In silico Compound Screening for Drug Discovery in the “Cloud”
Working with Vassa Informatics

- Founded (2007) to develop information-theory based technologies that would provide additional tools for scientists studying the functional effects of differences between similar nucleotide and amino acid sequences.
- BioVassa was the initial result of this work.
  - Collaborations with Indiana University-Northwest, Washington University - St. Louis and the University of Chicago further refined BioVassa.
- ChemVassa applies information content analysis to chemical sequences of arbitrary length with an eye towards small molecule screening for drug discovery.
  - Development and initial proof of concept work complete.
Information Content Overview

- We can present this information graphically in several ways; the important point (looking at Conotoxin, PDB: 1AS5) is that we are generally tracking binding or interaction sites.

Information content is a measurement of a unit’s (e.g., a small molecule) compressability versus a theoretical maximum. Units with high information content are not as compressible as those with low information content.
ChemVassa Overview

- ChemVassa works by calculating the information content of a molecule, utilizing spatial information (taken from PDB, converted SMILES, or other structural information files) to locate an atom within the molecule.
- Each atom is converted using a lexicon that accounts for the valence shell content, atomic number, and reactivity of the atom.
- The location of each atom is then compared and the reactivity between adjacent atoms is compared.
  - The average of the distance multiplied by the reactivity difference is the "G score".
- G scores for the backbone of the molecule are calculated as follows:
  - The average for connected non-main-chain molecules is added to the connected main carbon atom and summed across the backbone and averaged; this is the "M score".
- A string of G scores may then be searched across a database of compounds.
ChemVassa Validation

Test Molecule: Lipitor
Question:

Is ChemVassa able to predict novel binding partners for a chemical ligand that cannot be predicted by existing methods \textit{ab initio}?
Lipitor

- Lipitor was chosen as:
  - Commercially valuable
  - Crystal structures of HMG-CoA reductase in complex with six statins are available
  - All marketed HMG CoA reductase inhibitors are structurally similar – can we identify novel scaffolds and chemistry?
Lipitor Structure

Lipitor works by binding to and inhibiting the liver enzyme HMG-CoA reductase
Red Regions are high information content
Blue regions are low
ChemVassa correctly identified the binding region where Lipitor interacts with its target (Hmg-CoA reductase) and predicts most of the important interacting atoms that were determined experimentally.
LK1 is "most of the important interacting atoms..." the best way to say this?
Lisa Kenney, 1/29/2010

LK2 This should go on the Results slide (as written).
I think this third bullet should provide additional analysis information or explanation
Lisa Kenney, 1/29/2010
Results

- We searched a 600,000 ligand library using the Lipitor information signature.
- We categorized the results as: Positive (Validation), Known Binders (Neutral), False Positive, or Novel.
- Of these results, about 60% were known binders or novel results; 40% were false positives.
- We found 10 Novel, previously unknown results which can be tested for functionality at the bench.
  These novel compounds would not be able to be identified utilizing existing methods.
I rewrote this and it still isn't quite right. Theoretically, we should provide the breakdown by category...
Lisa Kenney, 1/29/2010

Are Known Binders Neural, or are they validation?
Lisa Kenney, 1/29/2010
Positive (Validation) Results

- We utilized the search to see if it would identify other statins
- Creating a statin library, we reliably pulled statins as results if the binding region was used as search input
- This shows that there is a shared set of physical properties that ChemVassa is able to detect within the statins
Known Binders (Neutral)

- In some cases, we pulled results that were not statins and NOT structurally similar to Lipitor that, however, are known binders of HmG-CoA Reductase.
- An example is Coenzyme A; it was returned as a search result though it is NOT structurally similar to Lipitor.
- However, as CoA binds HmG-CoA reductase, it is NOT a negative result and suggested that the algorithm is tracking a FUNCTIONAL property of HmG-CoA reductase binding, NOT just a physical one.
False Positives

- Of course, we also returned some results that do NOT bind Hmg-Coenzyme A reductase and are NOT structurally similar to Lipitor.
- An example is Vancomycin; it was returned as a search result though it is NOT structurally similar to Lipitor and DOES NOT bind Hmg-CoA reductase.
- These results fell into two categories; complete non-binders, and cases where a portion of the molecule would likely bind except cannot due to steric hindrance.
- About 40% of the experimental search results fell into this category.
Novel Results

- These results are not structurally similar to Lipitor, but that appear to be capable of binding Hmg-CoA reductase in a manner similar to Lipitor.
- Modeling allowed us to look at affinity and electrostatic contacts of these results.
- About 40% of the experimental search results fell into this category, most with exceptionally good binding.
- These included some hits where little biological information was present, and cases where biological information provided insight into the possible mechanism for the ligand function.
- Currently, VaSSA Informatics is utilizing these results for partnership development with several interested parties.
G2L (3'-o-methoxyethyl-guanosine-5'-monophosphate) also interacts with the Hmg-CoA reductase site. Although the compound is not well-studied, it is small and should be bio-accessible.

<table>
<thead>
<tr>
<th>G2L</th>
<th>AVS</th>
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</thead>
<tbody>
<tr>
<td>Glu:559</td>
<td>Y*</td>
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<tr>
<td>Arg:590</td>
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<td>Y*</td>
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<tr>
<td>Leu:853</td>
<td>Y*</td>
</tr>
</tbody>
</table>
YES, our models show that ChemVassa can *ab initio* predict novel binding partners for chemical ligands that cannot be predicted by existing methods.
Cost Model Discussion
How are we moving forward?

- Develop a compound library of about 9 million compounds, including about 1.5 million “sweet-spot” that have good drug-like qualities.
- Developing the infrastructure for this quickly and on a limited budget for deployment, we explored several options:
  - Server purchase
  - Machine rental
  - Cloud services
Cloud computing

- We have two tasks:
  - Initial candidate screening, using ChemVaSSA to generate a compound library and screen the library
  - Modeling the results to see if they are compatible with binding.

- Project-based pricing
  - Creating the library: about $300.
  - Screening the library: about $30 per compound.
  - Modeling the results: about $55 per 1000 models.
Conclusions

- Cloud computing may work for initial development of computing infrastructure.
  - Not ideal for all cases
- Allows accurate prediction of project times
- Allows quick set-up/tear down of infrastructure
- Costs can be billed back to a source (grant, client, etc)
- Low overhead.
Future Directions

- Cloud computing for development of Bioinformatic teaching infrastructure
  - Non-persistant nature of facilities fits well with semester-to-semester changes in enrollment.
  - Cost basis can be readily understood.
  - Limiting student access to ensure effective use of resources
- Development of trial web-based resources for grants and exploratory research.