

Learning To Predict Reaction Conditions: Relationships between Solvent, Molecular Structure, and Catalyst

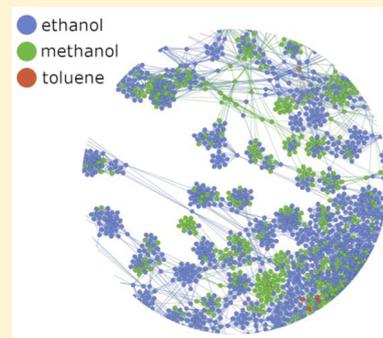
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S Supporting Information

ABSTRACT: Reaction databases provide a great deal of useful information to assist planning of experiments but do not provide any interpretation or chemical concepts to accompany this information. In this work, reactions are labeled with experimental conditions, and network analysis shows that consistencies within clusters of data points can be leveraged to organize this information. In particular, this analysis shows how particular experimental conditions (specifically solvent) are effective in enabling specific organic reactions (Friedel–Crafts, Aldol addition, Claisen condensation, Diels–Alder, and Wittig), including variations within each reaction class. An example of network analysis shows where data points for a Claisen condensation reaction break into clusters that depend on the catalyst and chemical structure. This type of clustering, which mimics how a chemist reasons, is derived directly from the network. Therefore, the findings of this work could augment synthesis planning by providing predictions in a fashion that mimics human chemists. To numerically evaluate solvent prediction ability, three methods are compared: network analysis (through the *k*-nearest neighbor algorithm), a support vector machine, and a deep neural network. The most accurate method in 4 of the 5 test cases is the network analysis, with deep neural networks also showing good prediction scores. The network analysis tool was evaluated by an expert panel of chemists, who generally agreed that the algorithm produced accurate solvent choices while simultaneously being transparent in the underlying reasons for its predictions.



1. INTRODUCTION

Reaction data sets contain a wealth of information that can be used to make informed decisions in the laboratory and in preparing for large-scale production. This data shows millions of individual syntheses that transform available substrates into interesting products, all resulting from sustained efforts of the chemical community over decades. Chemists often search these data sets for insight and examples when performing novel reactions, which of course are never present in the data set. This process therefore relies on chemical know-how and inference to make a reaction plan that is relevant to the current synthesis target. In our age of modern computation with its incredible advances in data science, it is natural to ask whether these inferences and plans might be greatly improved compared to current man-machine interchanges (Figure 1).

Recent progress in computational techniques to translate reaction data sets into predictive models has generated considerable enthusiasm for computer-aided synthesis planning. In the last ten years, notable studies on reaction prediction and synthesis planning algorithms have evolved, including expert systems developed from curated data sets^{1–3} as well as supervised machine learning tools^{4–10} or graph-based tools¹¹ applied to commercial reaction databases¹² or patent-harvested reactivity data.¹³ The intent to automate chemical decisions has been pursued long before contemporary

interest in machine learning and artificial intelligence.^{14–18} Recently, the area has received great interest, including the modern expert system called Chematica, which created synthesis plans for 8 biologically active molecules that were successfully demonstrated in the laboratory.⁷ Chematica achieved this by manual encoding tens of thousands of reaction rules, representing many years of input from expert chemists. On the machine learning front, reports by Segler and Waller^{19,20} have shown that a graph-driven neural network strategy can provide (without the extended human effort) synthesis plans that are equivalent in quality to literature reports, as judged by graduate-level organic chemists.

Even with these successes, serious limitations to computer-aided synthesis remain. To chemists, reactions are primarily known by their overall classification, not just specific instances of $A + B \rightarrow C$. When predicting the outcome or conditions for a reaction, chemists make decisions using generalized knowledge, called chemical intuition. Intuition is the skill gained from instruction and experience in using chemical principles—grounded in physical properties—to navigate experimental design and analysis of laboratory outcomes. The intuition of expert chemists is a powerful science that is fully applicable to

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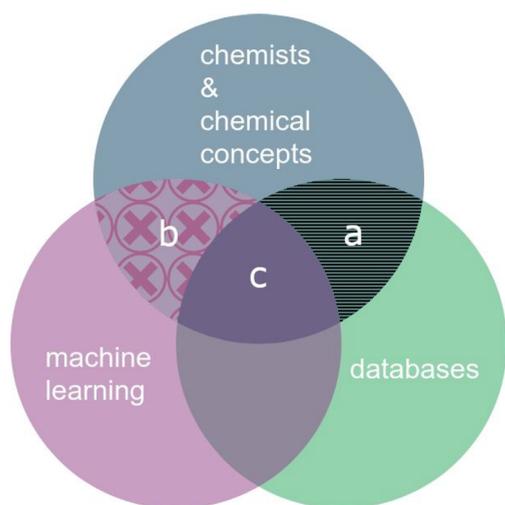


Figure 1. A conceptualization of machine learning in chemical applications. (a) Databases do not inherently form chemical concepts, but chemists can provide interpretations of their results and/or be informed by the database entries. (b) Machine learning in chemistry can make predictions without transparent reasoning and does not typically inform expert chemists about new chemical concepts. (c) The future of the field of chemistry research will seamlessly integrate machine learning to the current foundation of chemical concepts with established databases. Chemists will regularly utilize interpretable and predictive machine learning tools.

72 reactions outside the scope of any database, expert system, or
73 machine learning method. In other words, chemists are highly
74 effective at understanding the details of chemical reactions
75 using a set of broad physical principles, which are applicable to
76 reactions that have never before been performed. With this
77 consideration in mind, it becomes clear that machine learning
78 reaction prediction computations follow an entirely different
79 track and specialize in reaction types that most resemble their
80 training data. By Zipf's law,²¹ databases are primarily populated
81 by the most frequently used reactions, with a power law
82 decrease in number of data points with rank.^{22,23} Therefore,
83 data-driven algorithms—to no surprise—work best for the
84 most popular reactions, and it is nontrivial to generalize these
85 to untested, emerging, or even relatively low-population
86 reaction classes.

87 Based on these considerations, the basic issue with computer
88 generalization of reaction concepts might be traced to the (lack
89 of) interpretability of the underlying algorithms. Here, we
90 focus on machine learning techniques, where generalization is
91 attempted by machine, rather than by experts. Machine
92 learning techniques are notoriously “black box” in character
93 and provide no direct relationships between the predictions
94 that are made and the underlying reasons for the predictions.
95 The most advanced machine learning strategies, for example
96 the hugely popular area of “deep learning” through neural
97 networks, fall into this category. Without interpretability, any
98 machine learning exercise will face severe difficulty of justifying
99 its value to chemistry, as the generalizability of the model will
100 be suspect.

101 In addition to these challenges, computational researchers
102 face another key difficulty, due to the quality of available
103 reactivity data. The largest data sets inevitably contain
104 information from a wide variety of sources, and unlabeled or
105 mislabeled data (i.e., “label noise”) are commonplace.²⁴
106 Doubts regarding the reliability of the training data compound

with the lack of interpretability of black box machine learning
107 tools result in inevitable mistrust by seasoned experts. Even for
108 otherwise accurate entries in a data set, deciphering the
109 difference between “reagent” or “catalyst” can lead to
110 confusion for data-driven learning. Especially in the area of
111 chemical synthesis, where reactants, reagents, catalysts,
112 solvents, and other reaction conditions must be specified
113 precisely for the reaction to work, consistent information
114 regarding these factors is paramount. Along these lines, neural
115 network models for predicting suitable reaction conditions
116 have been reported by Gao and co-workers.²⁵ In their study, a
117 large data set of millions of reactions was used to train the
118 models, with accuracies of about 70% in the top-ten
119 computational predictions. As described herein, we take a
120 different approach where reaction data is partitioned into
121 named organic reactions, allowing focus into predictability of
122 specific types of reactions. This strategy is closer in spirit to
123 what is practiced by laboratory chemists and importantly will
124 allow improved verification of the machine predictions by
125 making transparent models for the reaction conditions. 126

In this article, we explore whether machine learning
127 techniques can be made interpretable while maintaining high
128 accuracy in predicting a key reaction condition. The reaction
129 condition we focus upon is the solvent, which is a deceptively
130 simple condition because one solvent choice may allow a
131 planned reaction to succeed, but another solvent choice may
132 lead to no reaction at all. Indeed, reports have shown that
133 choice of solvent can change reaction rates by orders of
134 magnitude.²⁶ Solvent compatibility therefore represents a key
135 question that is not only challenging but important for
136 progressing through synthetic space in the laboratory. 137
Ultimately, this article will show that solvents can be selected
138 at high accuracy with a fully interpretable, statistically sound
139 machine learning method across a testbed of five named
140 organic reactions, totaling over 50,000 specific examples. 141

2. METHODOLOGY

2.1. Data Source. All data used in this study was obtained
142 from the Reaxys database,¹² which contains approximately 45
143 million reactions. To focus our study, five named organic
144 reactions were chosen: Diels–Alder, Friedel–Crafts, Wittig,
145 Aldol addition, and Claisen condensation. These represent a
146 diversity of reaction conditions, including catalyst and solvent
147 choices. The data set was limited to single-step reactions,
148 reactants that are commercially available, interpretable solvent
149 designation, and contained a subset of the 78 most common
150 solvents. Data points with missing catalyst entries were treated
151 as uncatalyzed and remain in the data sets. After collecting this
152 data, the Diels–Alder, Friedel–Crafts, Wittig, Aldol addition,
153 and Claisen condensation reaction data sets contained 18,394,
154 29,021, 9,685, 6,603, and 12,151 total useable data points,
155 respectively. 156

The raw data from Reaxys required moderate amounts of
157 preprocessing to be useful. For example, many catalysts had
158 “aluminum”, “aluminium”, or “Al” specified: these are all
159 equivalent. Naming was standardized using the chemical
160 identifier resolver from the National Institutes of Health,²⁷
161 which transforms each name into the IUPAC convention. To
162 capture the remaining ambiguities, catalyst names were made
163 lowercase, metal names were replaced by their atomic symbol,
164 and a hand-crafted dictionary was created to eliminate
165 additional specific cases that were not otherwise handled 166

167 correctly. The full definition of this procedure is available in
168 the [Supporting Information](#).

169 Molecular structures were stored as SMILES^{28,29} strings,
170 which were provided by Reaxys. Molecular fingerprints were
171 generated through Open Babel³⁰ using the MACCS keys,^{31–33}
172 which contain 166 functional groups. Rather than use the
173 reactant structures, these fingerprints were generated for the
174 products to simplify the data structure from two reactants to
175 just one product. Tanimoto measures^{34,35}

$$T_{A,B} = \frac{\left[\sum_{j=1}^n x_{jA}x_{jB} \right]}{\left[\sum_{j=1}^n (x_{jA})^2 + \sum_{j=1}^n (x_{jB})^2 - \sum_{j=1}^n x_{jA}x_{jB} \right]} \quad (1)$$

177 between all product pairs within each reaction data set provide
178 a measure of chemical similarity between data points. Catalyst
179 similarity can also be measured by Tanimoto or by one-hot
180 encoding of the catalyst identity.

181 **2.2. Prediction Algorithms.** To provide solvent classi-
182 fication, a handful of machine learning algorithms was
183 employed. The first two, support vector machines^{36,37}
184 (SVM) and deep neural networks (NN),³⁸ are nonlinear
185 classification techniques that can predict on any number of
186 solvent identities represented by the training data set. SVM
187 classification requires a kernel function to measure similarity
188 between data points, and choices for the kernel are discussed
189 below. NNs do not require this measure, as the number of
190 input nodes can be scaled to the number of input variables.

191 The *k*-nearest neighbor algorithm (kNN) is the third solvent
192 classification technique.³⁹ The network match technique
193 requires a similarity metric (a kernel), and makes predictions
194 by finding *k* points in the training set that are most similar to
195 the test point. The most frequent solvent in the *k* neighbors in
196 the similarity network is the top solvent prediction. The
197 [Supporting Information](#) shows a small, labeled network to
198 demonstrate how kNN clusters similar molecules in practice.

199 **2.3. Similarity Measures.** The network match and SVM
200 algorithms are sensitive to the choice of similarity measure.⁴⁰
201 In typical machine learning analysis, one takes fixed-length
202 feature vectors and subjects them to standard kernels, for
203 example

$$204 \quad K = \exp(-\gamma \|x - x'\|^2) \quad (2)$$

205 where γ is a hyperparameter that is chosen during cross-
206 validation. When a “good” kernel is chosen, the data points
207 become implicitly organized by this measure, and predictions
208 can be highly accurate. Typical kernels used in machine
209 learning, however, are not necessarily useful measures for
210 chemical structures. For example, the kernels are not size
211 consistent, so large and small molecules will receive widely
212 differing similarity scores. This leads to inconsistency in
213 making predictions for large vs small molecules, and the
214 problem only becomes worse for larger and larger molecules.⁴¹

215 Alternatively, specialized kernels might provide higher
216 accuracy by more closely representing the underlying structure
217 of the data. One such choice is the Tanimoto measure (eq
218 1),³⁴ which is particularly well-suited for use in chemical
219 problems.³⁵ While Tanimoto is frequently applied to organic
220 molecules, it can also be applied to catalyst structures. We
221 denote the product Tanimoto by T_p and the catalyst Tanimoto
222 by T_C .

223 Two similarity measures will be examined in this work

$$K^{(1)} = T_p \delta_C \quad (3) \quad 224$$

$$K^{(2)} = T_p T_C \quad (4) \quad 225$$

where δ_C gives 1.0 for a catalyst match, where the two catalysts
226 are the same between the two reaction data points and 0.0
227 otherwise. 228

2.4. Cross-Validation and Computational Details. 229
230 Within each reaction class, training and predictions were
231 performed using 5-fold cross-validation, and accuracy results
232 are reported only for data points outside of the training set.
233 This procedure was repeated 10 times, shuffling the data
234 randomly with each training-test cycle. The mean, maximum,
235 and minimum errors can be found in the [Supporting](#)
236 [Information](#), and the mean accuracies are reported in the
237 main text.

238 The NN training was performed by the MLPClassifier
239 algorithm⁴² with a ReLU activation function in the scikit-learn
240 package.⁴³ The NN is 4 layers deep, with each of the two inner
241 layers having the same dimension as the input vector. The
242 output layer has the dimension equal to the number of solvents
243 in the neural network training data. For example, the training
244 data for Diels–Alder contains 15 solvents. Therefore, for each
245 of those solvents a predicted weight is assigned, and this weight
246 is normalized across the output layer. The predicted solvent is
247 the one with the top weight, and the second most likely solvent
248 has the second highest weight, and so on. The NN is trained
249 and cross-validated using the product features and the catalyst
250 fingerprints or with the product features and the catalyst
251 identity. Catalyst identities are encoded to number categories
252 based on the catalyst name, and therefore each type represents
253 one input feature to the neural network.

254 Support vector classification (SVC) was also performed
255 using scikit-learn. SVC was fed a concatenated vector of a
256 fingerprint of the catalyst and a fingerprint of the products.
257 SVC was tested for two types of kernels, the default radial-basis
258 function, for which the formula is displayed in eq 2, and a
259 linear (or dot-product) kernel. Recalling that a MACCS
260 fingerprint contains exclusively 1's and 0's, the linear kernel
261 counts the total number of functional groups common
262 between two fingerprints. Although Tanimoto kernels may
263 be applied to SVCs,^{37,40} for the data sets in this work
264 Tanimoto kernels did not increase solvent prediction accuracy,
265 and therefore the results from the Tanimoto kernel are
266 provided in the [Supporting Information](#). The [Supporting](#)
267 [Information](#) also contains a description of error handling when
268 generating the fingerprints required for these kernels.

269 The *k*-NN algorithm for solvent prediction and network
270 visualization was created in Python by our group. The two
271 similarity measures (eqs 3 and 4) were tested, but measure 3 is
272 used exclusively for the graphs shown in this work (with *k* =
273 10). Tests involving the similarity measure of eq 4 are shown
274 in the [Supporting Information](#). The number of neighbors was
275 tested to understand their effect on kNN performance, where
276 the *k* parameter is the only tunable parameter for this method.
277 The solvents predicted for each reaction are the most frequent
278 or popular solvents among the neighbors, and the second most
279 frequent solvent was the second solvent prediction, etc. To
280 break ties in frequency of solvents, the similarity measure itself
281 was used for sorting. Visualization of the reaction networks was
282 performed using the Force Atlas 2 algorithm⁴⁴ as implemented
283 in the Gephi software package.⁴⁵ The Python codes are freely

Table 1. Accuracy of 6 Solvent Prediction Methods Across Five Reaction Data Sets (Top 1)^a

reaction	kNN with catalyst labels	kNN using catalyst fingerprints	NN with catalyst labels	NN using catalyst fingerprints	SVC with radial basis function	SVC with custom kernel
Friedel–Crafts	79.0	43.4	56.8	70.1	45.9	54.9
Aldol addition	78.0	47.4	47.8	67.0	58.8	66.9
Claisen condensation	80.1	66.0	76.1	78.2	66.2	66.2
Diels–Alder	79.9	58.7	68.5	80.5	59.9	66.8
Wittig	68.8	45.1	59.6	69.4	49.6	58.4

^aValues are in %.

284 available at the repository located at https://bitbucket.org/ericawalk/solvent_selection/.

3. RESULTS AND DISCUSSION

286 **3.1. Statistical Results.** The five data sets were subjected
 287 to the above-described learning techniques for solvent
 288 prediction. Multiple feature sets and similarity measures were
 289 considered, and representative choices are shown in Table 1.
 290 In particular, 6 unique algorithms are presented: kNN with two
 291 different similarity measures, neural networks using two types
 292 of raw features, and SVC using radial basis functions or a
 293 Tanimoto similarity measure. All of these methods employ the
 294 full fingerprint feature set for the reactant molecules and either
 295 one-hot encoding of the catalyst identity or catalyst finger-
 296 prints. At a basic level, this means that the kNN and support
 297 vector classification use similarity measures as their basic
 298 variable for making models, whereas the neural network
 299 processes the full set of raw features to generalize the factors
 300 responsible for solvent choice. As explained in the computa-
 301 tional details, all results come from cross-validation, with errors
 302 reported only for points that were not used in training.

303 Among the evaluated models, kNN stands out as the best at
 304 predicting the experimental solvent, with success rates of 69 to
 305 80% using the one-hot encoding of the catalyst identity. The
 306 same model using catalyst fingerprints drops in accuracy to 43
 307 to 66% across the 5 reaction classes. The decrease in solvent
 308 selection accuracy might be attributed to the treatment of the
 309 catalyst by the MACCS keys. One aspect is the noise handling,
 310 where the kNN fingerprint vector doubles in length, in a sense
 311 diluting the quality of the reactant features toward less
 312 impactful catalyst features. An increase in catalyst features is
 313 not especially helpful for kNN because catalysts typically
 314 include metals, which are not particularly well represented in
 315 the MACCS keys, where MACCS keys are most useful for
 316 main-group compounds. Neural network models also perform
 317 reasonably well, reaching accuracies between 48 and 76% using
 318 the catalyst identity features. The neural network improves
 319 substantially when using the catalyst fingerprints, with
 320 improvements over kNN for the Diels–Alder and Wittig
 321 reactions by a small amount (<1%), while performing less well
 322 on the Friedel–Crafts, Aldol addition, and Claisen con-
 323 densation reaction classes. The NN, relative to kNN, is not as
 324 influenced by the increased size of the catalyst fingerprint as
 325 kNN and intrinsically avoids irrelevant features in the
 326 fingerprint. Support vector methods generally underperformed
 327 in comparison with the kNN and neural network models.

328 Since more than one solvent may be equally applicable to a
 329 given reaction, but databases report only the single solvent
 330 used for a particular experiment, testing the computational
 331 models for “top N” performance is a natural procedure. Table
 332 2 shows the accuracies of the kNN and neural network models

Table 2. Comparison of Prediction Accuracies if Any of the Top 3 Predicted Solvents Match the Database Entry^a

reaction	kNN top 3 allowed	NN top 3 allowed	worst case scenario
Friedel–Crafts	92.8	89.0	62.3
Aldol addition	94.5	92.1	71.5
Claisen condensation	98.0	98.7	94.5
Diels–Alder	93.9	93.5	80.5
Wittig	91.3	91.3	90.8

^aThe worst case scenario is always predicting the 3 most common solvents from the training data. Values are in %.

for top-3 prediction accuracy, i.e., whether the experimental
 solvent is in the top 3 predicted by the model. The best
 choices for the features from Table 1 are used for each
 algorithm, respectively. Accuracies improve across the board,
 as expected, with the kNN slightly outperforming the neural
 network. For 3 of the 5 reaction classes, the two models give
 accuracies within 1% of each other, and the kNN shows clearly
 a better performance for the Friedel–Crafts data set (which is
 the most challenging of the 5 as reflected by the worst-case
 scenario accuracy in Table 2). Overall, the prediction
 accuracies of 91 to 98% of the kNN tool show it to be highly
 capable of selecting good solvents.

These results of Table 2 show that the kNN and neural
 network models significantly outperform the baseline scenario,
 where the most prevalent solvents in the data sets are chosen.
 When simply taking the statistically most common solvents as
 the top 3 predictions, accuracies of 62 to 95% can be achieved.
 Interestingly, the models are unable to significantly outperform
 the worst case prediction for the Wittig reaction. On the other
 hand, the Claisen condensation worst case accuracy is 95%, but
 the 2 computational models give 98 to 99% accuracy, showing
 a significant improvement. Most dramatically, the Friedel–
 Crafts reaction worst case prediction gives 62% accuracy on
 the top 3, making it a more challenging case than the other 4
 reactions. The kNN technique shines brightest in this reaction
 class, with 93% accuracy, which is markedly better than the
 neural network at 89%.

3.2. Visualizing the Reaction Landscape. The high
 performance of kNN suggests that the underlying similarity
 measure provides a strong means for organization of the data
 sets. The specific similarity measure given in eq 3 uses a
 combination of catalyst identity and reactant Tanimoto, so the
 overall closeness between two data points depends only on
 these two factors. To better understand the relationships that
 lead to successful predictions, two-dimensional graphs of the
 data for the Friedel–Crafts reaction are shown in Figures 2 and
 3. Analogous plots are shown in the SI for the Claisen
 condensation and Diels–Alder data sets.

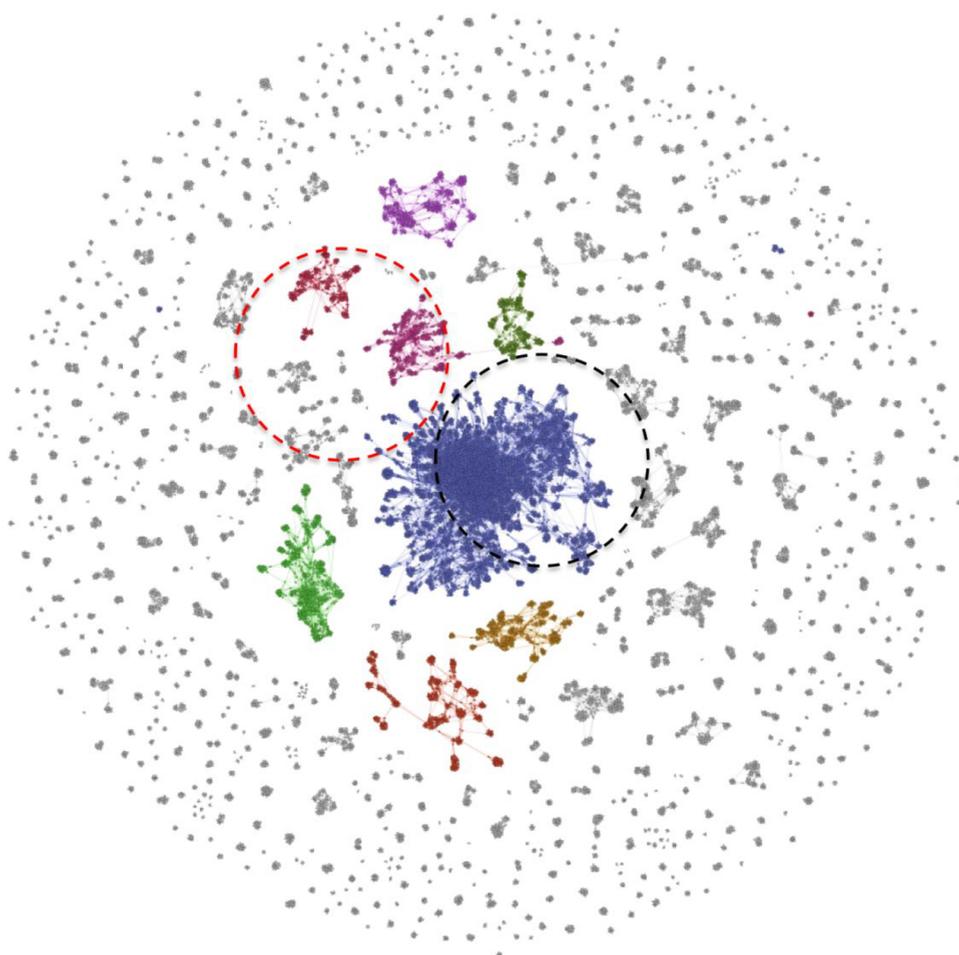


Figure 2. Friedel–Crafts reaction network. The network is chromatically labeled by a frequent catalyst with the scheme provided in the legend of Figure 3(a).

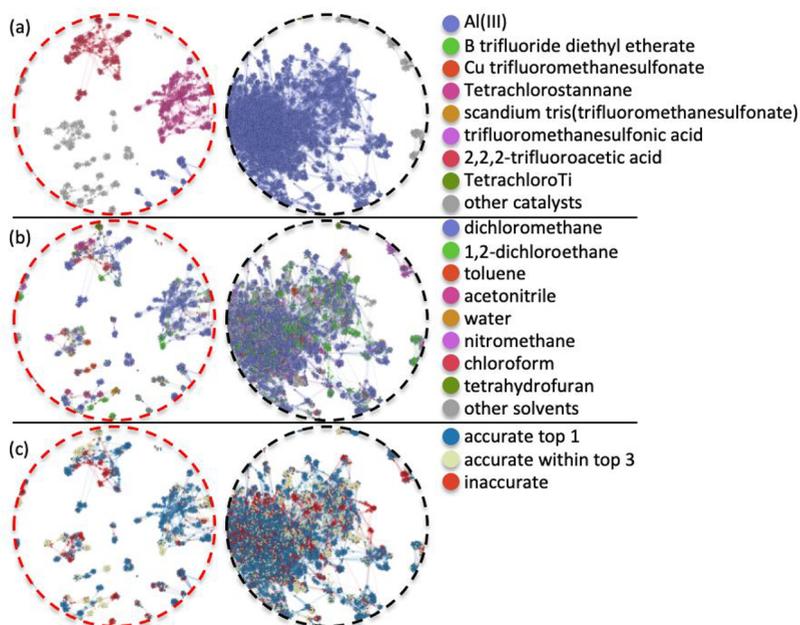


Figure 3. Two network cutouts chromatically labeled by property. One cutout is red, and the other cutout is black: (a) frequent catalysts chromatic label, (b) frequent solvents label, and (c) solvent prediction accuracy label.

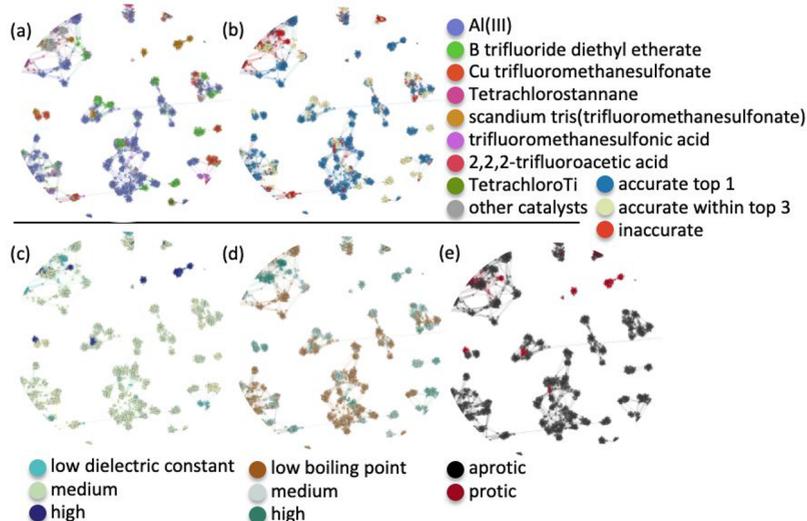


Figure 4. Frequent solvents cutout of the Friedel–Crafts network. The network is able to cluster reactions by solvent without any prior knowledge of solvent. Beyond solvent identity, solvent properties reveal clusters of consistency at least as large as solvent identity: (a) solvents, (b) solvent prediction accuracy, (c) dielectric constant, (d) boiling point, and (e) protic or aprotic.

371 **Figure 2** shows that a small fraction of the catalysts appears
 372 frequently within the data, while many others appear sparsely.
 373 For a small cluster consisting of a single catalyst, often only one
 374 solvent is used for all of the reactions (note that the clustering
 375 is performed *without* knowledge of solvent). These data points
 376 are easy to predict to high accuracy, with the solvent label
 377 matching one-to-one with the catalyst species. For the larger
 378 clusters, the same catalyst might appear with several different
 379 solvents, as is obvious in **Figure 3** (e.g., the Al(III) region of
 380 (a), with a colorful mixture of solvents shown in (b)). For the
 381 kNN algorithm, these clusters are harder to accurately predict
 382 compared to the more uniform, isolated smaller clusters. At the
 383 same time, these regions of the graph do contain subclusters
 384 that are consistent, so the ordering is not random. The
 385 overlaps between these subclusters lead to unavoidable errors,
 386 as classification algorithms cannot easily distinguish over-
 387 lapping data points. In these cases, solvent predictions through
 388 the top-3 classification (**Table 2**) will gain considerably in
 389 accuracy compared to top-1 classification (**Table 1**), as
 390 multiple solvents may perform just as well for similar
 391 substrate/catalyst combinations. In total, however, **Figures 2**
 392 and **3** show that there is a considerable degree of order in
 393 clustering, with many small clusters having highly consistent
 394 solvent designations.

395 Having the reactions ordered by solvent suggests an
 396 interesting possibility: does the reactant/catalyst ordering
 397 imply order in the solvent *properties*. **Figure 4** suggests that
 398 this is indeed the case, where the Friedel–Crafts reaction
 399 network is labeled with solvent descriptors. The three solvent
 400 properties—dielectric constant, boiling point, and protic/
 401 aprotic—form clusters of consistency, showing that the
 402 solvents are chemically similar to one another. Importantly,
 403 this ordering in solvent properties is found in the product/
 404 catalyst network and is not an ordering predetermined by the
 405 solvent properties. Instead, the product/catalyst network
 406 implies necessary traits of solvents, which then in turn are
 407 neatly represented in the graphs.

408 In addition to the graphical analysis, **Figure 5** shows that
 409 Zipf's law²¹ approximates the distribution of catalysts in all five
 410 reaction data sets. The fact that Zipf's law generally applies to

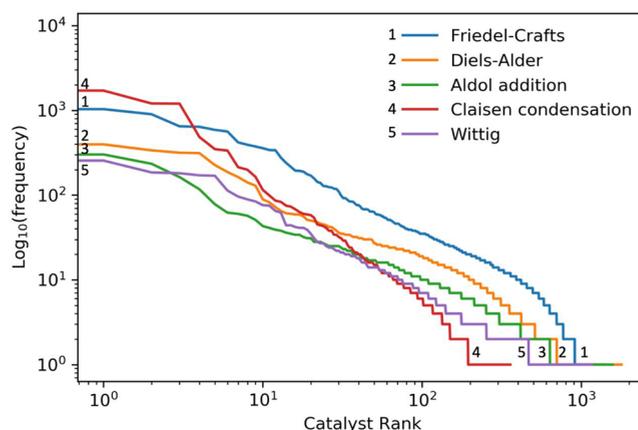


Figure 5. Zipf's law describes catalyst distributions. For all 5 reaction data sets, catalysts appear with a frequency described by a power law known as Zipf's law.

the catalyst distribution of all 5 data sets suggests a significant
 411 trend: there are a large number of catalyst identities which
 412 appear only once, forming a non-negligible slice of the data
 413 where predictions cannot be easily made. In the interpretable
 414 kNN solvent prediction algorithm, single-catalyst reactions
 415 have no neighbors. Not only does this greatly limit the ability
 416 of kNN to make predictions, it implies that there is not enough
 417 data to training machine learning algorithms in general for
 418 these important “outlier” cases. For the 5 reaction classes,
 419 0.76% to 7.30% of the data points are single-catalyst. 420

3.3. Human Chemist Focus Group Trials. To provide
 421 feedback on the algorithm, a small group of chemists was
 422 assembled for evaluation and trials. The purpose of gathering
 423 these chemists was 3-fold: 1. to provide comparisons between
 424 computer and expert solvent predictions, 2. to evaluate
 425 whether computer solvent predictions were within reason on
 426 unlabeled data points, and 3. to give a general discussion of
 427 strengths and weaknesses of the algorithm. See the **Supporting**
 428 **Information** for a complete description of the focus group
 429 procedure (Section VIII). 430

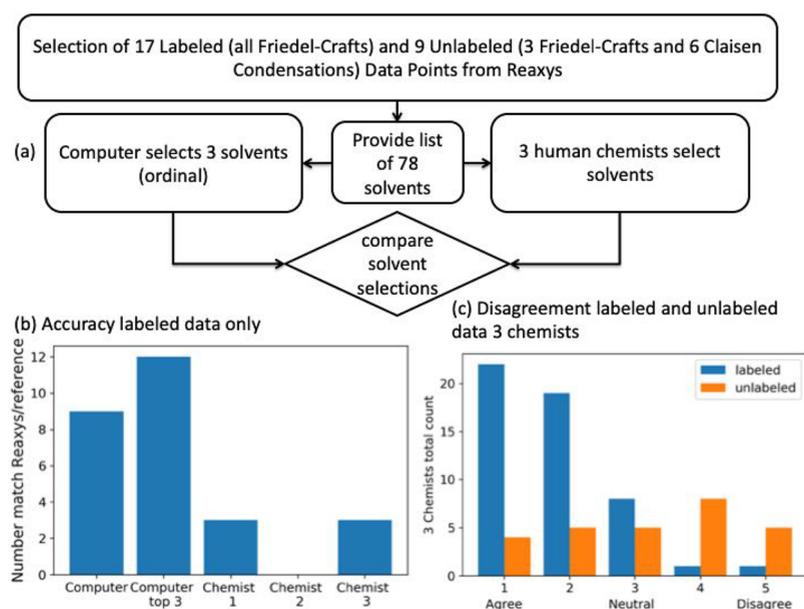


Figure 6. Human chemist focus group trials of computer solvent selection. (a) The computer ranks its top 3 solvents, and human chemists select solvents from a reaction test set. (b) The number of matches between the computer and the human chemists is counted for solvent-labeled reactions. (c) The spectrum of agreement to disagreement of the human chemists to the computer is totaled.

431 The focus group evaluated a set of Friedel–Crafts and
 432 Claisen condensation reactions and was asked to predict the
 433 correct solvent from a list of 78 possibilities. The chemists
 434 were given the reaction in ChemDraw format along with the
 435 specific catalyst used in the Reaxys data entry. Of the 26
 436 reactions in the evaluation set, 17 were labeled reactions (i.e.,
 437 solvent listed in the Reaxys data entry), and 9 of the set of
 438 reactions were unlabeled. The chemists were asked to select
 439 solvents over a time frame of 30 min, equating to a little over 1
 440 min per reaction on average.

441 The 17 labeled reactions in the test set were Friedel–Crafts
 442 reactions. Since the labels are available, accuracy of the
 443 computer and chemist can be evaluated on this subset, while
 444 for the 9 unlabeled points, “accuracy” is much more qualitative
 445 and will be discussed in the subsequent paragraph. In the
 446 labeled subset the computer’s first solvent choice matched the
 447 label in 9 occurrences (via the kNN algorithm), giving correct
 448 predictions of dichloromethane 3 times,^{46–48} water 3
 449 times,^{49–51} dichloroethane 1 time,⁵² and chloroform 2
 450 times.^{53,54} The second choice of the computer matched the
 451 Reaxys entry twice for dichloroethane and once for water. The
 452 chemists, however, performed at a lower success rate than the
 453 computer: an average of 2 matches per chemist was found with
 454 the 17 solvent labels. As discussed above, the Friedel–Crafts
 455 reaction is a particularly difficult one to make solvent choices,
 456 leading to apparent disagreement between chemists and
 457 available solvent labels. This disagreement was explicitly
 458 discussed after the expert testing to give additional insight.

459 After the human chemists completed their solvent selections,
 460 the computer solvent selections were revealed for labeled as
 461 well as unlabeled data points (26 in total). The human
 462 chemists were then asked to rate their level of agreement with
 463 the computer’s first solvent choice. The rating scale of 1 (no
 464 disagreement) to 5 (full disagreement) allowed the chemists to
 465 give subjective feedback about the performance of the
 466 computer. As shown in Figure 6c, the chemists more often
 467 sided with the algorithm than against, with a mean agreement
 468 level of 2.3 on the 1 to 5 scale. The human chemists therefore

469 regarded the algorithm as generally accurate, although one
 470 exception is shown below with a consistent, strong disagree-
 471 ment.

472 Figure 6c reveals a trend of the chemists disagreeing more
 473 regarding the unlabeled data points rather than the labeled.
 474 This may be explained by the unlabeled data point predictions
 475 from the computer being less informed than for labeled data
 476 points. This is evidenced by the computer not selecting second
 477 nor third solvents for 7 of the 9 unlabeled data points, due to
 478 the sparsity of neighbor connections from which to select
 479 solvents. Among the labeled data points, a lower fraction of 4
 480 missing second solvents and 14 missing third solvents out of 17
 481 allowed a better populated region of data and more informed
 482 solvent choices.

483 One example showed high levels of disagreement between
 484 the focus group and the computer (all chemists rated this point
 485 with a 5, full disagreement). In this case, the computer selected
 486 water for a reaction in which one of the reactants was acetic
 487 anhydride.⁵⁵ The chemists noted that water reacts with acetic
 488 anhydride, causing an undesired side reaction (resulting in a
 489 lower yield than an unreactive solvent). This side reaction
 490 could not be identified with the solvent prediction algorithms,
 491 leading to a knowledge gap that was swiftly noticed by the
 492 panel. In this particular case one would hope that a machine
 493 learning algorithm could be trained to learn the incompatibility
 494 with water as a solvent. As shown in Table S15 in the
 495 Supporting Information, however, using water as a solvent
 496 alongside reactant anhydride is based upon actual data in the
 497 literature. While the expert panel would object to this
 498 combination, the data-driven algorithm makes predictions
 499 based on the data it has available and is not able to learn from
 500 the expert objections.

501 A number of observations were made by the chemists
 502 regarding the solvent selection process, some of which are
 503 noted in Scheme 1. In addition to these points, the kNN
 504 algorithm was felt to be more transparent than other popular
 505 machine learning algorithms such as an artificial neural
 506 network. In other words, the concept of similarity measured

Scheme 1. Focus Group Observations

Focus Group Observations

- Chemists agreed that the computer algorithm was providing reasonable results. The chemists did not detect biases in solvent choice from the computer.
- The computer had access to a large data set of reactions which gave it an advantage over a human, who could look up reactions in the same database given sufficient time and effort.
- The computer made solvent predictions based upon the most popular solvents among its neighbors, but chemists did not believe it was thinking critically about whether the solvent was good or not.
- The nearest neighbor algorithm provides a list of data entries used in a particular solvent prediction, and this data points to original articles that allow for the prediction to be checked and interpreted.

507 by the kNN algorithm was acceptable to this group of experts.
 508 The algorithm “thought chemically” up to a point because the
 509 functional groups of the fingerprints were driving the similarity
 510 measures, and therefore the neighbor choices and ultimately
 511 the solvent predictions were seen as made through acceptable
 512 chemical reasoning.

4. CONCLUSIONS

513 Networks of named organic reactions show clusters of
 514 consistency that are predictive of experimental conditions.
 515 This technique was shown to accurately select solvents for
 516 these reactions, an essential component of experimental
 517 conditions. The kNN metric, a Tanimoto similarity with a
 518 catalyst label, was shown to be not only particularly effective in
 519 solvent classification but also rich in relevant conceptual
 520 chemical information. The raw molecular structure informa-
 521 tion was insufficient to accurately predict solvent, but the
 522 inclusion of a catalyst label provided the necessary chemical
 523 information to fill in this gap. Additionally, the solvent choices
 524 through this metric mimicked those of a human chemist and
 525 were visually interpretable, allowing an expert panel of
 526 chemists to view the algorithm favorably in critical testing.
 527 While the kNN method was tested on five common named
 528 reactions, it may be expanded to less-well-known classes of
 529 reactions based on the results of the present work. For
 530 example, a more general prediction algorithm could classify
 531 reactions by SMIRKS,⁵⁶ the reaction analogy to SMILES.
 532 SMIRKS would allow systematic classification of reactions by
 533 their mechanisms and the chemical substructure involved in
 534 those mechanisms, allowing treatment of essentially any class
 535 of reaction where the reactant/product pairs are known.
 536 In addition to having strong interpretive value, the kNN
 537 algorithm was the most accurate technique on 4 of the 5
 538 reaction data sets, with accuracies of 91.0 to 98.0% on top-3
 539 predictions. The highly popular technique, a deep neural
 540 network, was found to be numerically useful as well and
 541 slightly outperformed kNN on 1 of the 5 data sets (98.7% vs
 542 98.0% accuracy), performed similarly on 3 of the 5, and
 543 performed somewhat worse on the most challenging data set,
 544 the Friedel–Crafts reaction (89.0% vs 92.8%), cf. Table 2. In
 545 total, kNN was found to be a strong technique, having
 546 interpretive value as well as statistical accuracy, making it
 547 outcompete neural networks from our point of view.
 548 Continued studies using kNN are likely to provide a route
 549 for machine-expert interfaces, where feedback from the
 550 machine learning technique allows the expert chemist to
 551 learn deep insights from large data sets.

■ ASSOCIATED CONTENT

552

⑤ Supporting Information

553

The Supporting Information is available free of charge on the
 ACS Publications website at DOI: 10.1021/acs.jcim.9b00313. 554

Tanimoto similarities statistics, preprocessing flowchart, 556
 exception handling, catalyst dictionary, artificial neural 557
 network and k-nearest neighbor, accuracies statistics, 558
 Claisen condensation and Diels–Alder, human chemist 559
 focus group trials, and cluster example with chemical 560
 structure labels (PDF) 561

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Author Contributions

568

E.W. performed the calculations, created the graphs, and wrote 569
 the paper. P.Z. supervised the work and wrote the paper, and 570
 J.K. assisted with coding the algorithms. A.T. and J.G. provided 571
 guidance on designing networks, the deep neural net, and the 572
 support vector machine. M.R. organized the expert chemist 573
 panel. 574

Notes

575

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