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Compound Collection Analysis and Augmentation

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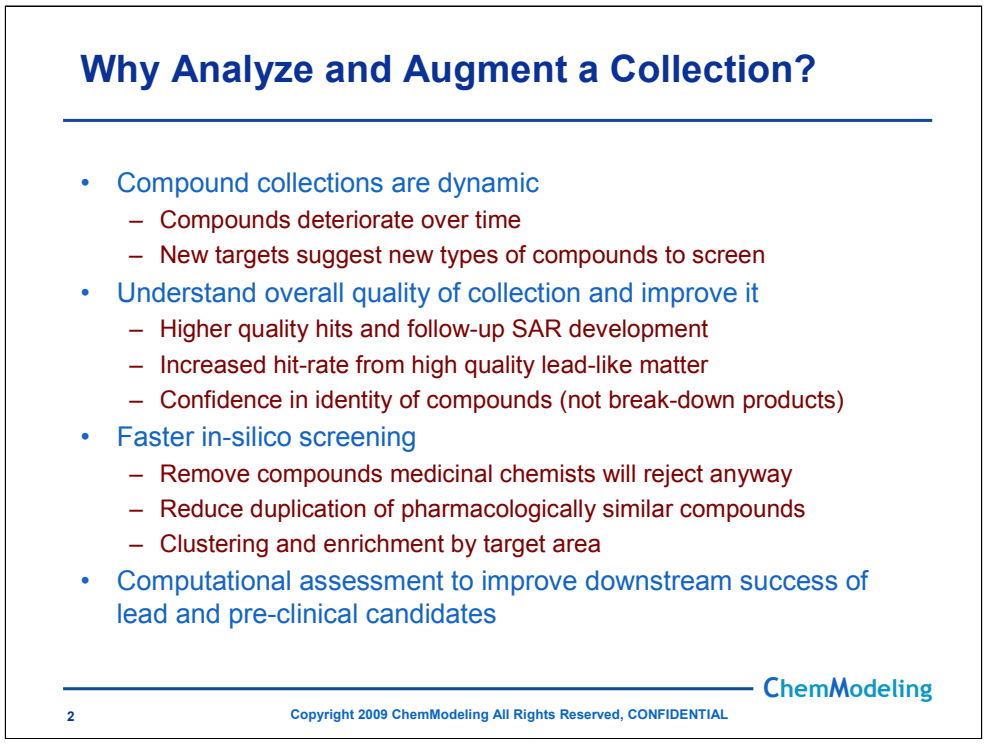
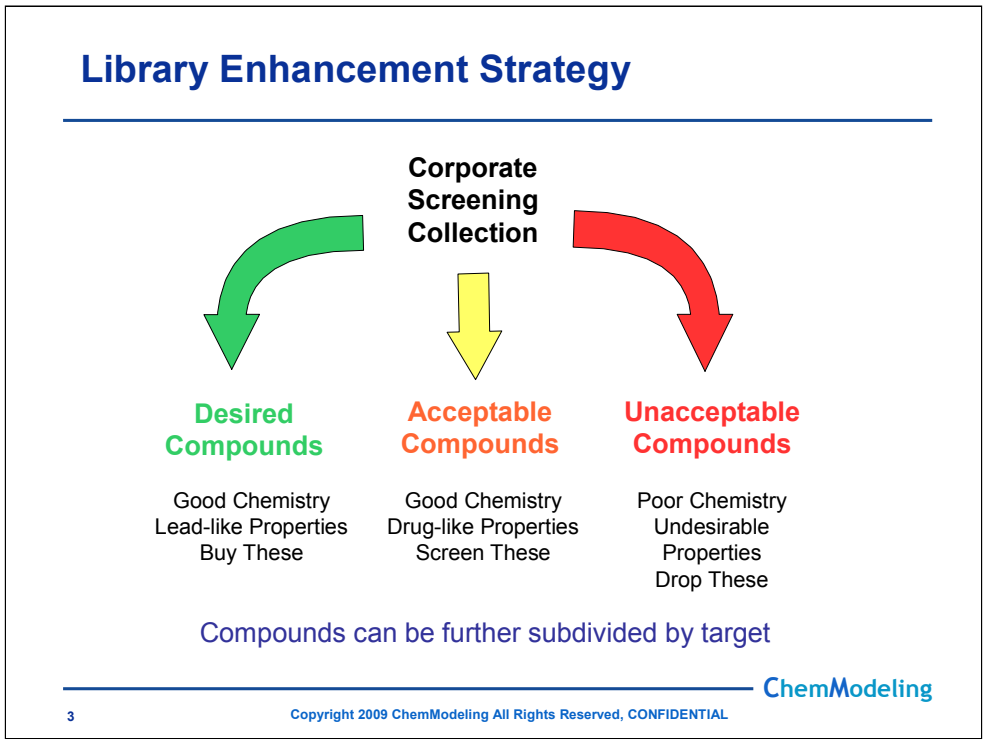
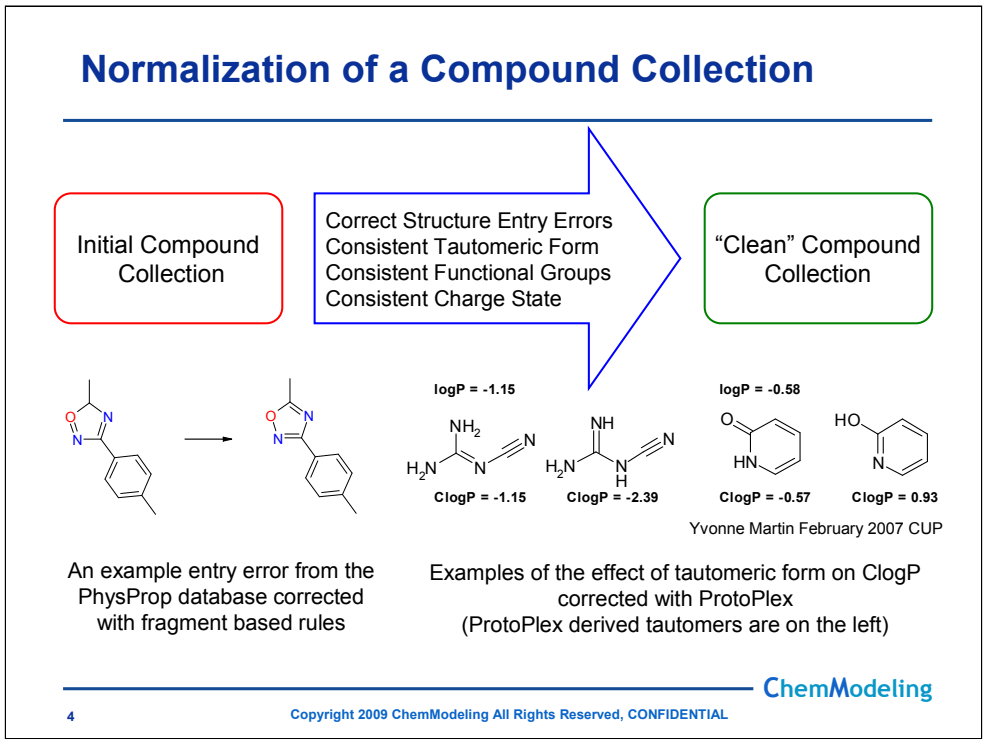


We have found that companies are starting to think more seriously about their existing compound collections. Compounds that are being screened should be periodically reanalyzed for purity and composition. Compounds that fail this analysis should be removed and replaced with new compounds. In addition, as priorities change with respect to screening targets, libraries should be periodically augmented with additional compounds available from a number of vendors who sell screening libraries. Judicious selection can minimize cost and maximize return. We have experience, having completed a project of this type with a large biotech company.



Typically the existing screening set is treated more gently than compounds that would be purchased, since the compounds are already in hand. However, even in this case, it may be desirable to weed out compounds that are unlikely to provide good hits. In the past the “acceptable compound” definition was used to filter the existing collection and the “desired compound” definition used to filter potential new purchases.



Our experience has been that compound databases often have a number of problems that our tools can correct. These include mis-entered structures, inconsistent representation of functional groups, multiple tautomeric forms, and inconsistent representation of salts. In the ~500K database we recently analyzed about 0.1% of the structures were mis-entered and about 2/3 could be corrected with fragment based rules. It was unclear what was intended for the other structrures. About 2% of the compounds had multiple tautomeric forms. About 2.5% of the structures were duplicates (including multiple salt forms of the same structure) and 3% of the compounds were eliminated due to undesirable functional groups.

Toward a Lead-like or Targeted Subset

Compounds in a screening set should have drug-like or lead-like properties

Lipinski's "Rule of 5" is the best known filtering criteria

Poor absorption or permeation of an orally administered drug is more likely to occur if any two of these criteria are violated:

- Molecular weight is greater than 500
- Lipophilicity is high (ClogP is greater than 5)
- Number of Hydrogen bond donors is greater than 5
- Number of Hydrogen bond acceptors is greater than 10

There are MANY others

=> Rules need to be tailored to specific customers needs

Properties of Oral Drugs Categorized by Gene Family

	90% MW	90% ClogP	90% HBD	90% HBA	90% Rbonds
Aminergic GPCRs	460	5.6	2	6	8
Ion Channels	430	4.7	3	6	7
Nuclear Hormone Receptors	495	7.3	2	6	10
Peptide GPCRs	752	6.5	8	10	17
Phospho-diesterases	465	5.2	2	8	9
Protein Kinases	505	5.7	4	7	9
Serine Proteases	572	4.8	4	8	12

Hopkins, et al, Nature Biotechnology **2006,** 7, 805-815

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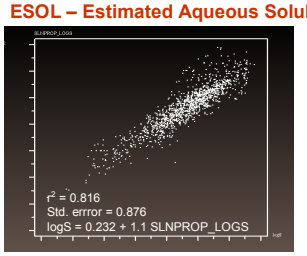
The exact property filters depend on the customer and the use for which the collection is intended. Prior to setting filters we will provide the distribution of property values in the collection to allow one to estimate how much the collection will be reduced. We also typically analyze the diversity of the collection to determine how evenly distributed the compounds are in the chemistry space.

Other Factors are also Important

- Fragment Based Filters
  - Unwanted
  - Unstable
  - Toxic groups
- Similarity/Dissimilarity to Known Targets
- Custom Scoring Functions

ESOL – Estimated Aqueous Solubility



Plot of ESOL predicted solubility implemented in slnProperty versus the experimental logS values for compounds used as a training set for ALOGPS program from the ALOGPS website.

log(S) = 0.16 – 0.63 * ClogP
– 0.0062 * MW + 0.066 * RotBonds
– 0.74 AromaticFraction

AromaticFraction is fraction of heavy atoms in aromatic 6-membered rings

Delaney, J. S. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1000 – 1005.

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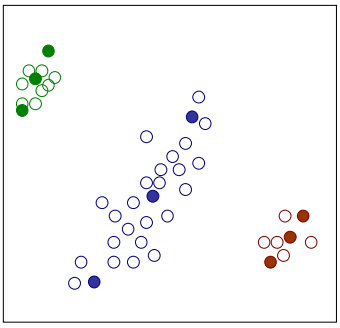
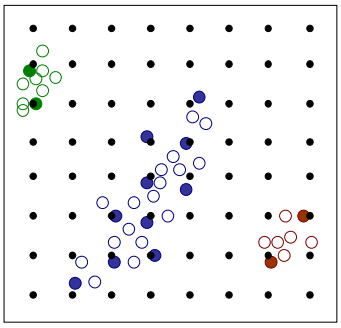
We have developed an extensive set of “undesirable” filters as a result of years of doing library design. We review these with the customer, who is free to add additional filters. We also have a fairly sophisticated scoring function built into our filtering program. It can take any combination of property or fragment filters and create a “score” value that can be filtered on. Either raw values (as in the ESOL implementation) or limits (as one might use to implement the Lipinski rules- i.e., at most two violations) can be encoded.

Toward a Representative Subset

Distance-based gridding of chemistry space allows representative selections



A typical cluster-based selection choosing 3 compounds per cluster



Selection based on equally-spaced grid points better samples clusters

Many different types of distances can be employed- 2D Taminoto fingerprint similarities, topomer distances, SurFlex-Sim similarities, or others.

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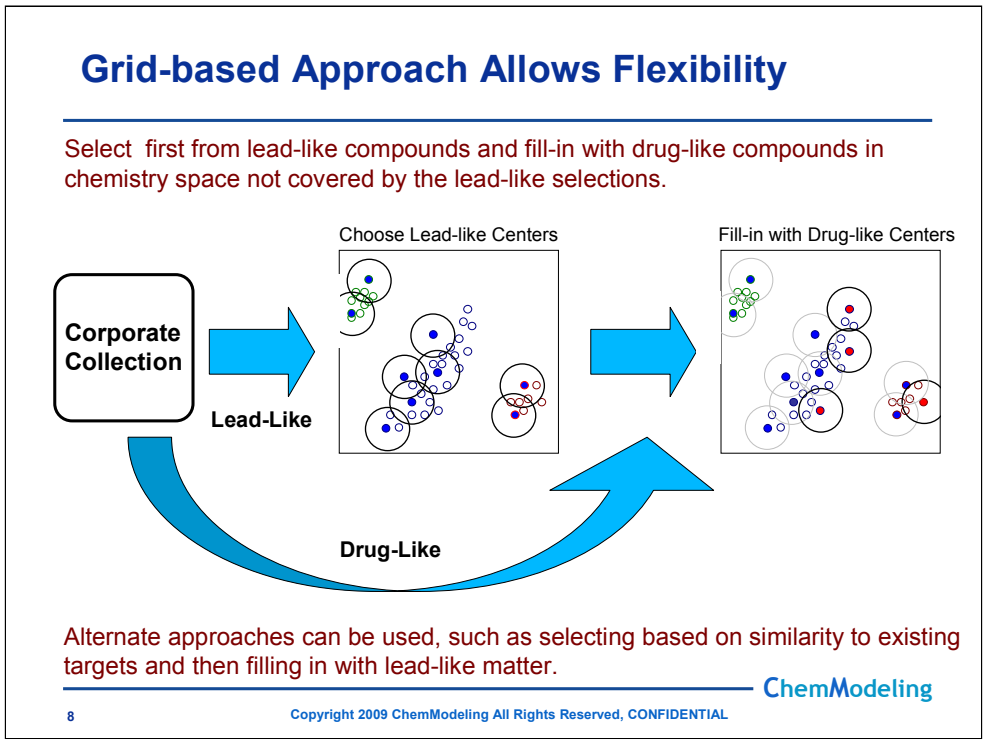
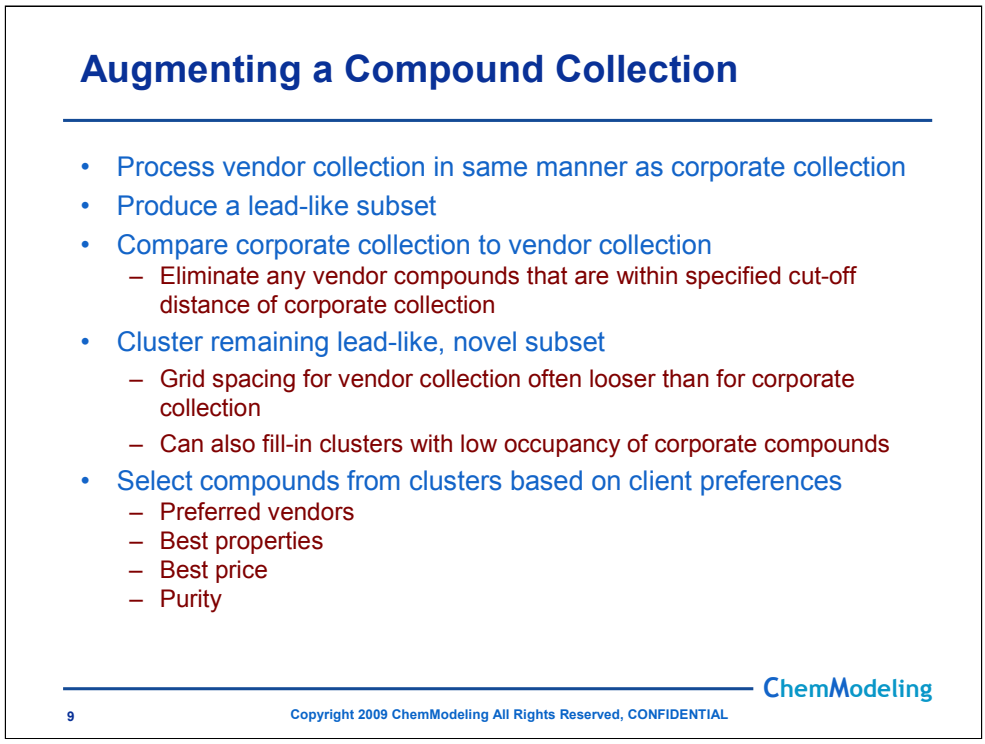
The neighborhood principle states that for a good metric, a small change in activity should correspond to a small change in the value of the metric. We choose metrics for our grid-based clustering that have good neighborhood behavior. This ensures that clusters should primarily consist of active (or inactive) compounds and that selecting a subset will not significantly reduce the chance of getting hits. In addition to the distance-based methods, we can also use low-D methods (BCUTS) or scaffold based (RECAP) clustering. We have added a k-means post-processor to the basic gridding algorithm that makes the centers chosen more central to the cluster.

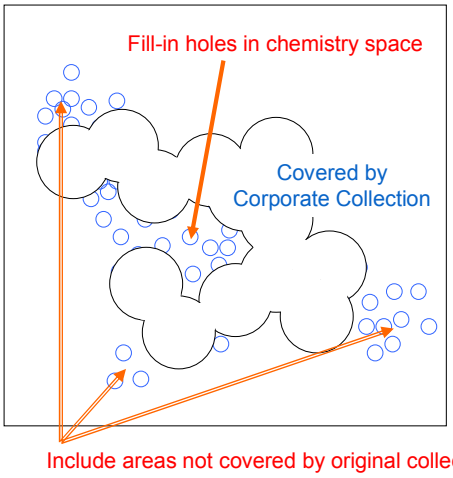


Our grid-based approach is fairly flexible. It accepts input seeds, so grid centers selected with a subset of the database can be used as input to select additional grid centers using a larger population. This allows sequentially selecting from several collections that would be ordered from most to least desirable. The method also successively refines the distances between centers. So that one can start with a larger distance between grid centers and later come back and cluster at a finer grid spacing. This can be useful when selecting sets of compounds to purchase.



We recently used a 3.5 million compound set provided by a customer to select compounds to augment their corporate collection. Roughly 40% of these compounds were unique with respect to their existing collection. The criteria used to filter this collection was much tighter than that used on the existing compounds.

Augmentation Can Be Tailored



- Select sequentially
  - Preferred Vendors
  - Preferred Targets
- Select based on target
  - Similarity to known actives
  - Privileged substructures
  - Meet pharmacophore model
  - Meet SAR model
- Select based on properties
  - Preferred vendors
  - Best properties
  - Best price
  - Purity

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In addition to selecting compounds, we can also analyze the various vendor datasets to determine how unique they are to each other, with respect to the corporate collection, or how many unique scaffolds are contained within the dataset. We can select compounds from an aggregate of vendor compounds or sequentially, allowing the maximum number of compounds to be selected from the most preferred vendors.