Reaction Fingerprints: an early story

Gregory Landrum

NIBR IT

Novartis Institutes for BioMedical Research

RDKit UGM 2013, Hinxton

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Public data sources in cheminformatics

an aside at the beginning

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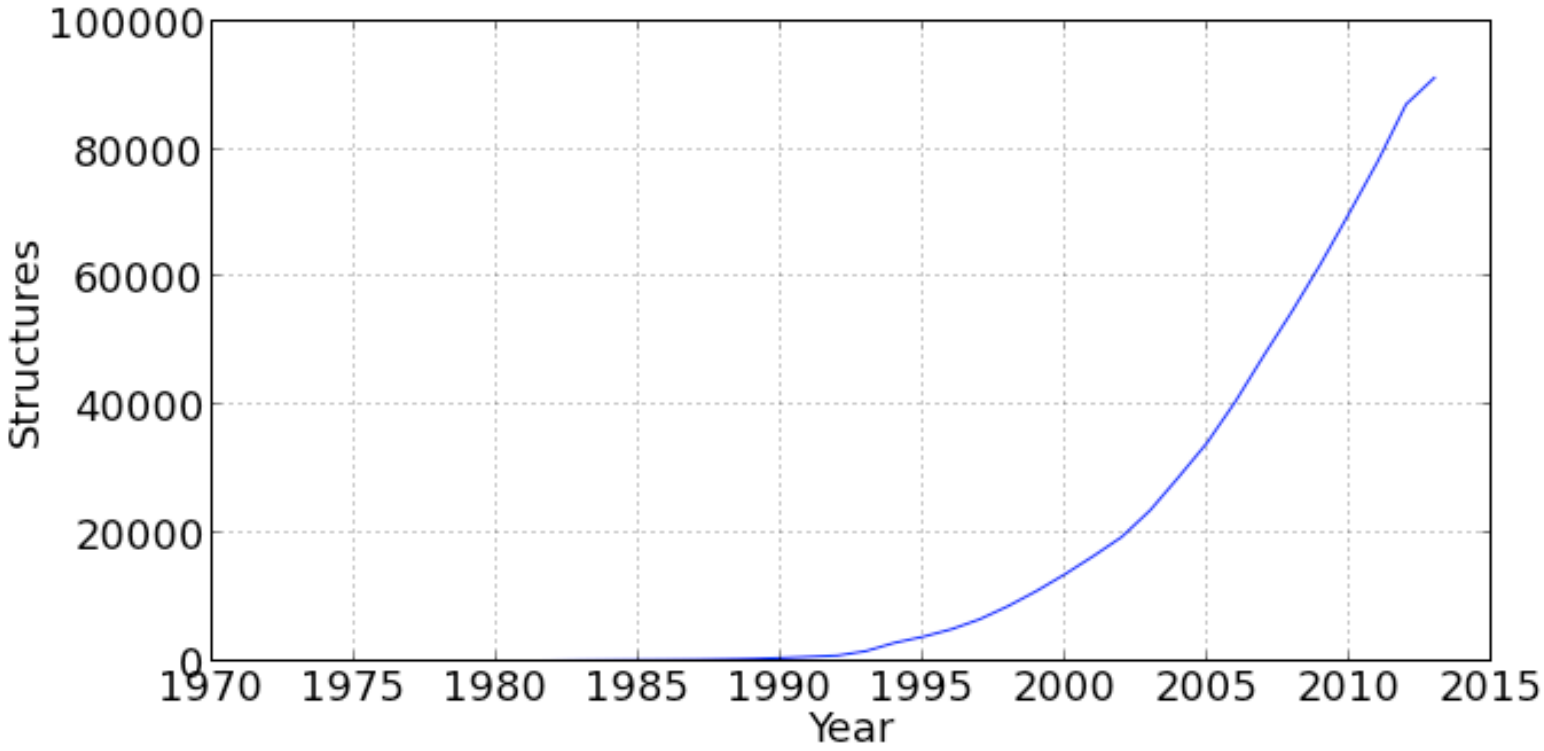
Protein data bank

the exception



- Crystal structures of proteins
- Deposition is mandatory for publishing protein crystal structures

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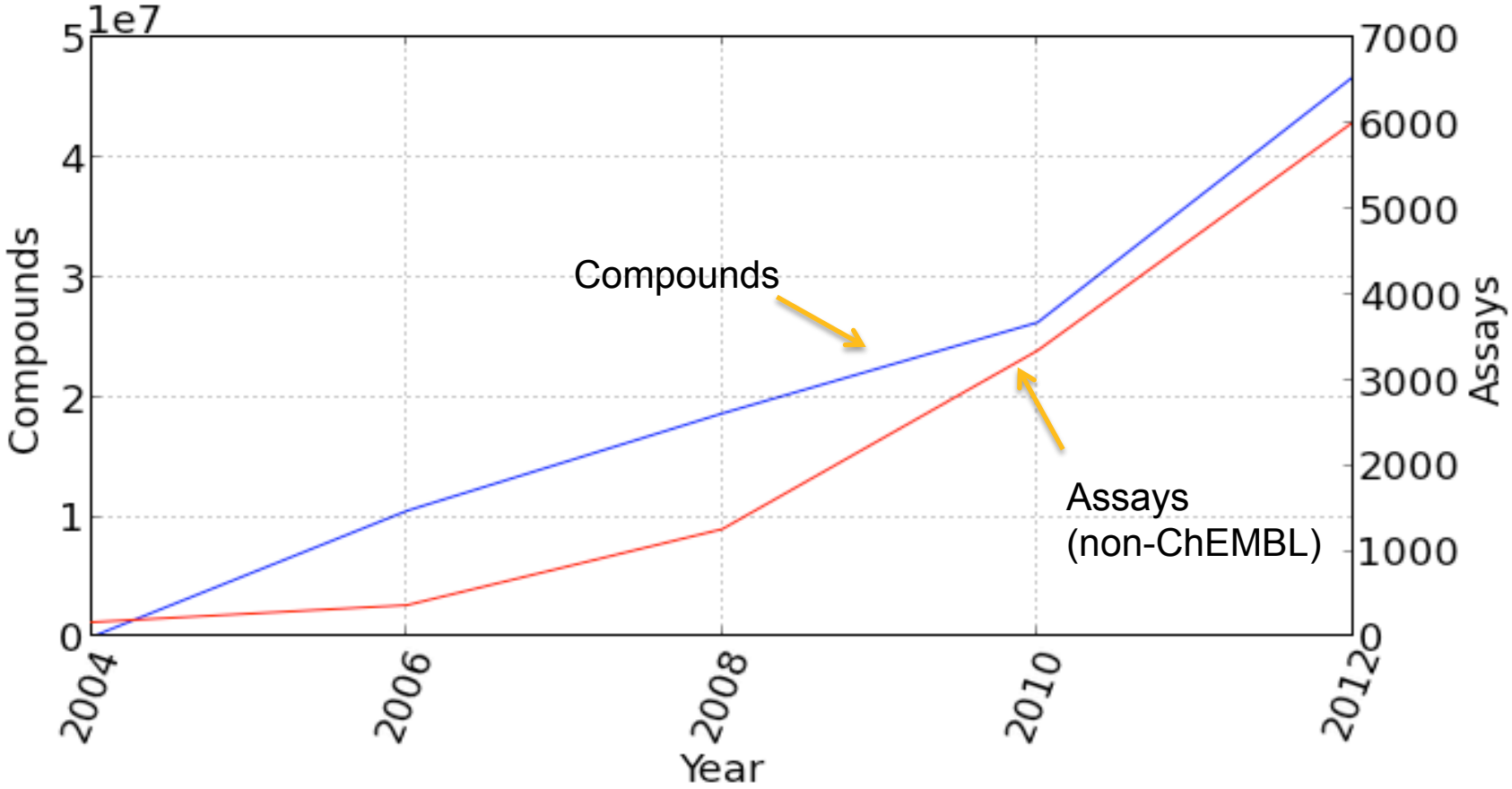
Pubchem

Evolution



Collection of molecules from vendors and patents together with some assay data, primarily from NIH-funded screening centers.

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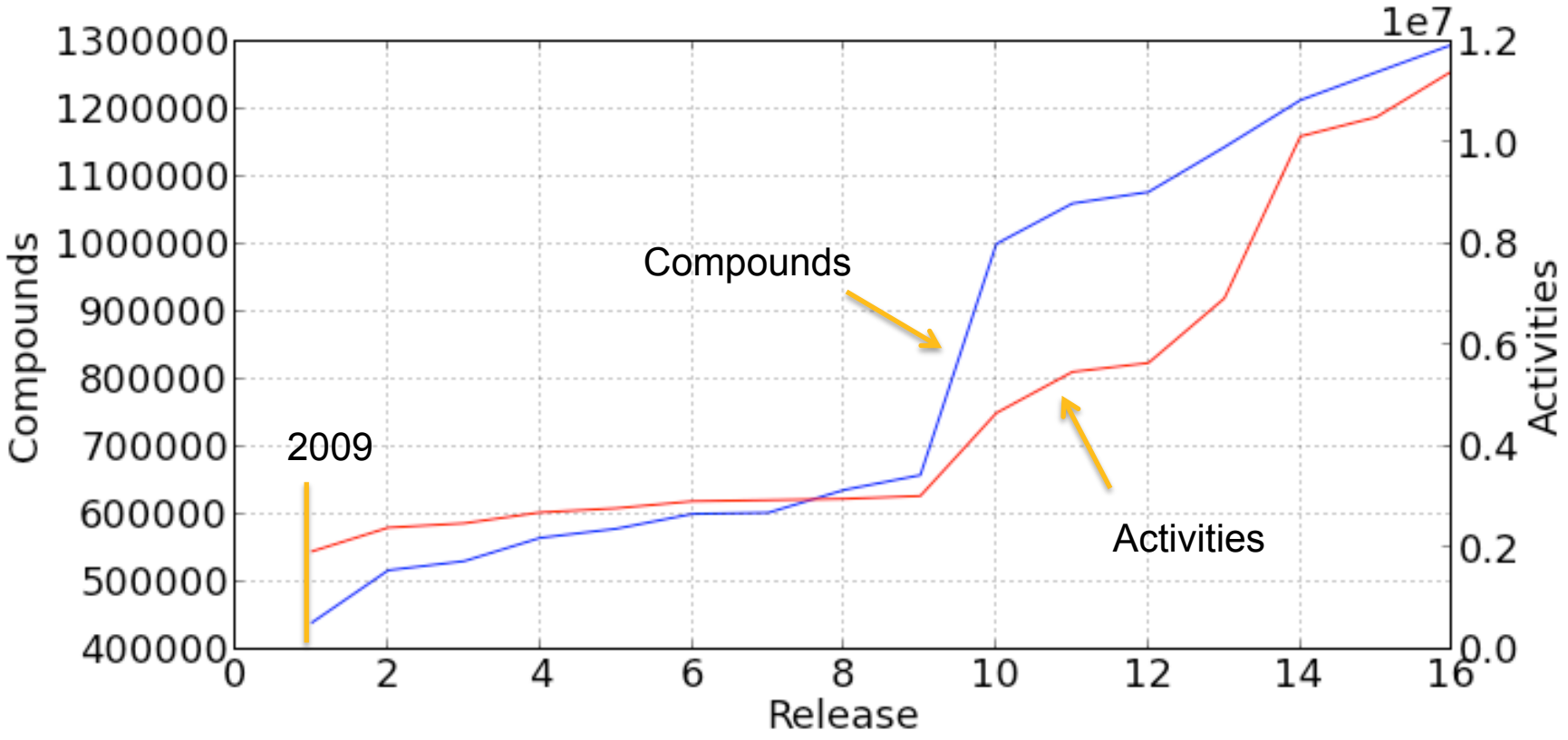
ChEMBL

Evolution



Collection of molecules and assay data curated (primarily) from the literature

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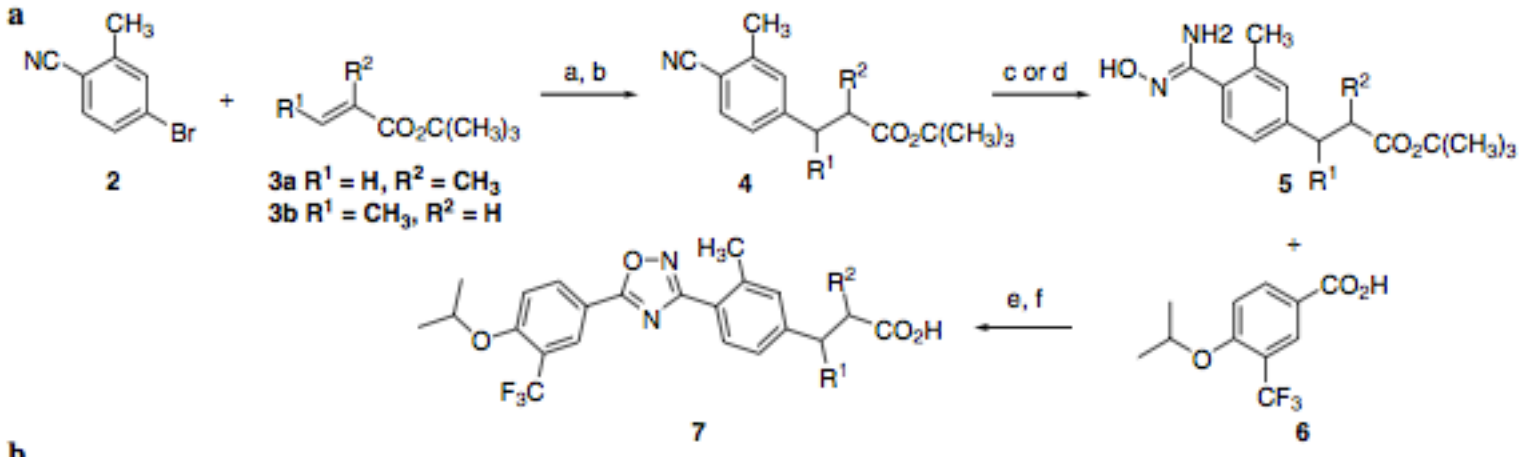
What about how we made those molecules?

Public reaction data?

- The literature:



- Plenty of data locked up in large commercial databases, very very little in the open

Yan, L. *et al.* SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 (S1P1) with enhanced pharmacokinetic properties. *Bioorganic & Medicinal Chemistry Letters* **17,** 828–831 (2007).

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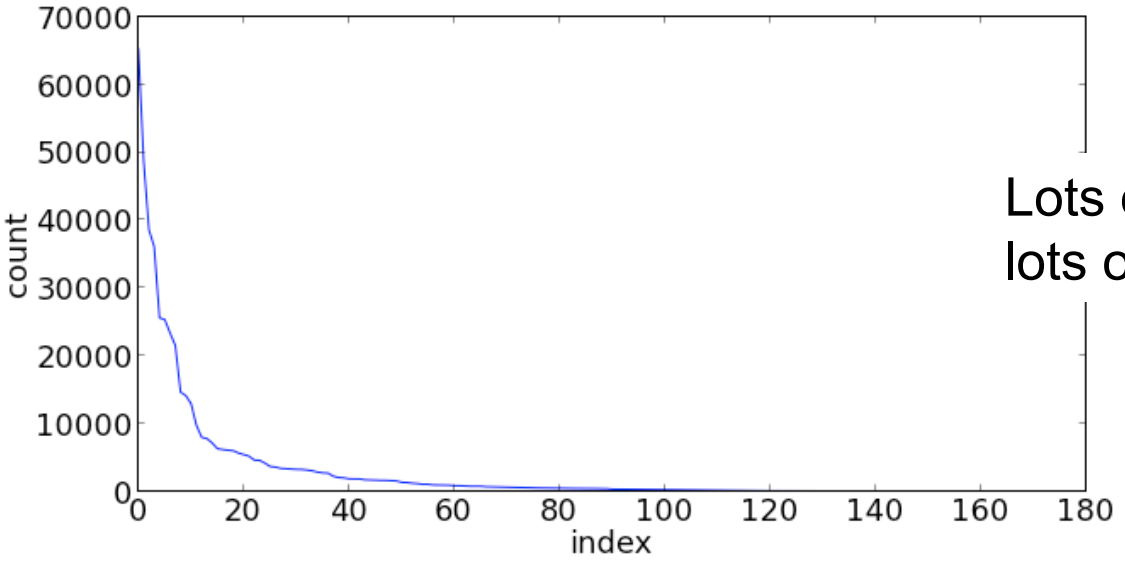
An emerging area: chemical reactions

Not just what we made, but how we made it

- Text-mining applied to open patent data to extract chemical reactions : 1.12 million reactions[1]
- Reactions classified, when possible, into 156 standard types : >500000 classified reactions[2]



Lots of reactions,
lots of repeats

[1] Lowe DM: "Extraction of chemical structures and reactions from the literature." PhD thesis. University of Cambridge: Cambridge, UK; 2012.
[2] Reaction classification from Roger Sayle and Daniel Lowe (NextMove Software)

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Got the reactions, what about reaction fingerprints?

Criteria for them to be useful

- Question 1: do they contain bits that are helpful in distinguishing reactions from another?

  Test: can we use them with a machine-learning approach to build a reaction classifier?

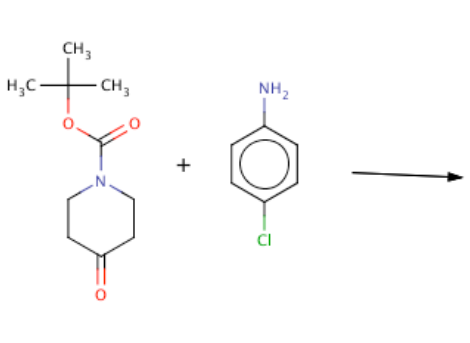
- Question 2: are similar reactions similar with the fingerprints

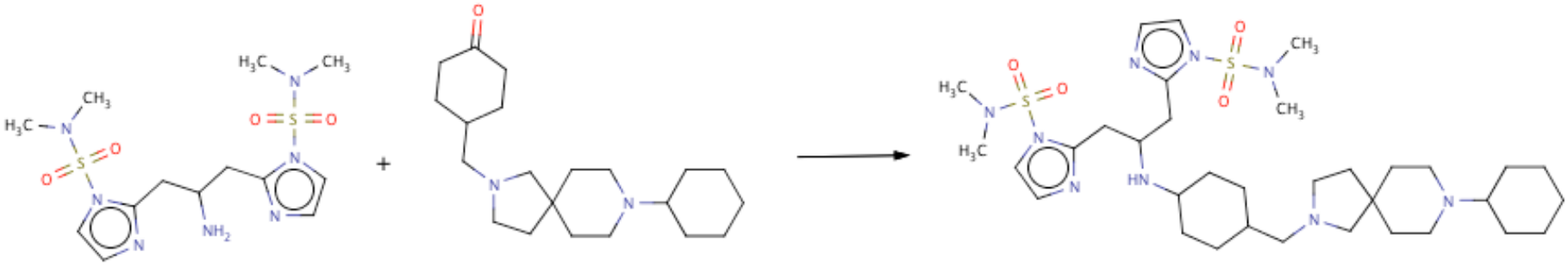
  Test: do related reactions cluster together?

Similarity applied to reactions

What are we talking about?

- These two reactions are both type: “1.2.3 Ketone reductive amination”





It’s obvious that these are the same, right?

Got the reactions, what about reaction fingerprints?

Start simple: use difference fingerprints:

$$FP_{\text{Reacts}} = \sum_{i \in \text{Reactants}} FP_i$$

$$FP_{\text{Products}} = \sum_{i \in \text{Products}} FP_i$$

$$FP_{\text{Rxn}} = FP_{\text{Prods}} - FP_{\text{Reacts}}$$

```
rapfp=None
for ri in range(rxn.GetNumReactantTemplates()):
    m = rxn.GetReactantTemplate(ri)
    fp = AllChem.GetAtomPairFingerprint(m,includeChirality=True)
    if rapfp is None:
        rapfp = fp
    else:
        rapfp += fp

papfp=None
for ri in range(rxn.GetNumProductTemplates()):
    m = rxn.GetProductTemplate(ri)
    fp = AllChem.GetAtomPairFingerprint(m,includeChirality=True)
    if papfp is None:
        papfp = fp
    else:
        papfp += fp

apfp = papfp-rapfp
```

Similar idea here: Ridder, L. & Wagener, M. SyGMa: Combining Expert Knowledge and Empirical Scoring in the Prediction of Metabolites. *ChemMedChem* **3,** 821–832 (2008).

Are these fingerprints useful?

- **Question 1:** do they contain bits that are helpful in distinguishing reactions from another?

  Test: can we use them with a machine-learning approach to build a reaction classifier?

- Question 2: are similar reactions similar with the fingerprints

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Machine learning and chemical reactions

- Validation set:
  - The 40 reaction types with at least 2000 instances from the patent data set
    - 2 separation reaction types removed (11.2 Separation [Resolution] and 11.3 Chiral separation [Resolution])
    - Final: 38 reaction types

- Process:
  - Training set is 200 random instances of each reaction type
  - Test set is 1000 random instances of each reaction type
  - Learning: random forest (scikit-learn)

Learning reaction classes

Results

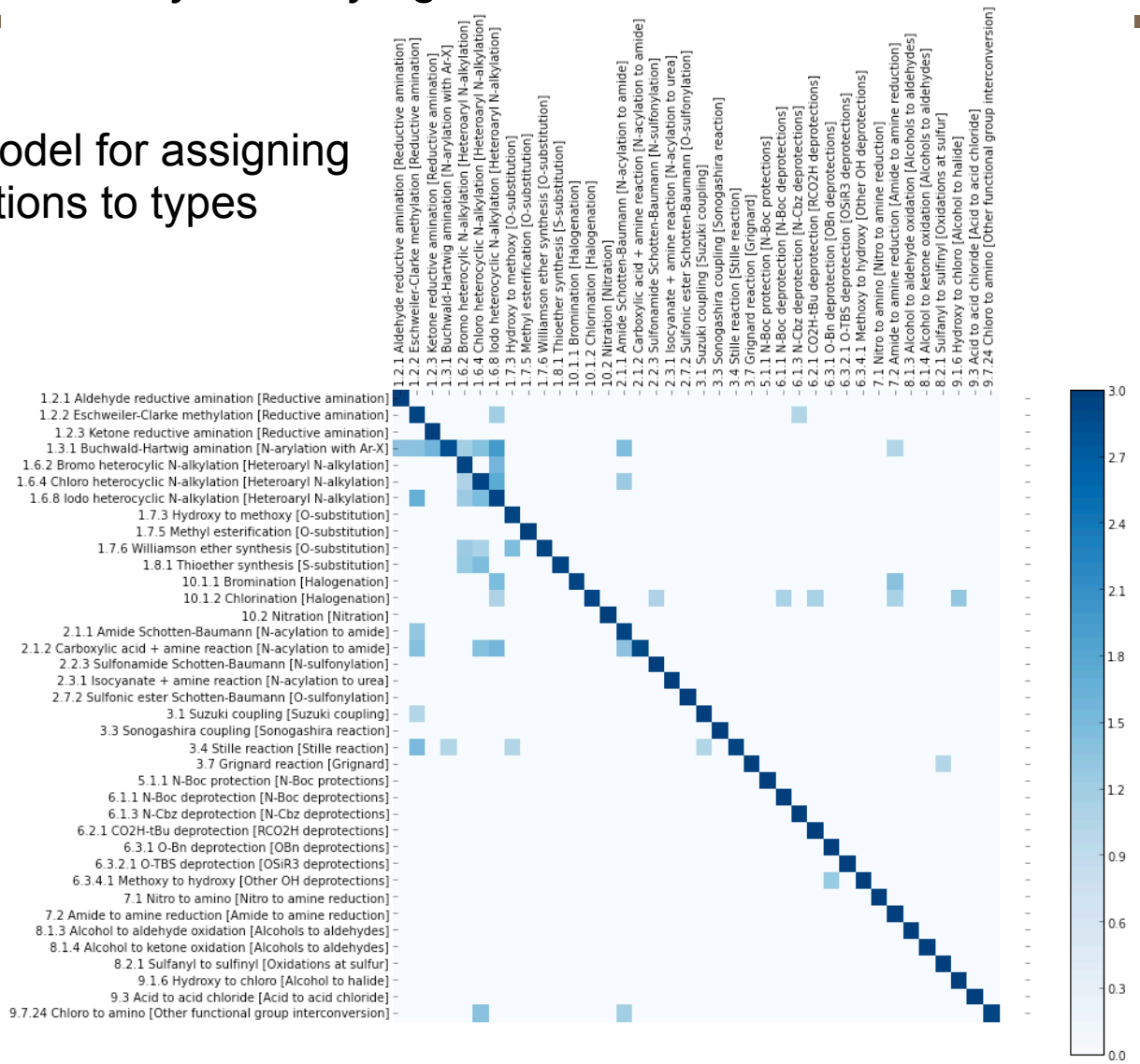
0 0.9890 0.9687 1.2.1 Aldehyde reductive amination [Reductive amination]
1 0.9410 0.8508 1.2.2 Eschweiler-Clarke methylation [Reductive amination]
2 0.9880 0.9518 1.2.3 Ketone reductive amination [Reductive amination]
3 0.6840 0.9434 1.3.1 Buchwald-Hartwig amination [N-arylation with Ar-X]
4 0.9200 0.9037 1.6.2 Bromo heterocylic N-alkylation [Heteroaryl N-alkylation]
5 0.8550 0.8350 1.6.4 Chloro heterocyclic N-alkylation [Heteroaryl N-alkylation]
6 0.8710 0.7400 1.6.8 Iodo heterocyclic N-alkylation [Heteroaryl N-alkylation]
7 0.9440 0.9347 1.7.3 Hydroxy to methoxy [O-substitution]
8 0.9770 0.9879 1.7.5 Methyl esterification [O-substitution]
9 0.9170 0.9797 1.7.6 Williamson ether synthesis [O-substitution]
10 0.9410 0.9731 1.8.1 Thioether synthesis [S-substitution]
11 0.9060 0.9912 10.1.1 Bromination [Halogenation]
12 0.8560 0.9761 10.1.2 Chlorination [Halogenation]
13 0.9710 0.9959 10.2 Nitration [Nitration]
14 0.9280 0.9143 2.1.1 Amide Schotten-Baumann [N-acylation to amide]
15 0.8160 0.9680 2.1.2 Carboxylic acid + amine reaction [N-acylation to amide]
16 0.9960 0.9774 2.2.3 Sulfonamide Schotten-Baumann [N-sulfonylation]
17 0.9940 0.9871 2.3.1 Isocyanate + amine reaction [N-acylation to urea]
18 0.9930 0.9960 2.7.2 Sulfonic ester Schotten-Baumann [O-sulfonylation]
19 0.9690 0.9808 3.1 Suzuki coupling [Suzuki coupling]
20 0.9960 0.9651 3.3 Sonogashira coupling [Sonogashira reaction]
21 0.9000 0.9688 3.4 Stille reaction [Stille reaction]
22 0.9700 0.9898 3.7 Grignard reaction [Grignard]
23 0.9560 0.9917 5.1.1 N-Boc protection [N-Boc protections]
24 0.9930 0.9315 6.1.1 N-Boc deprotection [N-Boc deprotections]
25 0.9980 0.9122 6.1.3 N-Cbz deprotection [N-Cbz deprotections]
26 0.9920 0.9538 6.2.1 CO2H-tBu deprotection [RCO2H deprotections]
27 0.9890 0.8966 6.3.1 O-Bn deprotection [OBn deprotections]
28 0.9990 0.9852 6.3.2.1 O-TBS deprotection [OSiR3 deprotections]
29 0.9670 0.9719 6.3.4.1 Methoxy to hydroxy [Other OH deprotections]
30 0.9940 0.9660 7.1 Nitro to amino [Nitro to amine reduction]
31 0.9780 0.8956 7.2 Amide to amine reduction [Amide to amine reduction]
32 0.9920 0.9754 8.1.3 Alcohol to aldehyde oxidation [Alcohols to aldehydes]
33 0.9850 0.9676 8.1.4 Alcohol to ketone oxidation [Alcohols to aldehydes]
34 0.9920 0.9773 8.2.1 Sulfanyl to sulfinyl [Oxidations at sulfur]
35 0.9770 0.9635 9.1.6 Hydroxy to chloro [Alcohol to halide]
36 0.9750 0.9750 9.3 Acid to acid chloride [Acid to acid chloride]
37 0.9250 0.9716 9.7.24 Chloro to amino [Other functional group interconversion]

overall >90% accuracy

Machine learning and chemical reactions

Automatically classifying reactions

Build a model for assigning new reactions to types



>90% accuracy

much of the confusion is between related types

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Are these fingerprints useful?

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- **Question 2**: are similar reactions similar with the fingerprints

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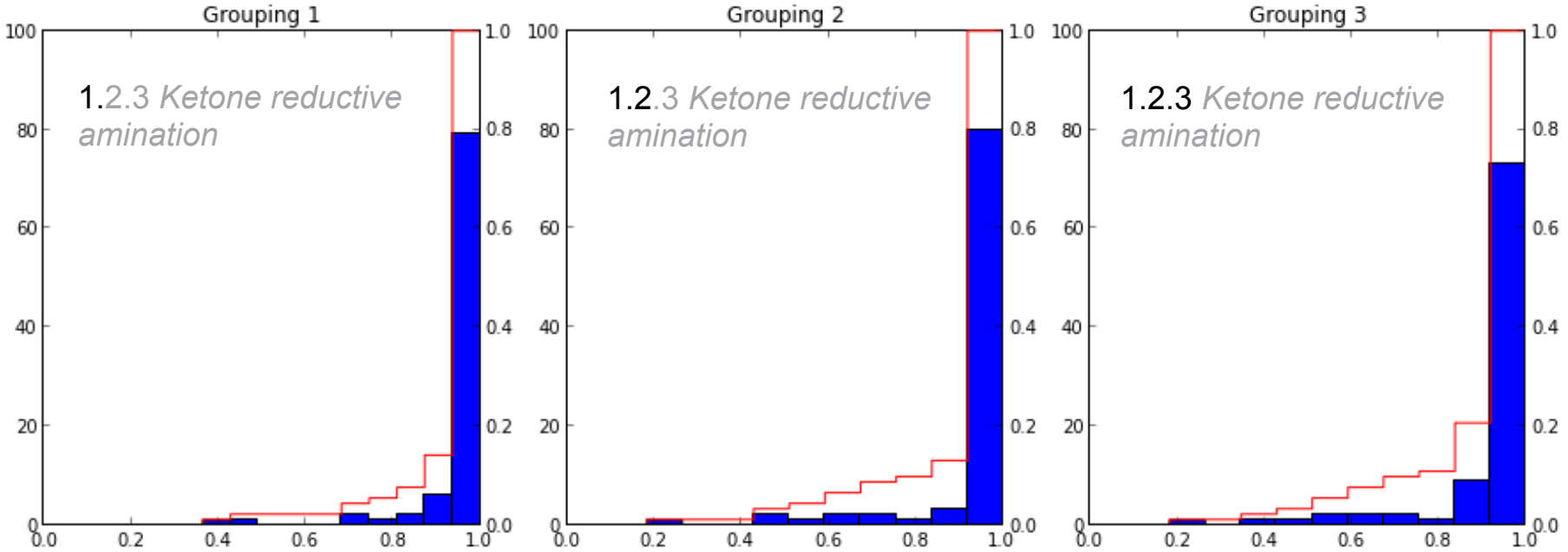
Clustering reactions

- Reaction similarity validation set:
  - The 54 most common reaction types from the patent data set
  - Look at the homogeneity of clusters



More effort needed, but this is a pretty strong start.

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Similarity applied to reactions

Can we help classify the remaining 600K reactions?

- Starting point: we have a similarity measure that clusters related reactions together
- We can apply the machine-learning model to the unclassified reactions and see if the original assignment missed any instances
- We can then look for big clusters of unclassified molecules and (manually) assign classes to them.

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  - Roger Sayle
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