

Machine Learning Transition Temperatures from 2D Structure

Andrew E. Sifain,[†] Samuel H. Yalkowsky,[‡] Betsy M. Rice,[†] and Brian C. Barnes^{*,†}

[†]*CCDC U.S. Army Research Laboratory, Aberdeen Proving Ground, MD 21005, USA*

[‡]*Department of Pharmaceutics, College of Pharmacy, University of Arizona, Tucson, AZ
85721, USA*

E-mail: brian.c.barnes11.civ@mail.mil

Abstract

A priori knowledge of physicochemical properties such as melting and boiling could expedite materials discovery. However, theoretical modeling from first principles poses a challenge for efficient virtual screening of potential candidates. As an alternative, the tools of data science are becoming increasingly important for exploring chemical datasets and predicting material properties. Herein, we extend a molecular representation, or set of descriptors, first developed for quantitative structure-property relationship modeling by Yalkowsky and coworkers known as the Unified Physicochemical Property Estimation Relationships (UPPER). This molecular representation has group-constitutive and geometrical descriptors that map to enthalpy and entropy; two thermodynamic quantities that drive thermal phase transitions. We extend the UPPER representation to include additional information about sp^2 -bonded fragments. Additionally, instead of using the UPPER descriptors in a series of thermodynamically-inspired calculations, as per Yalkowsky, we use the descriptors to construct a vector representation for use with machine learning techniques. The concise and easy-to-compute representation, combined with a gradient-boosting decision tree model, provides an appealing

framework for predicting experimental transition temperatures in a diverse chemical space. An application to energetic materials shows that the method is predictive, despite a relatively modest energetics reference dataset. We also report competitive results on diverse public datasets of melting points (*i.e.*, OCHEM, Enamine, Bradley, and Bergström) comprised of over 47k structures. Open source software is available at <https://github.com/USArmyResearchLab/ARL-UPPER>.

Introduction

Transition temperatures such as melting and boiling point are fundamental thermodynamic properties that influence applications including the design of pharmaceuticals,^[1] melt-casted explosives,^[2-4] and energy harvesting materials.^[5,6] Discovering materials with acceptable transition temperatures is difficult, in part because they are not known prior to synthesis and measurement. Theoretical prediction of such properties may reduce the chemical space of candidate compounds and expedite discovery. Thus, a great amount of effort has been expended in both high-fidelity physics-based simulations and in regression-based modeling of phase transition temperatures. The main advance in this work is the extension of a set of thermodynamically-inspired descriptors, combined with a gradient-boosting machine learning technique to create a new, accurate, and rapid model for predicting phase transition temperatures.

Atomistic simulations of phase transitions are computationally demanding. Furthermore, in the case of melting, such simulations often require knowledge of crystal structure,^[7-10] thus limiting their use during materials discovery. An alternative approach is to utilize surrogate models that map descriptors to reference data. Linear regression-based quantitative structure-property relationships (QSPRs) have had success,^[11-16] but by design cannot discover a new, nonlinear mapping between descriptors and melting point. Nonlinearity may be provided in advance using knowledge of relevant physics and chemistry. Nonlinear machine learning (ML) algorithms have no such requirement for prior knowledge of nonlinear relation-

ships^[17–20] and when carefully applied, possess other advantages such as transferability to species outside of the reference dataset and computational efficiency.^[21–23] An accurate ML model may help identify target compounds and circumvent expensive atomistic simulations.

ML is becoming an indispensable and versatile tool in the chemical sciences^[24] with application to molecular properties,^[25–31] spectroscopy,^[32–36] and chemical synthesis.^[37–40] Model performance depends concomitantly on the learning algorithm, the quality of the reference training set, and the input representation of the chemical system.^[41–47] The focus of this paper is on the combination of a molecular representation, derived from a microscopic basis, with a gradient-boosting algorithm in order to predict macroscopic properties such as melting and boiling point.

The molecular representation reflects the level of chemical resolution needed for predicting the target property.^[48,49] For quantum molecular properties, geometry and atom type are typically chosen as input because even the slightest changes in geometry can affect the wavefunction and its observables.^[50–53] On the other hand, macroscopic properties are more robust to higher-level or coarse-grained descriptors.^[54–58] In the case of melting, for example, a molecular crystal may be identified by descriptors^[59–62] derived from its repeating structural unit.^[20] The mapping of a multi-molecule process from a single molecule is ambiguous however, thus emphasizing the importance of suitable descriptors.

The proposed representation is both inspired by and is an extension of the UPPER method of Yalkowsky and coworkers.^[63] UPPER, which stands for Unified Physicochemical Property Estimation Relationships, is a comprehensive QSPR based on intuitive and thermodynamic relationships relating phase transition properties to one another including transition enthalpies, entropies, and temperatures. The method extends to other properties including heat of sublimation and solubility. UPPER’s descriptors are derived purely from 2D structure (*i.e.*, Simplified Molecular-Input Line-Entry System or SMILES^[64]), allowing for simple and fast property prediction following regression with a learning algorithm. While it is a challenge to train models to limited and noisy experimental data, we find that this molecu-

lar representation combined with gradient boosting,^[65] provides an appealing framework for accurately predicting experimental transition temperatures in a diverse chemical space. Our software is freely available at <https://github.com/USArmyResearchLab/ARL-UPPER>.

Methods

We provide an overview of the UPPER method for transition properties and the underlying descriptors that will be supplied as input for ML. The addition of heat to a thermodynamic system increases its temperature. When a first-order phase transition occurs, the temperature levels off, remaining constant even as the system continues absorbing heat. Intermolecular binding forces are overcome as heat converts the state of the system from solid to liquid or liquid to gas. When the two phases of matter are in equilibrium with one another, the Gibbs energy is $\Delta G_{tr} = 0$. The first-order transition temperature can therefore be written as

$$T_{tr} = \frac{\Delta H_{tr}}{\Delta S_{tr}}, \quad (1)$$

where ΔH_{tr} and ΔS_{tr} are enthalpy and entropy of transition, respectively. Here, ΔH_{tr} is the amount of heat absorbed per mole for the transition to take place, while ΔS_{tr} is the change in the system’s entropy. UPPER defines analytical forms for ΔH_{tr} and ΔS_{tr} with parameters determined using separate linear regression analysis of composition for ΔH_{tr} and geometry for ΔS_{tr} .

Group-Constitutive Descriptors

Within UPPER, enthalpy is computed as a group-constitutive property,

$$\Delta H_{tr} = \sum_i p_i n_i, \quad (2)$$

where p_i is the contribution of the i -th fragment and n_i is the number of i fragments in the molecule. Fragmentation is based on the scheme proposed in Ref. [66], where each fragment consists of the least number of atoms (including all carbons, hydrogens, heteroatoms, and nonbonded electrons) that are not separated by an isolating carbon. An isolating carbon is a carbon that is not doubly or triply bonded to a heteroatom. Such carbons and their attached hydrogens are considered hydrophobic fragments and the remaining groups of atoms are polar fragments. Fragments are represented by their SMARTS (SMiles ARbitrary Target Specification) strings and subsequently assigned to an environmental group (Fig. 1). Environmental groups (Table 1) reflect interactions such as the connectivity and hybridization that each fragment has with its neighboring fragments. New environmental groups added in this work include YYY, YYYY, YYZ, and YYYYZ. These groups generalize the featurization to fragments with several sp^2 -hybridized bonds. Throughout this work, we use our extended set of descriptors as described in Table 1.

Table 1: Environmental groups.

Group	Description
X	Group bonded to only sp^3 atoms
Y	Group singly bonded to 1 sp^2 atom
YY	Group bonded to 2 sp^2 atoms
YYY	Group bonded to 3 sp^2 atoms
YYYY	Group bonded to 4 sp^2 atoms
Z	Group bonded to 1 sp atom
YZ	Y and Z group
YYZ	YY and Z group
YYYYZ	YYY and Z group
RG	Group within an aliphatic ring
FU	Aliphatic bridge-head group
AR	Group within an aromatic ring
BR2	Aromatic carbon shared by 2 rings
BR3	Aromatic carbon shared by 3 rings
BIP	Central carbon in biphenyl substructure

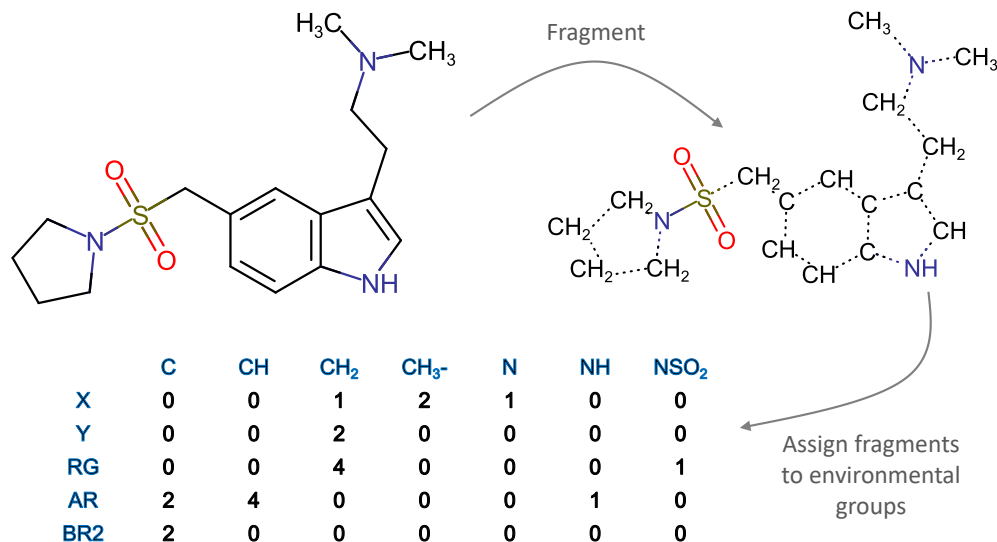


Figure 1: 2D structure of almotriptan molecule fragmented according to the isolating carbon method. Dashed lines represent broken bonds. Fragments (actually labeled by SMARTS strings in the software to avoid ambiguity) are then assigned to environmental groups.

Geometrical Descriptors

Entropy depends on molecular geometry and encodes translational, conformational, and rotational changes of a molecule that affect properties such as packing efficiency and the likeliness for initial and final states of a phase transition to exist. Entropy is given by

$$\Delta S_{tr} = \Delta S_{tr}^{trans} + \Delta S_{tr}^{conf} + \Delta S_{tr}^{rot}. \quad (3)$$

Components of ΔS_{tr} are computed from geometrical descriptors (descriptions below): eccentricity (ϵ), flexibility (ϕ), and symmetry (σ).

Eccentricity is computed as the sum of atoms in and directly attached to aromatic rings. It is a qualitative measure of the packing efficiency since flat molecules tend to have less than average free volume due to their efficient packing, requiring more energy and a higher temperature to melt. Conversely, crystals made up of spherical molecules pack less efficiently and are more prone to attaining their free rotation.

Flexibility is a measure of the internal conformational freedom of a molecule. Flexible

molecules tend to have a greater entropy change during melting than rigid molecules. In UPPER, flexibility is calculated by an *ad hoc* expression uniting flexible segments,

$$\phi = 0.3\text{ROT} + \text{LINSPP3} + 0.5(\text{BRSP3} + \text{SP2} + \text{RING}) - 1 \quad (4)$$

where LINSPP3 is the number of nonring, nonterminal, nonbranched sp^3 atoms, ROT is the extra entropy produced by freely rotating sp^3 atoms and is calculated as $\text{ROT} = \text{LINSPP3} - 4$, BRSP3 is the total number of nonring, nonterminal, branched sp^3 atoms, SP2 is the number of nonring, nonterminal sp^2 atoms, RING is the number of single, fused, or conjugated ring systems. Compounds with negative ϕ computed using Eq. 4 are assigned ϕ equal to zero.

Symmetry affects entropy and in particular the melting point. Symmetric molecules have a higher probability of being in the right orientation for crystallization than nonsymmetrical molecules of roughly the same weight. As a result, they tend to have a lower entropy of melting and higher melting point. Here, the method to compute σ (see Ref. [67]) operates by locating the center or centers of graphical symmetry and the equivalence classes of atoms connected to those centers. σ is estimated based on a few simple rules determined by the hybridization of the graphical center as well as the number of connected atoms and their equivalence classes.

UPPER-Inspired Fingerprint

A combination of group-constitutive and geometrical descriptors make up what we call an UPPER-inspired fingerprint. It is single vector molecular representation, which can be used as input for machine learning techniques. The overall size of this fingerprint depends on the molecules in the dataset, as this affects the types of fragments and environmental groups (Table 1). Figure 2 shows example fingerprints for two molecules.

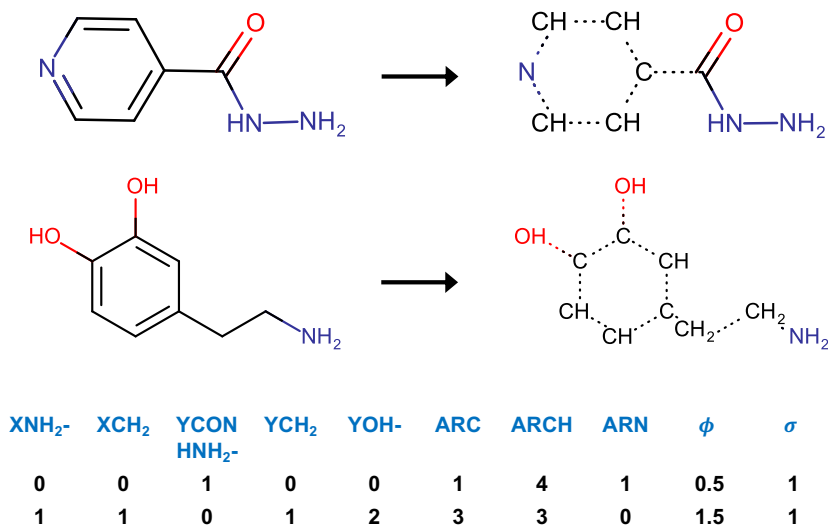


Figure 2: Isoniazid and dopamine molecules fragmented and their UPPER-inspired fingerprints consisting of group-constitutive and geometrical (ϕ , σ , and ϵ) descriptors.

Datasets and Learning Algorithms

The dataset used in this work includes experimental transition enthalpies, entropies, and temperatures for both melting and boiling. Compounds of this dataset include open-chain, aliphatic, and aromatic compounds including polyhalogenated biphenyls, dibenzo-p-dioxins, diphenyl ethers, anisoles, and alkanes. There are a wide variety of functional groups such as alcohol, aldehyde, ketone, carboxylic acid, carbonate, carbamate, amine, amide, nitrile, acetyl, and nitro groups. The minimum, maximum, and mean number of atoms of the dataset are 2 (4), 42 (122), and 12 (24), where values in parentheses include hydrogen atoms. See Supporting Information showing a small subset of the compounds in this dataset as well as distributions of enthalpies, entropies, and temperatures. The exact dataset used is proprietary, supplied by an industrial collaborator of one of the authors. Thus, we cannot provide that particular dataset with this report. However, for the sake of transparency, another dataset that is very similar to the one used here is provided and described in Ref. [68]. This dataset has been collected and provided in our GitHub repository, allowing readers to reproduce our methods using the source code and data provided at the repository.

In order to highlight usefulness of the proposed method of this work, two applications are carried out. The first is to predict melting points of energetic materials. Energetic materials must meet strict criteria to be developed and designated viable for applications. Knowledge of melting temperatures prior to synthesis would be particularly beneficial for the design of melt-casted explosives.^[2-4] A small dataset of energetic materials made up of ~ 130 melting points of nitroaliphatic and nitroaromatic compounds is added to the dataset. Finally, we carry out another application using large and diverse public datasets of melting points, labeled OCHEM, Enamine, Bradely, and Bergström. We refer readers to Refs. [69] and [20] for descriptions of these datasets. Both the energetic and public datasets are provided in the GitHub repository.

Calculations are carried out with two learning algorithms. UPPER is the reference model, where coefficients p_i for enthalpy (Eq. 2) are determined using ridge regression. Ridge regression is a variant of linear regression with regularization to reduce overfitting. Although linear regression is actually used for Yalkowsky’s UPPER,^[63] ridge regression proves to be significantly better on the held-out test sets and thus will be used here as the standard. Entropies are also parameterized using ridge regression. The second model is a variant of Gradient Boosting (GB) called eXtreme GB or XGBoost.^[65] A GB model is an ensemble of decision trees, where subsequent trees are trained to the residual error of the preceding tree.^[70] XGBoost controls overfitting better than GB, giving it strong performance.^[71] An added advantage is XGBoost’s computational speed.^[72] Ref. [72] compares XGBoost to deep neural networks for QSPRs and found that XGBoost achieved the same accuracy of neural networks with significantly less computational resources. XGBoost achieved its results on a single CPU, whereas efficient neural networks generally run on GPUs. This detail is an important practical advantage of XGBoost, especially in the laboratory setting with a standard workstation class computer. Although nonlinear machine learning generally provides more flexibility to learn the input data, it is important to note that the experimental datasets can be rather limited and noisy, greatly influencing a model’s accuracy and transferability.

Thus, the learning algorithms should be adequately assessed. Training details for the models including hyperparametrization are provided in Supporting Information.

Results and Discussion

We compare UPPER using ridge regression (UPPER-RR) and gradient boosting (UPPER-GB). Models of enthalpy (ΔH_{tr}) and entropy (ΔS_{tr}) are compared across these two learning algorithms. Following enthalpy and entropy predictions, we compare transition temperatures (T_{tr}), evaluated using Eq. 1. Our analysis suggests that gradient boosting does not provide significant improvement over ridge regression for enthalpies, entropies, and transition temperatures within the UPPER framework.

The main advance of this work is to use all group-constitutive and geometrical descriptors of UPPER and train directly to T_{tr} with the GB algorithm, eliminating intermediate models for ΔH_{tr} and ΔS_{tr} . We find this approach (ARL-UPPER) predicts T_{tr} to greater accuracy than UPPER-RR and UPPER-GB. Finally, ARL-UPPER is applied to predict the melting points of energetic materials and large public datasets. Throughout this work, data are randomly split into 90% for training and 10% for testing. Prediction errors are quantified by the Root-Mean-Square-Error (RMSE) and the Mean-Absolute-Error (MAE).

Enthalpy

Fig. 3 shows parity plots of enthalpy of melting (ΔH_m) and boiling (ΔH_b). Only group-constitutive descriptors (Table 1) were used in the models of Fig. 3. The results using UPPER-RR and UPPER-GB are comparable, showing that the nonlinear GB algorithm does not provide any added improvement in predicting ΔH_{tr} given group-constitutive descriptors. The prediction accuracy of ΔH_m is not as strong as that of ΔH_b likely due to missed intermolecular interactions in the crystal and liquid phases such as hydrogen bonding. These interactions are not as significant during a liquid-to-gas transition since molecules are more

spatially separated. As a result, ΔH_b is predicted with greater accuracy than ΔH_m (*i.e.*, RMSEs of ~ 2 compared to ~ 4 kJ/mol) using knowledge of only a single molecular unit.

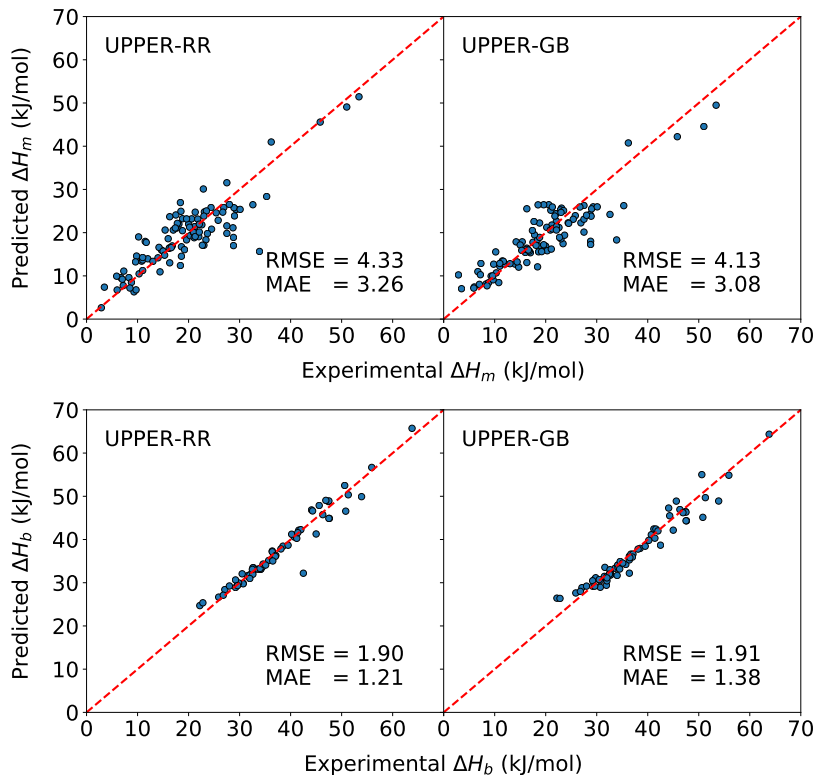


Figure 3: Parity plots of predicted versus experimental ΔH_m (top panels) and ΔH_b (bottom panels) using UPPER-RR (left panels) and UPPER-GB (right panels). Results are of the 10% held-out test set consisting of 108 and 68 molecules for ΔH_m and ΔH_b , respectively. Prediction errors are shown in subpanels. Intermolecular interactions in the crystal-liquid phases (*e.g.*, hydrogen bonding) are not completely accounted for with the group-constitutive descriptors. These missed interactions are likely the cause for the difference in prediction accuracy between ΔH_m and ΔH_b .

Entropy

Parity plots of ΔS_m and ΔS_b are provided in Supporting Information. Similar to ΔH_{tr} , ΔS_{tr} predictions are not significantly improved using GB. Trends in the entropy data can be explained by considering physical differences between melting and boiling. For the majority of the data, ΔS_m is smaller than ΔS_b ; a consequence of the relative change of molar volume during a crystal-to-liquid transition versus a liquid-to-gas transition. In particular, boiling produces a volumetric change of usually more than 20 liters per mol, whereas melting pro-

duces a smaller change of a few cubic centimeters per mole. Further, ΔS_b data are clumped around $85 - 90$ J/mol.K (Trouton’s rule¹), whereas ΔS_m shows more variability with a few compounds in the $150 - 350$ J/mol.K range. The high ΔS_m compounds are long chain-like structures with single bonds that tend to orient themselves in parallel fashion to achieve maximum dispersion in the crystal phase (see Supporting Information). In the liquid phase, their flexible segments have a high degree of conformational freedom. Cross-validation results of ΔH_{tr} and ΔS_{tr} are provided in Supporting Information.

Transition Temperatures

Given trained models of ΔH_{tr} and ΔS_{tr} , the ratio of their predictions (Eq. 1) gives T_{tr} (Fig. 4).² UPPER-GB slightly outperforms UPPER-RR, but the overall prediction error is still quite high (RMSEs of $45 - 55$ K). This result raises the question whether indirectly training to T_{tr} and enforcing Eq. 1 impedes the model’s predictive ability. Constructing the ARL-UPPER model, we may feed the entire set of group-constitutive and geometrical descriptors into the GB algorithm and train the model directly to T_{tr} . In this way, Eq. 1 is not directly enforced, allowing the learning algorithm to choose respective weights over its input features. The same 90-10 split is used here. The parity plots of Fig. 5 suggest that this flexibility is important as RMSEs decrease by about 20 K for T_m and T_b . For reliable evaluation, averaged results (\pm one standard deviation) over a 10-fold cross-validation are provided in Table 2. To identify the added benefit of using a combination of group-constitutive and geometrical descriptors, models were trained solely to group-constitutive descriptors, resulting in slightly increased RMSEs (Table 2).

ARL-UPPER provides a systematic way of assessing new descriptors. For example, Ref. [73] relates molecular mass (m) to T_m using an expression for atomic vibrations in a monatomic solid in a thermal environment. The use of m as a descriptor has been shown

¹Trouton’s rule states that the ratio of the volume of an organic compound as a gas to its volume as a liquid is constant at about 84 J/mol.K.

²Due to limited experimental data, ΔH_{tr} and ΔS_{tr} models were trained to all available data. Therefore, results of Fig. 4 are likely biased.

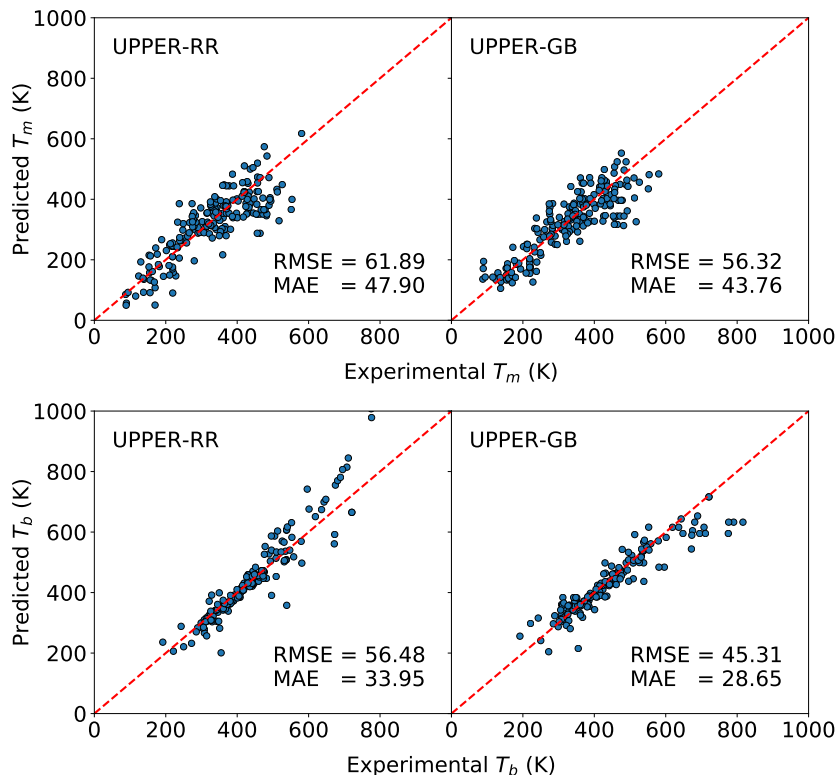


Figure 4: Parity plots of predicted versus experimental T_m (top panels) and T_b (bottom panels) using UPPER-RR (left panels) and UPPER-GB (right panels). Trained models of ΔH_{tr} and ΔS_{tr} were used to supply predictions of ΔH_{tr} and ΔS_{tr} to compute T_{tr} (Eq.1). Test results consist of 202 and 168 molecules for T_m and T_b , respectively. Prediction errors are shown in subpanels. Despite clear correlations, prediction errors are rather high and could use improvement.

to improve T_m predictions.^[17] Indeed, we find that the cross-validation RMSE of T_m reduces slightly (Table 2). Significant improvement of ~ 5 K is observed in the case of T_b . Lighter molecules have greater thermal motion than heavier molecules with the same kinetic energy. Thus, lighter molecules boil at lower temperatures, justifying the strong dependence of T_b on m .

The results of ARL-UPPER are certainly encouraging (Table 2). However, it is important to acknowledge weaknesses of the approach. For example, the method’s descriptors inadequately represent certain compounds. In particular, an example in Supporting Information shows structurally similar compounds with different T_m . Each molecule has an anthracene substructure functionalized by a methyl group, differing only by the methyl’s position. Their UPPER-inspired fingerprints are the same, yet T_m of 2-methylanthracene

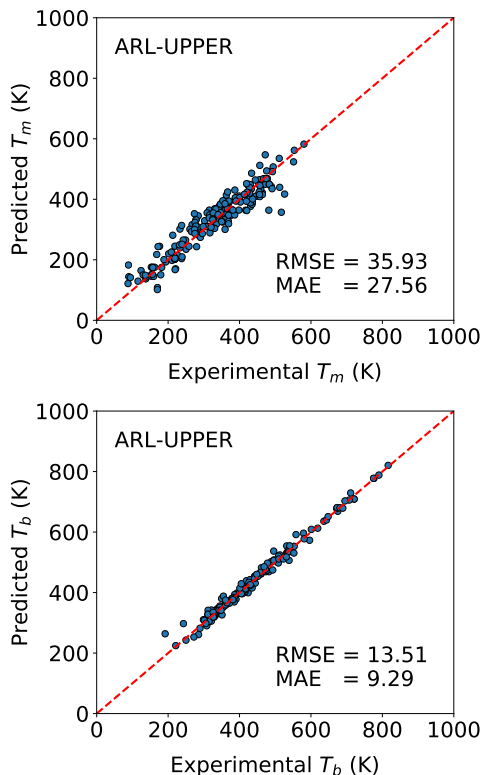


Figure 5: Parity plots of directly predicted T_m (top panel) and T_b (bottom panel) values using ARL-UPPER vs. experiment. Results are of the 10% held-out test sets consisting of 202 and 168 molecules for T_m and T_b , respectively. Prediction errors are shown in subpanels. Compared to Fig. 4, ARL-UPPER shows significant improvement in predicting T_{tr} .

is much larger than 1- and 9-methylanthracene. This significant difference is likely the result of packing arrangement. Unfortunately, packing is difficult to predict from molecular shape, especially when only using the 2D structure. We attempted replacing the current 2D eccentricity descriptor with 3D descriptors of eccentricity (ϵ_{3D}) and asphericity (q_{3D}).^[74] Cross-validation predictions are slightly improved (Table 2), but while these conformational descriptors help distinguish the methylanthracene compounds, the added information is not sufficient enough for the model to map to their correct melting points. Thus, new descriptors encoding the effect of molecular shape on intermolecular interactions and subsequent expansion that occurs during melting are needed. The Wiener index—famous for its ability to encode topological information and its strong connection to boiling points of alkanes^[75]—was also tested as a descriptor (w). Prediction errors further improved (Table 2), but overcoming

Table 2: Prediction errors (RMSEs) of T_m , T_b averaged over the 10-fold cross-validation test sets (\pm one standard deviation). Models were trained to combinations of group-constitutive (gc), geometrical (geo), and mass (m) descriptors. Significant improvement in predictive ability is observed by directly training to T_{tr} (ARL-UPPER) and adding descriptors that map to T_{tr} .

Method	Descriptors	T_m, T_b
UPPER-RR	$\Delta H_{tr}(gc), \Delta S_{tr}(geo)$	$62.9 \pm 4.1, 59.2 \pm 6.8$
UPPER-GB	$\Delta H_{tr}(gc), \Delta S_{tr}(geo)$	$59.2 \pm 5.9, 44.2 \pm 5.5$
ARL-UPPER	gc	$37.9 \pm 3.4, 22.3 \pm 3.4$
ARL-UPPER	gc, geo	$36.0 \pm 3.5, 21.8 \pm 4.4$
ARL-UPPER	gc, geo, m	$34.7 \pm 2.6, 19.5 \pm 5.9$
ARL-UPPER	$gc, geo(\epsilon_{3D}, q_{3D}), m$	$31.4 \pm 2.5, 19.3 \pm 4.6$
ARL-UPPER	$gc, geo(\epsilon_{3D}, q_{3D}), m, w$	$30.6 \pm 2.5, 17.2 \pm 3.9$

the indistinguishability of the methylanthracene compounds remains a challenge (Supporting Information). Quantum-chemical prediction of crystal density^[76] relates to packing and may provide useful information. Besides packing, the symmetry descriptor^[67] warrants improvement and is an opportunity for future research, as it does not distinguish stereoisomers such as *cis-trans*.

Melting Points of Energetic Materials

Fig. 6 shows an application of ARL-UPPER to predict T_m of energetic materials containing many nitro groups. The descriptors of the model include all those used to produce the best cross-validation predictions of Table 2 (*i.e.*, gc , $geo(\epsilon_{3D}, q_{3D})$, m , and w). The melting points reference dataset of the preceding subsection was augmented with energetics, making up about 5% of the entire training set (~ 130 compounds). The test set is a diverse set of nitroaliphatic and nitroaromatic compounds including nitropyrimidines and nitropyridines. Prediction accuracies are experimentally informative with overall test set RMSE of 35 K. The model is particularly strong in the case of nitroaliphatic compounds with a RMSE of 25 K. These results give promise toward predictive ML models of exotic energetics given comprehensive datasets.

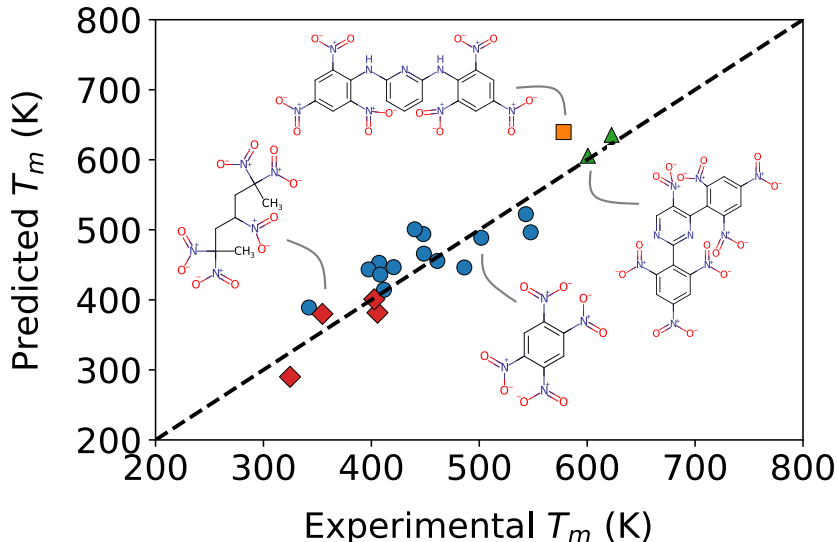


Figure 6: Parity plots of predicted versus experimental T_m of energetic materials using ARL-UPPER. Test set includes nitroaliphatics (\diamond), nitroaromatics (\circ), nitropyridines (\square), and nitropyrimidines (\triangle).

Melting Points of Public Datasets

Finally, we apply ARL-UPPER to train and test on public datasets of T_m (*i.e.*, OCHEM, Enamine, Bradley, and Bergström). Due to their relatively small sizes and comparable temperature ranges, Bradley and Bergström are combined into one dataset, labeled BradBerg. Further details of the datasets can be found in Refs. [69] and [20]. *Separate models were trained and tested on each dataset, again using the same 90-10 split.* The top panel of Fig. 7 shows prediction error as a function of temperature for each of the datasets, while the bottom panel shows the distribution of temperatures. Not surprisingly, smallest errors are obtained for temperatures that make up the majority of the data. Table 3 reports cross-validation errors over the middle 50% and 323.15–523.15 K; the latter being a popular range for medicinal compounds.^[69] The 30–40 K RMSE performance is very encouraging given the diversity of these datasets.

The datasets used for this application are unique in that they are both large and diverse

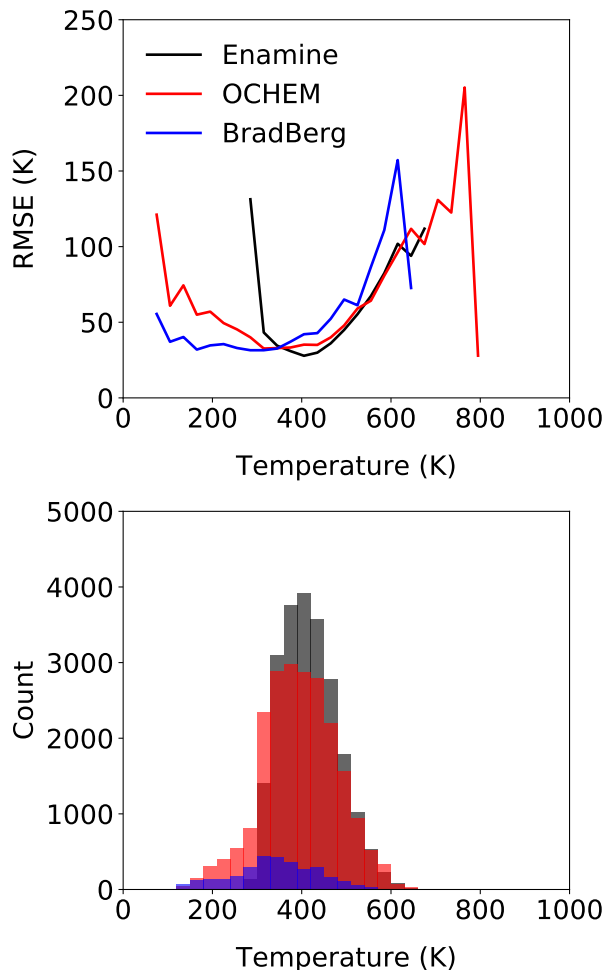


Figure 7: ARL-UPPER prediction errors (RMSEs) as a function of melting temperature for each dataset (top panel). *Models were trained and tested on each dataset separately.* Distributions of melting points for each dataset (bottom panel). Temperatures are binned every 30 K. Performance correlates to the density of available data.

and can therefore be used for further curation, which would likely benefit applications targeting a specific chemical space. A model’s applicable chemical space and accuracy are largely determined by the training dataset.^[69] Thus, building a robust model is heavily dependent on the use of sufficient and high-quality data. Future work may benefit from advanced sampling techniques such as active learning; a semi-supervised procedure for data generation that interactively queries from a large dataset.^[77] As opposed to merely increasing the size of the dataset, active learning finds the right data for the task. During the curation process, it is also important to be mindful of sources of error such as experimental conditions and

human error as trained models cannot overcome this irreducible error. It is worth noting that the Bradley and Bergström datasets are highly curated datasets of melting points and are considered the “gold standards”.

Table 3: ARL-UPPER prediction errors (RMSEs, MAEs) of T_m over the 10-fold cross-validation test sets for the middle 50% and 323.15–523.15 K ranges.

Dataset	Size	T_m , middle 50%	T_m , 323.15–523.15 K
Enamine	22381	29.7, 22.9	34.1, 26.3
OCHEM	21840	34.4, 25.7	37.3, 27.7
BradBerg	3161	34.2, 25.3	41.8, 30.9

Conclusion

We presented a method that shows significant promise toward predicting experimental melting and boiling points of molecular materials. The descriptors originate from a linear regression based QSPR developed by Yalkowsky and coworkers known as UPPER (see Ref. [63]). UPPER’s descriptors are primarily categorized as group-constitutive or geometrical, which model enthalpy and entropy; two thermodynamic quantities that drive thermal phase transitions. A notable advantage of UPPER’s descriptors is that they are derived purely from SMILES string. Thus, besides simple structural characteristics such as connectivity and hybridization, there are no numerically intensive calculations necessary. This attribute of the method differs from other molecular representations that use expensive quantum mechanical calculations.^[20,69] In this work, we generalized UPPER to a more diverse chemical space by including descriptors that capture fragments with several sp^2 -hybridized bonds. We also showed that an UPPER-inspired molecular representation, consisting of group-constitutive and geometrical descriptors, combined with eXtreme Gradient Boosting (denoted ARL-UPPER) produces highly competitive transition temperature predictions compared to the best results from the literature.^[20,69] Open-source software of our work is available at <https://github.com/USArmyResearchLab/ARL-UPPER>.

Cross-validation RMSEs of melting and boiling points were found to be 36 and 20 K, respectively (Table 2). Meanwhile, the dataset ranged from about 90–700 K and 150–850 K. The model improved (reducing RMSEs to 31 and 17 K) with mass, 3D descriptors of eccentricity and asphericity, and topological information using the Wiener index. ARL-UPPER also provided experimentally informative prediction of melting temperatures of energetic materials, highlighting its transferability to materials containing a significant number of nitro groups (compared to the majority of compounds used for training). The proposed method also achieved strong prediction errors within 30–40 K on melting points of large diverse public datasets. Its easy-to-compute descriptors, in combination with the accuracy and computational efficiency of XGBoost, makes ARL-UPPER a practical tool for screening transition temperatures in a laboratory setting.

This work has inspired other projects such as how the present method compares to common molecular fingerprints (see Supporting Information showing ARL-UPPER outperforming MACCS or Molecular ACCess System^[78] structural keys using XGBoost). This task goes hand-in-hand with thorough evaluation of fingerprints across learning algorithms. Additionally, the intelligent sampling of a training set and more robust descriptors of hydrogen bonding^[79] and polymorphs^[80] could further improve the model’s performance. In its original form, UPPER is a comprehensive QSPR, combining structural information to physicochemical properties including heat of sublimation, solubility, and vapor pressure. Furthering this work could make the ARL-UPPER framework a user-friendly screening tool for the design and discovery of materials in chemistry, physics, and materials science.

Supporting Information Available

Dataset information, training details, model predictions of phase transition properties including transition enthalpies, entropies, temperatures, and an example calculation of the ARL-UPPER fingerprint. Our software and datasets are freely available at

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Graphical TOC Entry

