’ – an extreme modification that still has the desired properties and has truly allowed us to move out of the region of chemical space that would be considered by chemists alone.

There are no conflicts to declare.

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