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Outlook

Dataset Design for Building Models of Chemical Reactivity

Priyanka Raghavan, Brittany C. Haas,[⊥] Madeline E. Ruos,[⊥] Jules Schleinitz,[⊥] Abigail G. Doyle, Sarah E. Reisman, Matthew S. Sigman, and Connor W. Coley*

Cite This: https://doi.org/10.1021/acscentsci.3c01163

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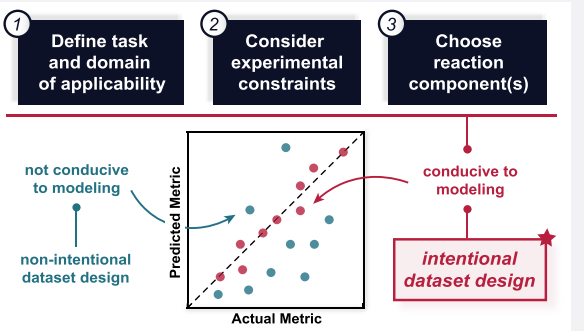
ABSTRACT: Models can codify our understanding of chemical reactivity and serve a useful purpose in the development of new synthetic processes via, for example, evaluating hypothetical reaction conditions or in silico substrate tolerance. Perhaps the most determining factor is the composition of the training data and whether it is sufficient to train a model that can make accurate predictions over the full domain of interest. Here, we discuss the design of reaction datasets in ways that are conducive to data-driven modeling, emphasizing the idea that training set diversity and model generalizability rely on the choice of molecular or reaction representation. We additionally discuss the experimental constraints associated with generating common types of chemistry datasets and how these considerations should influence dataset design and model building.



INTRODUCTION

Data-driven modeling in organic chemistry dates back almost a century.[1] Since then, researchers have explored various approaches to correlate molecular properties with reaction performance by using a broad range of techniques from linear free energy relationships (LFERs) to multivariate linear regression to deep learning. Besides the type of model itself, approaches have varied with respect to their application domain, diversity of inputs, and performance measure or prediction target. Here, we focus on models that are trained on experimental data to anticipate quantitative performance metrics, such as reaction yields, selectivities, or even rates.

The major themes and trends in building such structure−property relationships[2,3] and the broader landscape of predictive chemistry[4] have been the subject of recent reviews. However, in addition to the many publicized success stories using models to predict the performance of chemical reactions, we have witnessed many cases where modeling has been less successful. Our ability to train models that support chemistry objectives is dependent on data in ways that may be underappreciated and underreported.

In this Outlook, we discuss the concept of dataset design (Figure 1)—the construction of experimental datasets with modeling applications in mind—and some of the pitfalls that we have encountered when learning from datasets that have not been intentionally designed for machine learning. We have organized our discussion around the primary considerations when the aim is model building and describe at each stage how those model considerations should directly influence dataset design.

DEFINING THE DESIRED DOMAIN OF APPLICABILITY

A primary consideration of model building is the desired domain of applicability: the range of inputs over which we would like a model to make accurate predictions. Do we want to be able to query the model with any set of reactants, conditions, and products and have it estimate the yield? Or, are there specific combinations of known substrates that we want to study? Is it acceptable to assume a constant, unvarying temperature and reaction time, or do we also want to understand how those factors influence the reaction performance? Here, we can draw a distinction between "global" and "local" models. The former might involve using a corpus of literature data (for example, the Chemical Abstracts Service (CAS) Content Collection or the Pistachio, USPTO, or Reaxys datasets) containing millions of examples and spanning thousands of reaction types. The latter might involve focusing on a single reaction type and a well-defined set of substrates and reaction conditions; in most substrate scope studies, the reaction conditions are not varied. While a globally useful model is appealing in its scope, it is generally advantageous to have a sufficiently narrow domain of applicability to minimize

Received: September 20, 2023
Revised: November 6, 2023
Accepted: November 15, 2023

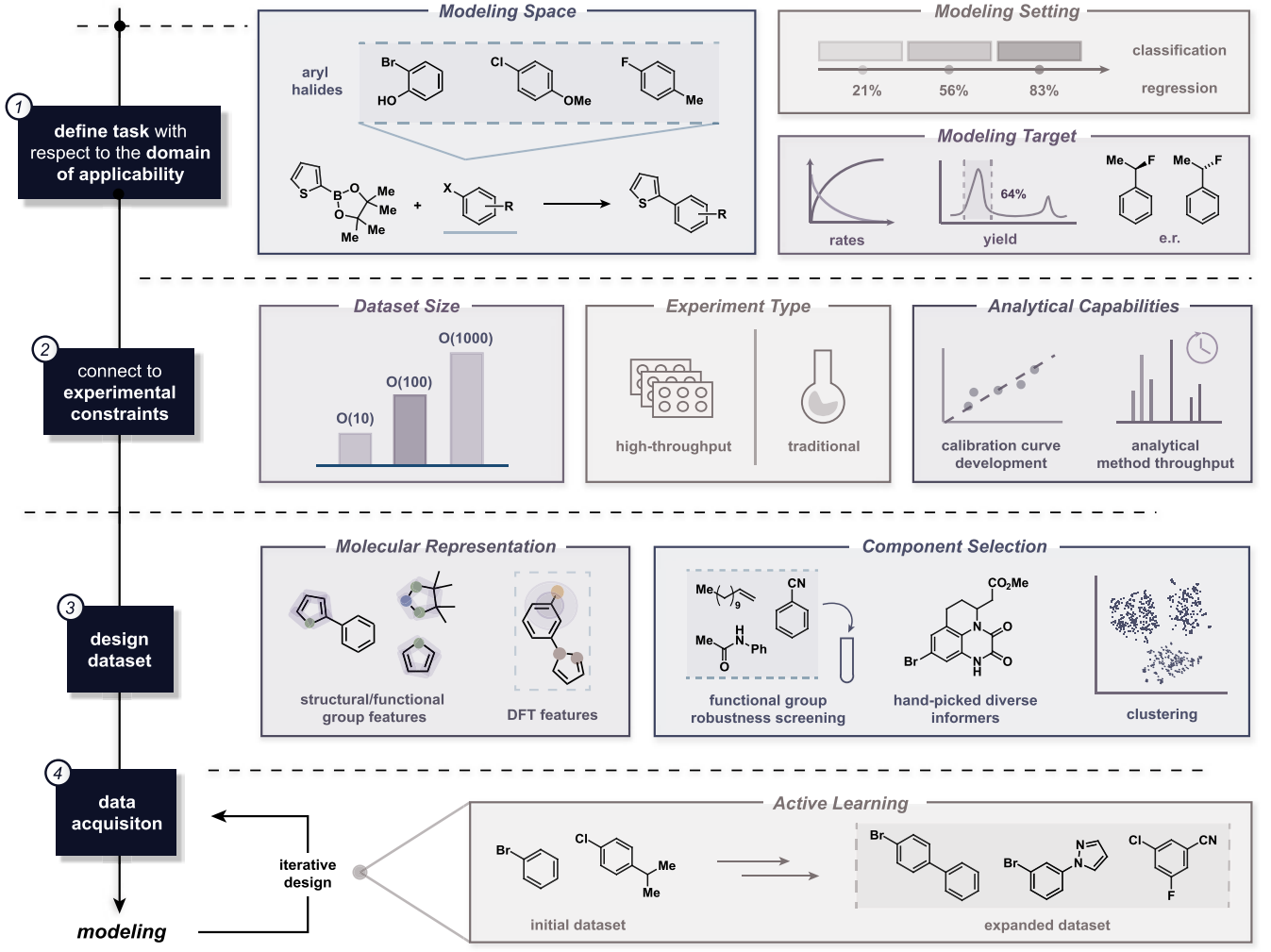


Figure 1. Recommended conceptual workflow for dataset design. From top to bottom, (1) task definition with respect to the modeling space, setting, and target; (2) experimental constraints, including the number of reactions and throughput of the analytical method; and (3) intentional dataset design, emphasizing feature-based reaction component selection.[5,6] These steps culminate in (4) data acquisition and modeling, with an optional active learning loop for iterative dataset expansion.

underlying mechanism changes, reactivity cliffs, or interaction effects in the dataset. These are factors that not only increase modeling difficulty but also are seldom accounted for in model inputs. This perhaps explains why predicting selectivity has seen more consistent success than predicting yield, as is discussed later. Furthermore, some literature-derived datasets are algorithmically extracted from text and have not undergone extensive manual curation or validation, so certain fields may be omitted or incorrect.

The datasets we can use for model training exhibit diversity along different axes (Figure 2A). Data derived from the published literature span a wide range of substrates and reaction types, but each reactant−product combination might be reported only once or twice. In contrast, public datasets from high-throughput experimentation (HTE) exist only for a few reaction types so far (Buchwald−Hartwig amination[7] and Suzuki coupling[8] being the most popular datasets), although more varied datasets, both in terms of reaction types and design workflow, are emerging.[9,10] Most HTE datasets are generated through parallel plate-based chemistry in 24-, 96-, 384-, or even higher density well formats. In these experimental campaigns, some reaction variables are easy to vary via automated liquid handling capabilities (e.g., the diversity of concentrations and the combinations of additives), while other aspects (e.g., heterogeneous reactants and the diversity of solvents) are harder to vary given the practical challenges of stock solution preparation.

Acquiring and screening a large number of diverse substrates is the most salient challenge that tends to limit the number of distinct components used in HTE campaigns, which often leverage the combinatorial nature of discrete variable selection. For example, the C−N coupling dataset from Ahneman et al.[7] covers 4140 reactions defined by the combination of 15 choices for the aryl halide, 23 additives, 4 Pd catalysts, 3 bases, 1 amine, and 1 solvent, at fixed time, temperature, and concentrations. Similarly, the dataset from Perera et al. of 5760 Suzuki reactions[8] was defined by combinations of 5 electrophiles, 6 nucleophiles, 11 ligands, 7 bases, and 4 solvents. Even a few choices for each component can quickly represent a large experimental space, for which there tends to be a higher cost associated with the HTE campaigns and, particularly with significant numbers of distinct products, a higher analytical burden.

The variation of individual components or aspects of reaction conditions is directly tied to the applicability domain, as a model should not be expected to generalize to a new

https://doi.org/10.1021/acscentsci.3c01163
ACS Cent. Sci. XXXX, XXX, XXX−XXX

molecule or input that is too dissimilar from what it has been trained on. As an extreme example, a model that has only seen reactions performed at room temperature cannot understand the influence of temperature on the reaction outcome. In the Ahneman et al. study,[7] the component with the greatest variation in the dataset was the additive species with 23 total choices, which justifies the evaluation of model generalization to unseen additives in the original paper. With only three bases explored, it is unrealistic to expect the model to anticipate the performance of a fourth unseen base. At the same time, a model trained on a narrow subset of reaction space cannot, in general, be expected to generalize well to other areas of that space, making it vital to select an appropriate set of representative examples.

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Mathematically, extrapolation is generally thought of as data that falls outside of the convex hull of training data; however, high-dimensional datasets almost always represent extrapolative tasks by this definition.[12] The notion of similarity between training and testing points and what constitutes extrapolation in a chemical sense has no strict definition, but distance in chemical feature space (e.g., using descriptors or molecular/reaction fingerprints) is a natural approach. Structural similarity has been used to estimate the domain of applicability and uncertainty of predictive models.[13,14]

SELECTING A REACTION PERFORMANCE METRIC AS AN OUTPUT VARIABLE

There are many commonly reported reaction performance metrics that can be used as the prediction target (output variable) in data-driven models. The two most common are yield, bounded between 0 and 100, and selectivity (e.g., the enantiomeric ratio, regioselectivity, etc.), which is a continuous scalar metric. Other metrics such as the reaction rate or rate constants are less common[15,16] but are of high interest to process chemists in particular. Rate is a time- and resource-intensive measurement to collect, requiring yields/conversions at many time points. However, rate can be reliably assayed across orders of magnitude and provides insight for practical experimental considerations, such as the reaction concentration, temperature, and time. Enantioselectivity, as reflected by $\Delta\Delta G^{\ddagger}$, is a compelling choice for an output variable and has been used in a significant number of successful workflows:[3,17,18] it is a scalar metric that is centered at 0 when unselective and, due to the relative precision of measuring the enantiomeric ratio (e.r.), does not tend to have a long-tailed distribution. Furthermore, the e.r. most often corresponds to the difference between enantio-determining transition states with the general reaction mechanism otherwise being the same, allowing one to neglect factors that confound modeling yield as an output, such as side reactions or differences in turnover rates of a catalyst. Likewise, regioselectivity is an internally consistent metric that relies only on direct comparisons between candidate atom sites.[19−22]

While selectivity is a useful metric for a subset of reactions, the more universal and widely reported metric in synthetic organic chemistry is yield. Generally, yield prediction has only been successful within large, high-throughput datasets in single/narrow reaction classes. Similar attempts to model diverse literature or "real-world" electronic laboratory notebook (ELN) data produce poorer results given the abundance of confounding variables (e.g., concentrations, time, scale, experimental hardware, the experimentalist) that may be unaccounted for in the reaction description.[23,24] Different

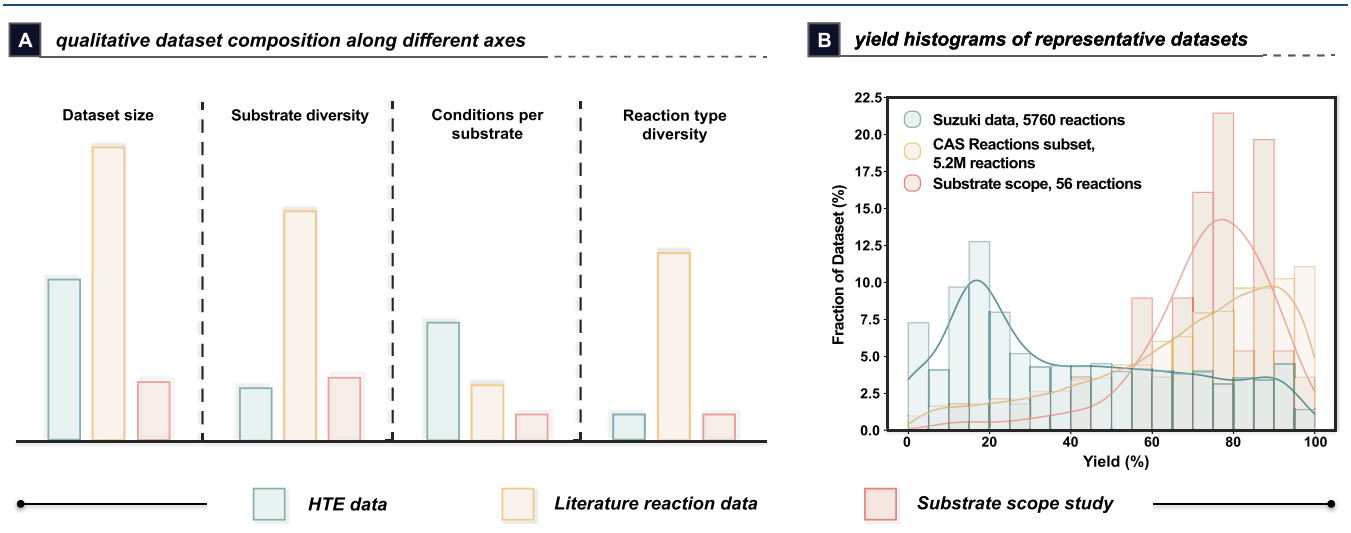

Figure 2. Common types of reaction datasets and their attributes: HTE datasets, literature databases, and substrate scope studies. (A) Each dataset type qualitatively placed within axes of size, substrate diversity, unique conditions per substrate, and reaction type diversity. (B) Yield distribution histograms for a sample dataset of each type: Suzuki HTE data from Pfizer,[8] a subset of the CAS Content Collection covering published single-step reactions from 2010 to 2015, and a reported reaction scope for the preparation of benzamides.[11]

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data sources tend to exhibit different distributions of reported reaction yields (Figure 2B).

Yield is a particularly challenging target to predict. It quantifies the efficiency of several successive microscopic steps and is implicitly affected by changes in the reaction conditions that may prompt different mechanistic pathways. It is an inherently noisier value that may include issues related to isolation of the product, which challenges modeling efforts, as the reported yield incorporates both reactivity and purification. Importantly, this is also a time-dependent process, wherein the relative yields across conditions are sensitive to the choice of when the reaction is assayed. For example, the ability to distinguish the efficacy of two catalysts (one fast and one slow) can be lost if the reactions are performed on long time scales. Most datasets are acquired using a single time point without regard for the rate dependence of yield; furthermore, researchers may intentionally choose longer reaction times to achieve higher yields, not realizing that this might be obfuscating differences in the reaction rate.

Reported yields can also be of several types, such as isolated yields, assay yields, or even LCAPs (liquid chromatography area percents), further increasing modeling complexity (Figure 3). Selectivity can suffer from the same ambiguity, but it is more consistently assayed without isolation. LCAP is a common output from HTE campaigns, where it is unrealistic to calibrate yields using product standards for every example. The well-defined range of yield values (0−100%) additionally presents a modeling complication, as many architectures from linear regression to neural networks are able to make predictions outside of this physical range. Compressing or truncating predictions using techniques such as logistic regression or sigmoid activation functions does not tend to improve modeling in our experience. Simplifying the task to a binary (0% versus >0% yield) or categorical (binned yield intervals) classification rather than a regression lowers the analytical burden for data acquisition and mitigates the impact of noise, but it still does not guarantee the ability to train a useful model.

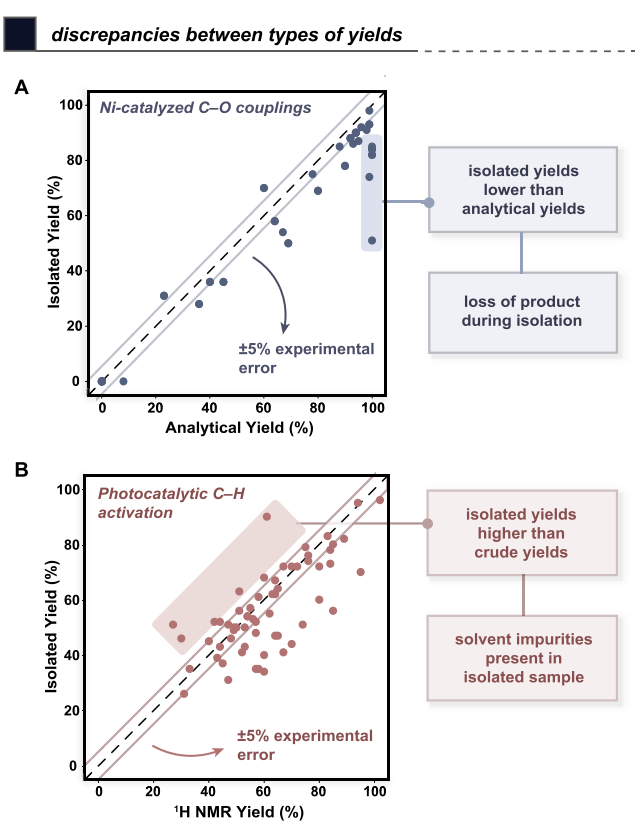

Figure 3. Isolated versus analytical yields for (A) literature-extracted Ni-catalyzed C−O couplings[25] and (B) a reported photocatalytic C−H activation substrate scope.[26] Common reasons for the discrepancies between the yields are given.

The range of reaction output values represented in a particular dataset will influence the range of output values in its predictions. This is a consideration that is similar to the domain of applicability, where it is necessary to see sufficient diversity during training if one expects it when making predictions. If, for example, the training set has its outputs within a narrow interval (e.g., yields within 70−95%), it is unlikely that the model will be able to make accurate predictions outside of that interval. Common types of models such as random forests (RFs) and Gaussian processes (GPs) are fundamentally incapable of doing so. Multivariate linear models, neural networks, and others can in principle, but their extrapolations will have a higher degree of uncertainty than their interpolations. Nevertheless, studies have shown successful (at times, retrospective) extrapolation during e.r. prediction to select catalysts that achieve selectivity better than anything observed during training.[27−29] To simplify matters, models that are meant to guide experimental design (e.g., optimize reaction conditions[30]) need not make accurate predictions extrapolating to output values beyond the training set in order to be useful, as evidenced by the success of GPs for Bayesian optimization in chemistry[31] and beyond.

IDENTIFYING A MOLECULAR/REACTION REPRESENTATION TO HELP DEFINE "DIVERSITY"

Supervised learning of complex input/output relationships is the basis of most modeling for chemical reactivity; thus, this goal should guide dataset design. A model's ability to generalize depends heavily on the representation we use; for example, a categorical (one-hot) encoding of bases does not allow a model to predict the performance of unseen bases, but a representation based on the pK_a values of the conjugate acids potentially could. If we intend to train a model to understand the impact of base strength, we might plan to run experiments using diverse bases, wherein diversity is defined in terms of base strength, as reflected by the pK_a of the conjugate acid.

Our ability to design a dataset that leads to a useful, generalizable model relies on our definition of molecular diversity, whether that be based on descriptors, functional group fingerprints, or more general notions of chemical structure. Whenever we are designing a dataset for the purpose of model training, we should be intentional about aligning the goals of generalization with the diversity of data points.

If we hypothesize that there are certain molecular features relevant for modeling, those features should form the basis for defining a diverse set of experiments. This may include using density functional theory (DFT)-based descriptors, which directly capture the electronic and structural properties of molecules that often greatly influence reactivity, or simple physicochemical features such as Mordred descriptors.[32,33] While the latter type of descriptor is readily calculable with cheminformatics packages in milliseconds, the computational cost of deriving descriptors from DFT calculations can be significant and render these workflows inaccessible or

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impractical for many researchers. Efforts like kraken[34] and OSCAR[35] seek to precompute and/or predict descriptor values for hundreds, thousands, or even millions of hypothetical ligands or catalysts.

A hypothesis-driven approach provides the ability to take an active role in descriptor selection; for example, using a steric parameter and an electronic parameter to define a two-dimensional (2D) array of diverse ligands.[36] The expert selection of features in this manner introduces bias, which is sometimes beneficial and sometimes detrimental, into dataset generation and modeling. Even when we do not know the importance of different descriptors in a modeling task, however, we can still define diversity with respect to a generic "holistic" set of descriptors. In both settings, the selection of diverse reaction components on the basis of descriptor diversity (through clustering) has been shown to be more informative than those selected less systematically.[16,37]

If we have even less of a prior notion about what will influence reactivity, we can focus on the more abstract "structural diversity". This might be the case when working with novel reaction types or ones with ambiguous mechanisms. If we anticipate that functional group presence/absence will be most predictive of performance/behavior, we might plan to use a MACCS key,[38] an extended functional group (EFG),[39] or another structural fingerprint as the molecular representation in our machine learning model. A dataset can then be designed with this in mind so that experiments directly probe the influence of functional groups on performance. This may be achieved simply by clustering a large set of possible substrates and selecting cluster representatives by using any structural fingerprint representation of choice (Figure 4A). An alternative experimental approach to probing the influence of functional group presence is Glorius robustness screening[5] (Figure 4B), which uses one-pot addition of several additives to estimate functional group tolerance and preservation in a pooled experiment. Similar high-throughput screenings of additive tolerance have led to an improved understanding of reaction robustness.[40]

The prototypical example of using structural diversity as a proxy for functional diversity (or "synthetic diversity") is the use of chemistry informer libraries[6,41] (Figure 4C), as proposed by Merck. One of the original informer libraries is a set of 18 structurally diverse and moderately complex aryl halides meant to sample aryl halide substrates used in medicinal chemistry campaigns. Evaluating substrates with this level of structural complexity might come at the expense of cost, convenience, or interpretability, particularly if an in-house synthesis is required.

Even with the approaches for dataset design we have outlined thus far, identifying useful features might only be possible with a more intimate knowledge of the reaction,

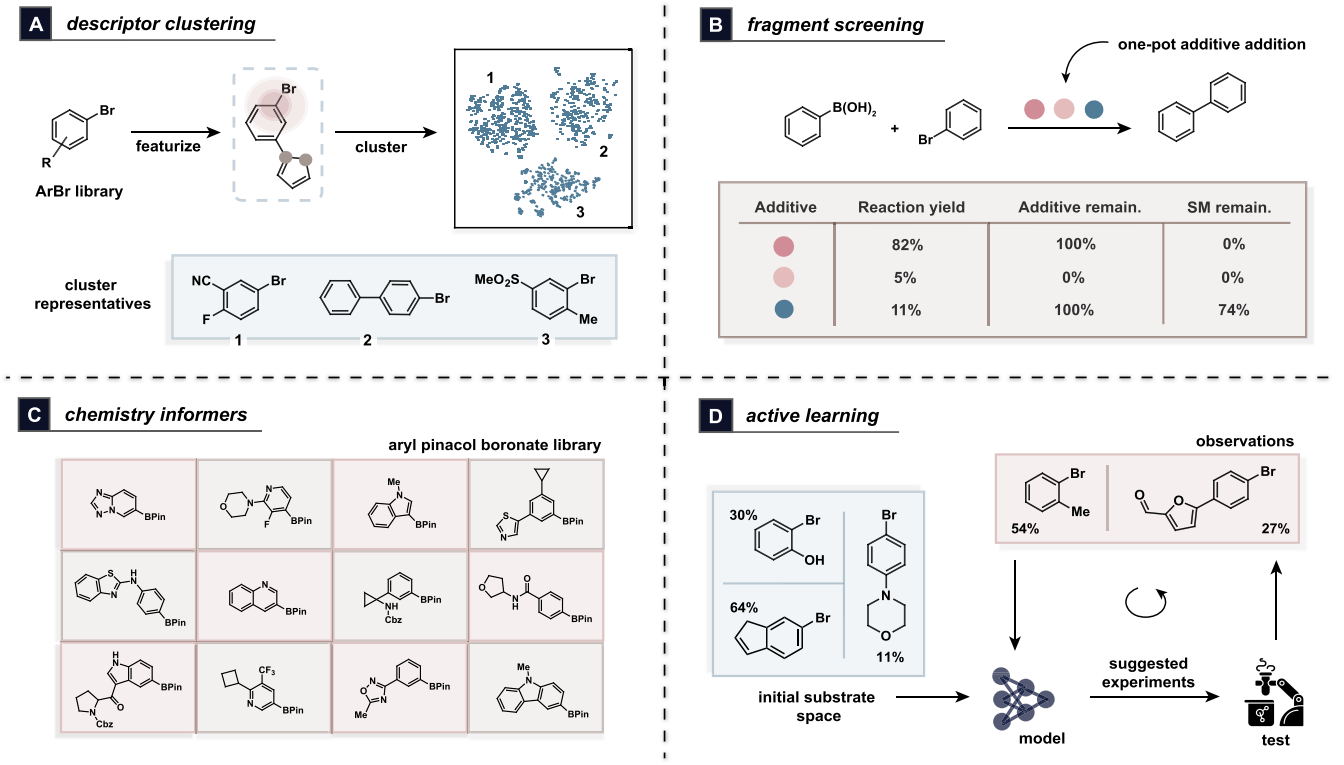

Figure 4. Existing strategies for substrate selection using principles of intentional dataset design. (A) Descriptor-based definition of diverse compound subsets using clustering;[37] (B) fragment screening to study robustness to additives;[5] (C) hand-picked structurally diverse chemistry informers;[6] and (D) active learning to iteratively select experiments based on model predictions.[43]

https://doi.org/10.1021/acscentsci.3c01163
ACS Cent. Sci. XXXX, XXX, XXX−XXX

particularly for novel chemistry. In such cases, while clustering approaches are still valuable, the selection of substrates that cover the desired domain of applicability can also be done, in principle, in a model-guided manner using active learning.[42] Rather than selecting the full set of experiments up front, we can use iterative experimental design to train an initial model on a small dataset and then select which hypothetical experiments will be the most informative to perform (Figure 4D). This approach is closely related to Bayesian optimization, but rather than defining the value of an experiment in a manner designed to optimize a performance metric (e.g., yield), the value of an experiment is quantified in a manner designed to maximize model accuracy or minimize uncertainty. Though not commonly employed, active learning for reaction screening has already shown success in retrospective evaluations. Eyke et al. demonstrated that models trained on actively selected subsets of HTE screens can outperform those trained on random subsets.[43] There have also been efforts to combine active learning and transfer learning for small dataset expansion.[44] In principle, these approaches have the additional advantage of being able to incorporate existing data, such as literature data, into the model prior to initialization.

REFLECTING ON OUR EXPERIENCE: FACTORS INFLUENCING SUCCESS IN REACTIVITY MODELING

Confounding Variables Lead to Unexplainable Variation in Outcomes. Many attempted prediction tasks are ill-posed. We cannot expect to predict yield values from tabulated literature data when those data do not specify concentrations, purification details, or other essential aspects of reaction conditions; when these are not held constant, they might explain the variance in the output that our models cannot account for. Aggregating multiple existing datasets into a training set for model building is appealing but unlikely to be successful with good accuracy.[45] This is also true for reaction product prediction, which we and others have, nevertheless, worked on extensively. Using literature data for pretraining and fine-tuning with a designed dataset is also attractive but has not been established as a successful workflow.

Ambiguous or Noisy Output Variables Obfuscate Reactivity Trends. The meaning of "yield" within one dataset might not match another: does it mean isolated yield, assay yield, LCAP, or conversion? Does 0% mean that no product was formed, or could it mean that it was not able to be isolated or quantified?[46] Human error, variations in reaction conditions, time dependency, and the effects of purification clashing with the reactivity all complicate modeling efforts. Even within a single dataset, small variations in the reaction and purification conditions may go unreported, further serving to confuse models. Models for the prediction of $\Delta\Delta G^{\ddagger}$ or regioselectivity can benefit from error cancellation by focusing on head-to-head comparisons between outcomes.[47]

Spurious Correlations from Dataset Biases Can Distract Models from the Underlying Chemistry. Confounding variables relating to purification conditions and different data sources, which are particularly present in literature data, hinder models from learning reactivity. For example, recent yield prediction work using a literature-extracted dataset of ∼2000 nickel-catalyzed C−O couplings found that the most important model features implicitly encoded the reaction scale or publication type.[25] None of these identified features held chemical importance, and the model's fixation on these extraneous properties likely explains its inability to extrapolate to other substrates.

Dataset Size Is Often Conflated for Diversity or Coverage. Recent discussions have asserted that a larger substrate scope table is not necessarily more informative than a smaller one.[48] This is consistent with our experience, where the size of a dataset is not a useful predictor of surrogate model performance. As an example, a larger training set of 37 aryl bromides derived from the literature failed to outperform a dataset of 15 selected via dimensionality reduction and clustering of DFT descriptors in a yield prediction task.[37]

Combinatorial Design Spaces Are Often Sparse. Yield prediction models trained and evaluated using random splits of combinatorial HTE data work very well. While the initial impression might be that this works because the datasets are large, we argue that it works because it is a simple interpolation (which is clear based on the comparable performance of one-hot representations). Generalization to new species, which is only reflected by certain structured data splits,[49] is where model limitations are revealed.

The Buchwald−Hartwig[7] and Suzuki[8] HTE datasets represent exhaustive explorations of two combinatorial spaces of $\sim 10^3$ reactions. In contrast, AstraZeneca's Suzuki ELN dataset[23] consists of 781 measured reactions out of $\sim 10^8$ possible combinations of substrates and discrete conditions. The most sparse datasets are, of course, literature-derived datasets, where the millions of known compounds could produce an immeasurably large enumerated space, representing the difficult interpolative and extrapolative challenges for models. While low dataset sparsity seemingly helps models interpolate effectively, it does not ensure extrapolation ability.

Learning Interactions Is Difficult Even with "Dense" Data. A primary reason sparsity complicates modeling is that interactions are, in general, not additive (though many LFERs add contributions from each component and not their interactions). If the design space of interest is a dense 2D matrix of pairwise substrate combinations, there are techniques that focus on screening small numbers of rows/columns and trying to interpolate,[50] which is a strategy also used for the validation of building blocks when building DNA-encoded libraries.[51] However, even models designed to learn interactions may not outperform models that focus on the contributions of each component alone.[52]

Desiderata Are Not Universal and Depend on Modeling Goals. Modeling reactivity should be done with particular objectives in mind. For example, identifying important descriptors to improve fundamental understanding (interpretability), generalizing small numbers of experiments to combinatorial design spaces (interpolation), predicting the performance of yet untested substrates or catalysts (extrapolation), or guiding experiments in a direction that leads to improved selectivity, yield, etc. (optimization). For each objective, certain simplifying assumptions might be appropriate. Anticipating the performance of novel substrates in a discovery chemistry setting might be compatible with a binary formulation using discretized yields rather than regression. Guiding a yield optimization campaign does not actually require that a model be accurate but merely that the conditions it identifies are promising to lead to improved outcomes. Developing a model without a focused application in mind leads to ambiguity in the importance of different evaluation metrics.

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There Is a Tension in Dataset Design between What Is Ideal for Machine Learning and What Is Tractable to Acquire. In practice, experimental constraints such as time, cost, and resources tend to influence the type of data that can be acquired in terms of the number and diversity of experiments. For example, we have seen that HTE campaigns tend to offer large, clean datasets that are convenient to use for training data, but this comes at the cost of diversity (and, subsequently, the ability to extrapolate) due to the limitations of chemistry (e.g., infrastructure costs, the commercial availability of compounds, analytical chemistry, and the curse of dimensionality). The most relevant output variable is influenced by the intended application of the model and also by the analytical capabilities of the lab and the (in)ability to develop yield calibration curves in many situations. Having consistency and clarity in reporting "yields", whether that be assay yields, isolated yields, or simply LCAPs, will help identify confounding variables, such as purification strategies or product response factors. Other procedural confounding variables, such as inconsistent room temperatures or differences in human operations, are important to capture and report, if not to control for.

There is a tension in dataset design between what is ideal for machine learning and what is tractable to acquire.

OUTLOOK AND FINAL PRACTICAL RECOMMENDATIONS FOR DATASET DESIGN

The intended representation of a reaction directly informs what a diverse set of input features might look like. In the absence of any prior knowledge, structural or functional diversity (as approximated by descriptors) is defensible; however, as more is known about a particular reaction, focusing on the most relevant features provides an opportunity to maximize the information gained per experiment, e.g., through active learning. Although there is no singular definition of diversity, this paper provides several considerations and recommendations for the field. We summarize our main observations below:

- Formulating problems in terms of selectivity (or relative rate) prediction rather than yield is beneficial; if using yield as the modeling target, avoiding isolated yields can help disentangle reactivity from purification trends.
- Measuring multiple time points provides better opportunities to understand reaction efficiency than measuring single-point yields. A few pilot experiments can help determine the ideal time point(s) at which to measure performance in lieu of a full kinetic profile.
- In the absence of prior knowledge, the selection of the desired reaction component(s) should be done by clustering each component from the design space of interest using computational descriptors or fingerprint representations.
- Generalizable models require more extensive experimental work, both to have sufficient data to train and to perform structured extrapolative evaluations.
- Active learning is the most principled approach for selecting substrates or conditions to evaluate if experimental capacity is limited. Relevant literature data, while not the main focus of this Outlook, can be used at the outset of an active learning campaign.

The ideal "dataset design" will always be a moving target that depends on our modeling goals and experimental capabilities. We encourage readers to explore and adopt more systematic ways of designing HTE campaigns and substrate scope tables.

AUTHOR INFORMATION

Corresponding Author

Connor W. Coley − *Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States;* orcid.org/0000-0002-8271-8723; Email: ccoley@mit.edu

Authors

Priyanka Raghavan − *Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States*

Brittany C. Haas − *Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States;* orcid.org/0000-0001-5344-4375

Madeline E. Ruos − *Department of Chemistry & Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States;* orcid.org/0009-0007-6955-8642

Jules Schleinitz − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-7116-4772

Abigail G. Doyle − *Department of Chemistry & Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States;* orcid.org/0000-0002-6641-0833

Sarah E. Reisman − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-8244-9300

Matthew S. Sigman − *Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States;* orcid.org/0000-0002-5746-8830

Complete contact information is available at: https://pubs.acs.org/10.1021/acscentsci.3c01163

Author Contributions

⊥These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support of this work through the NSF Center for Computer Assisted Synthesis (C-CAS) under Grant CHE-2202693. We also thank CAS for providing the subset of the CAS Content Collection to enable our visualization of the reaction yields shown in Figure 2.

https://doi.org/10.1021/acscentsci.3c01163
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