QUANTITATIVE MEDICINE

TRANSFORMING DRUG DISCOVERY

Technology Evaluation Consortium
Cambridge Healthtech Associates

September 10, 2013

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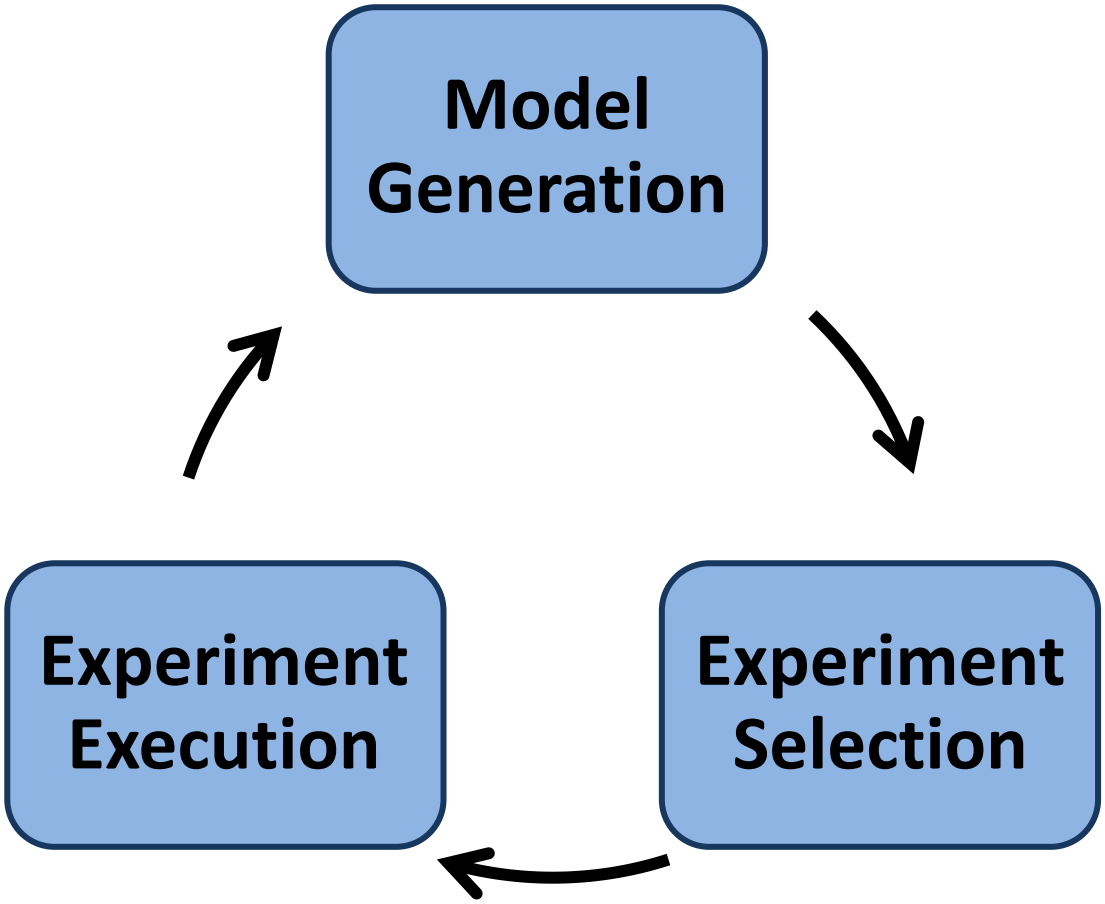
Agenda

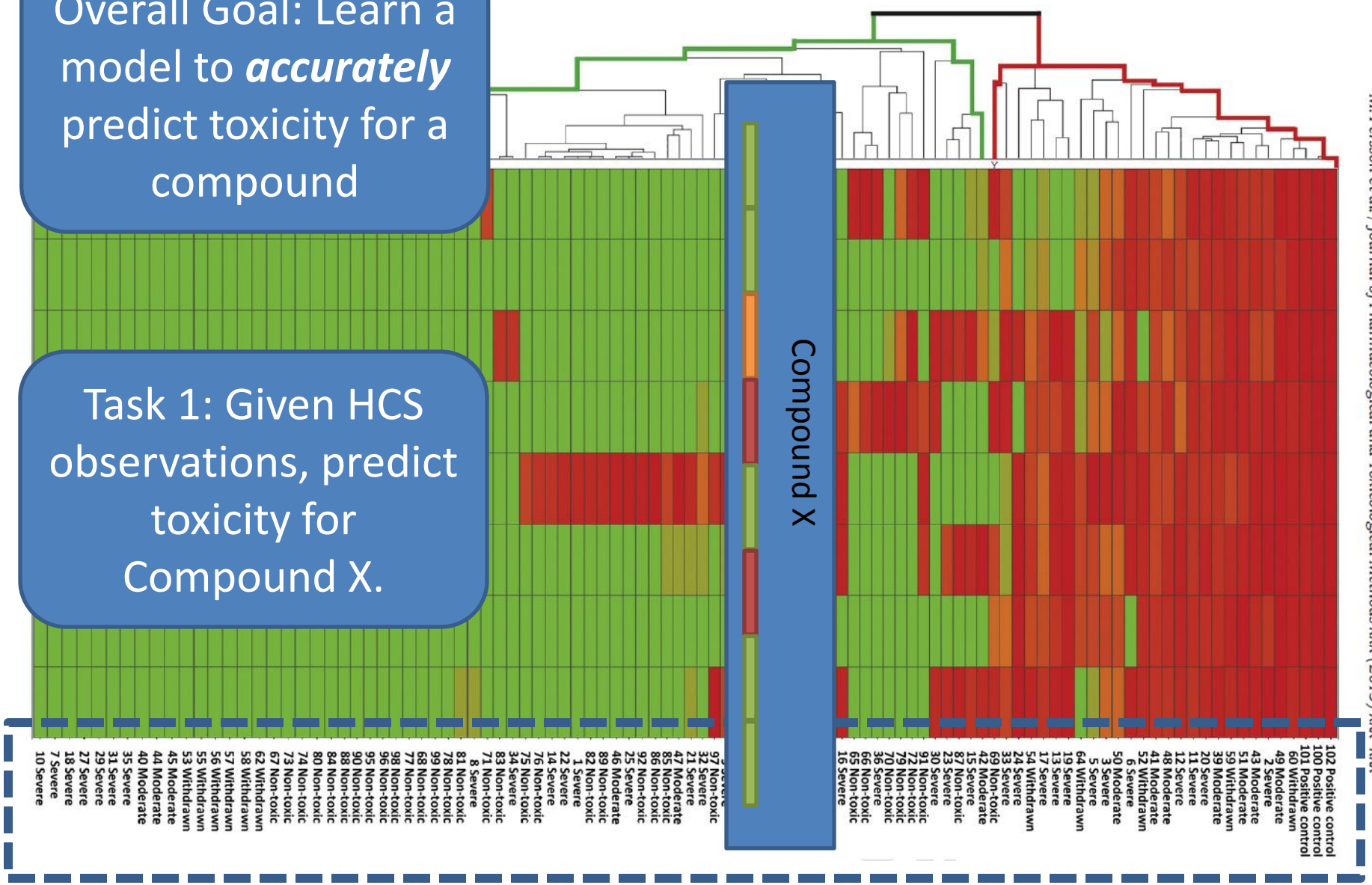
- Persson et. al Paper
- Potential Study Design
- Next Steps

Active Learning



Overall Goal: Learn a model to ***accurately*** predict toxicity for a compound

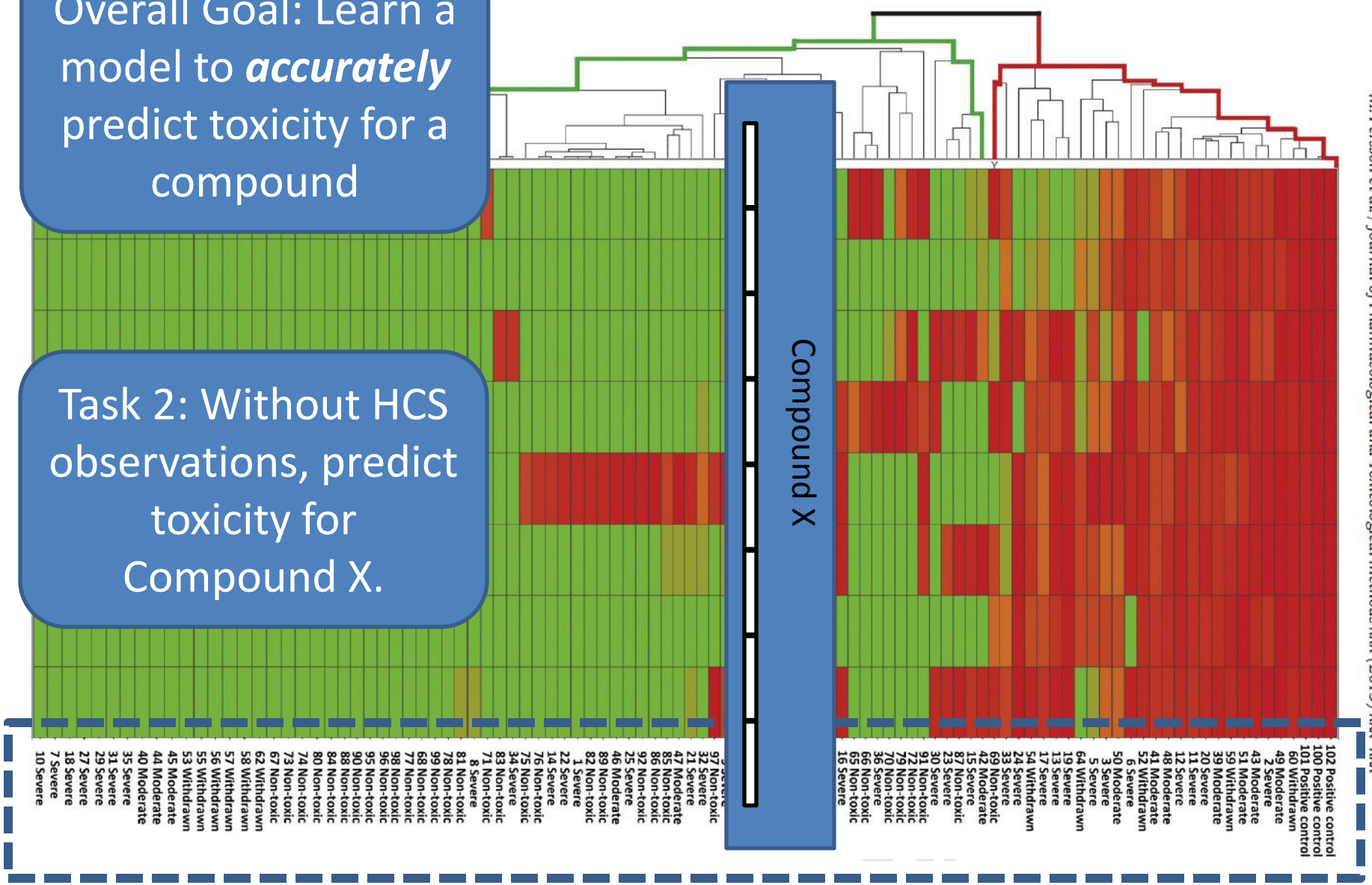
Task 1: Given HCS observations, predict toxicity for Compound X.



M. Persson et al. / Journal of Pharmacological and Toxicological Methods xxx (2013) xxx–xxx

Overall Goal: Learn a model to ***accurately*** predict toxicity for a compound

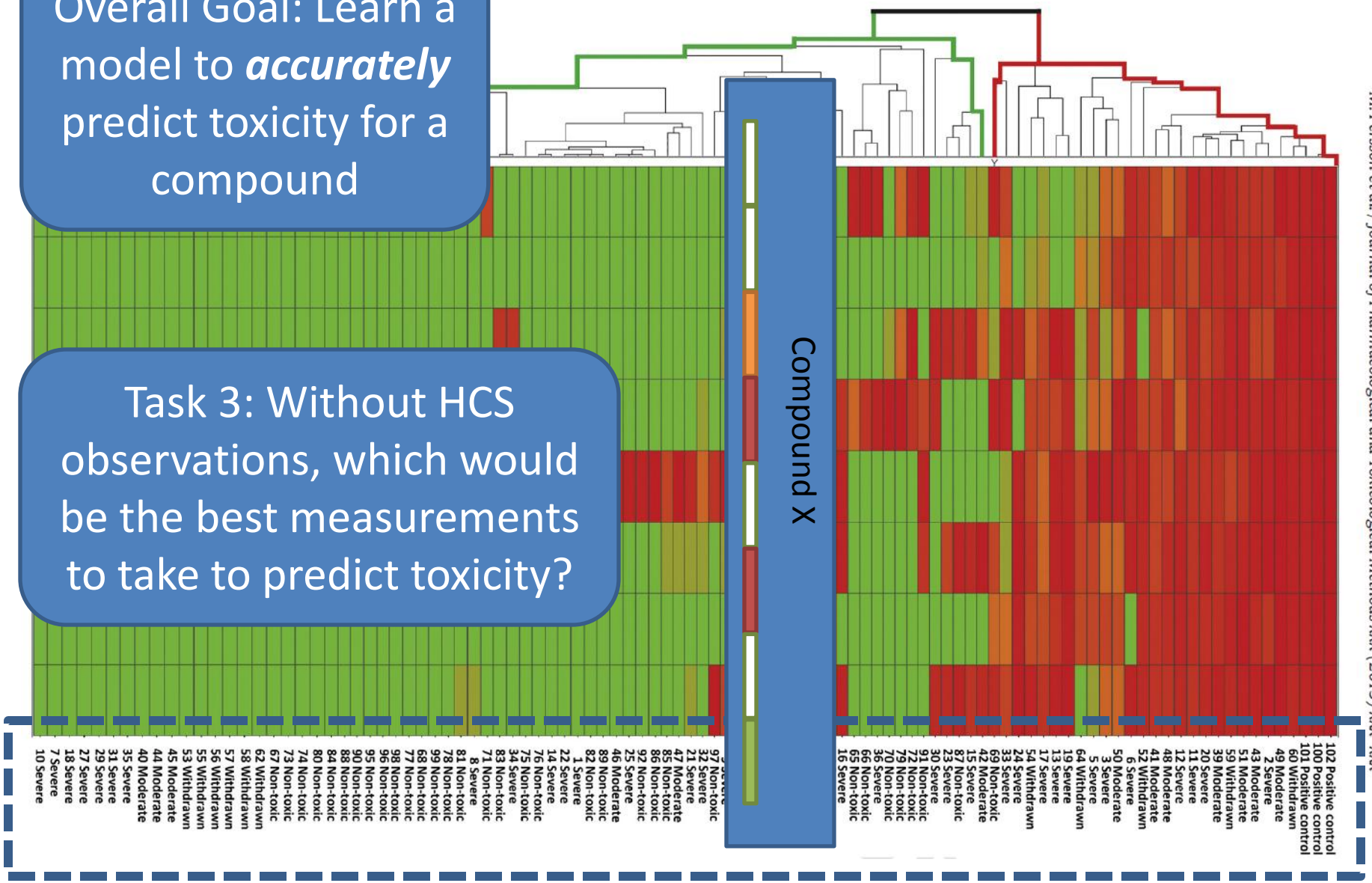
Task 2: Without HCS observations, predict toxicity for Compound X.



M. Persson et al. / Journal of Pharmacological and Toxicological Methods xxx (2013) xxx–xxx

Overall Goal: Learn a model to ***accurately*** predict toxicity for a compound

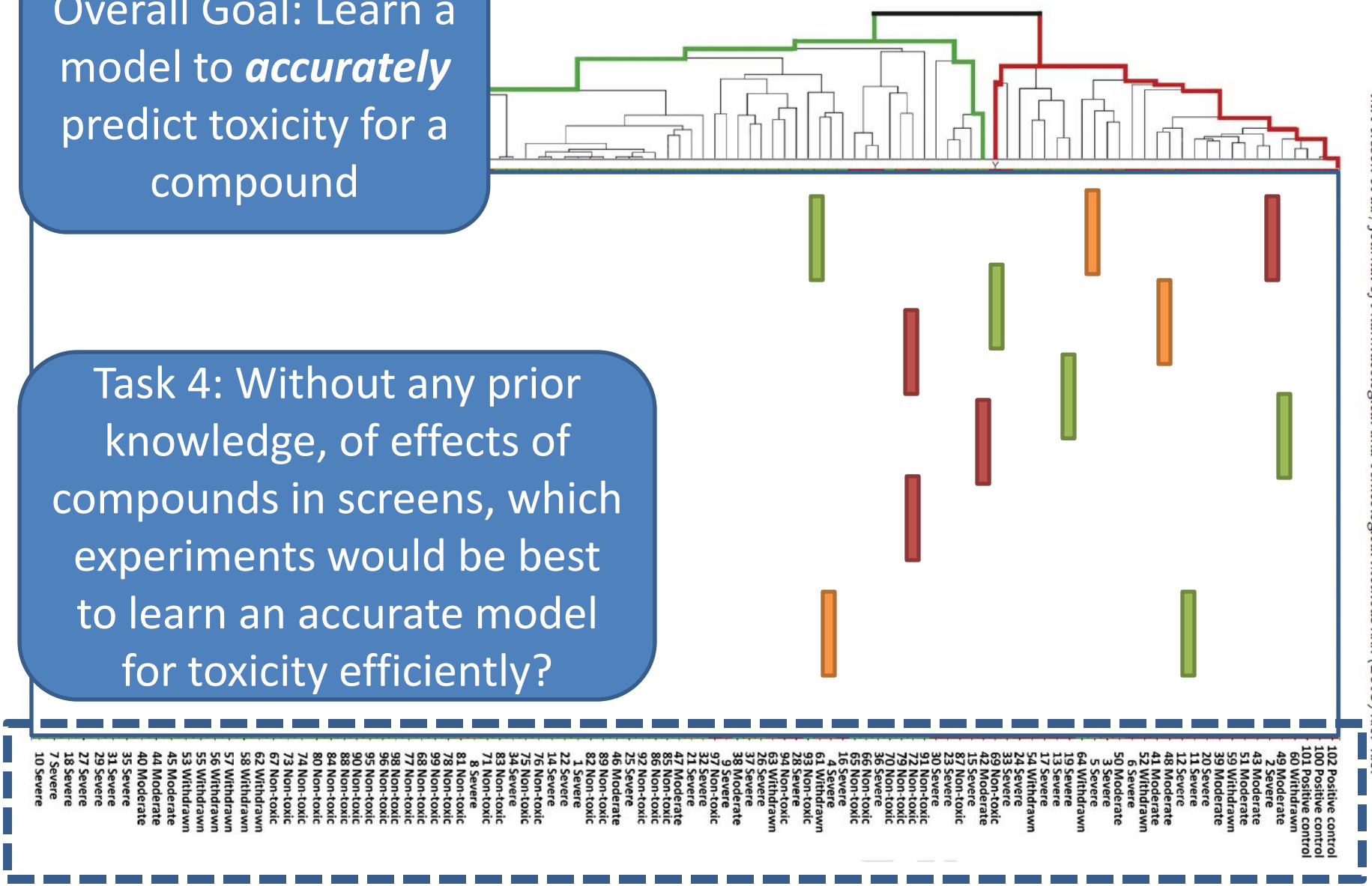
Task 3: Without HCS observations, which would be the best measurements to take to predict toxicity?



M. Persson et al. / Journal of Pharmacological and Toxicological Methods xxx (2013) xxx–xxx

Overall Goal: Learn a model to ***accurately*** predict toxicity for a compound

Task 4: Without any prior knowledge, of effects of compounds in screens, which experiments would be best to learn an accurate model for toxicity efficiently?



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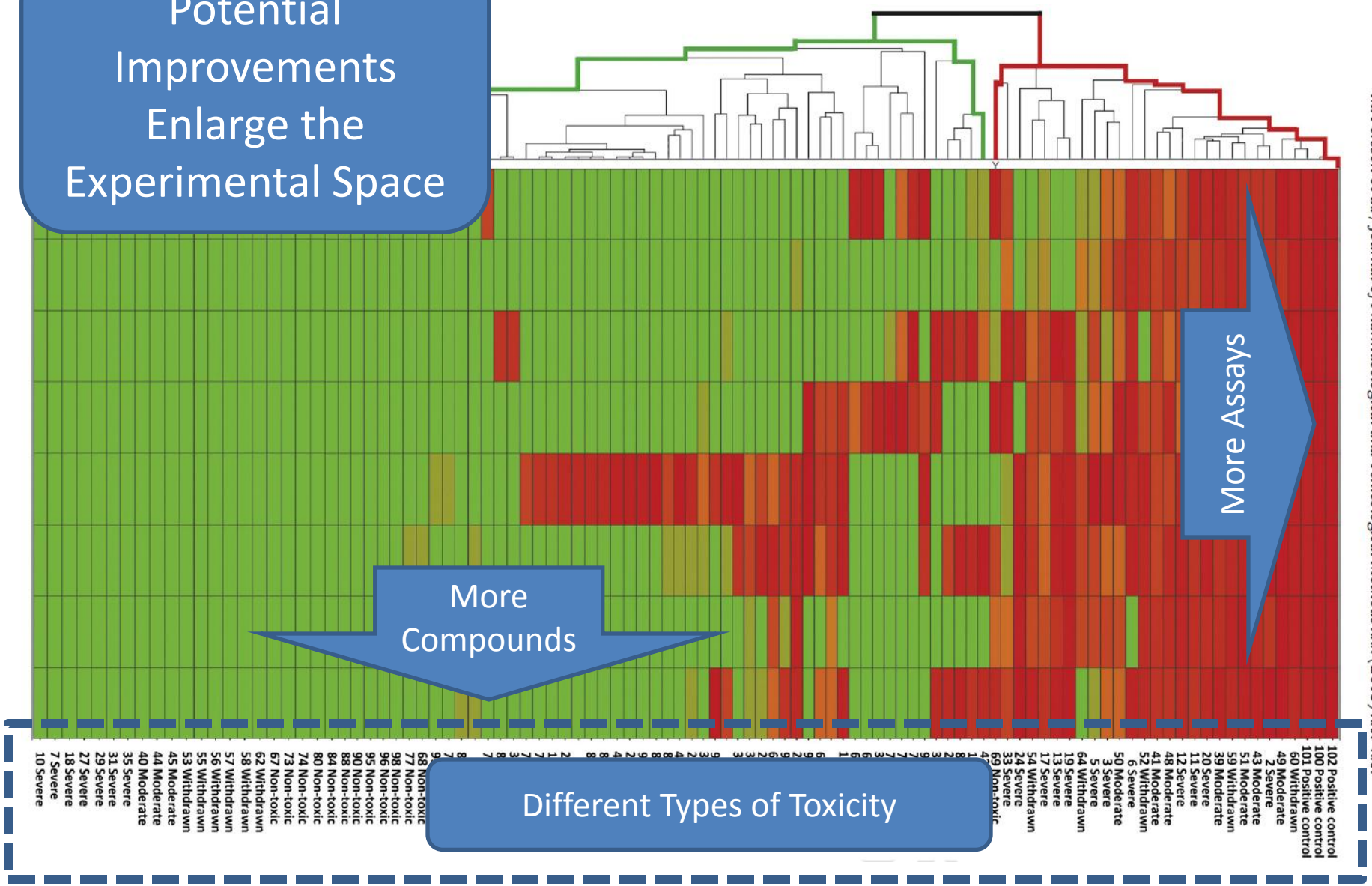
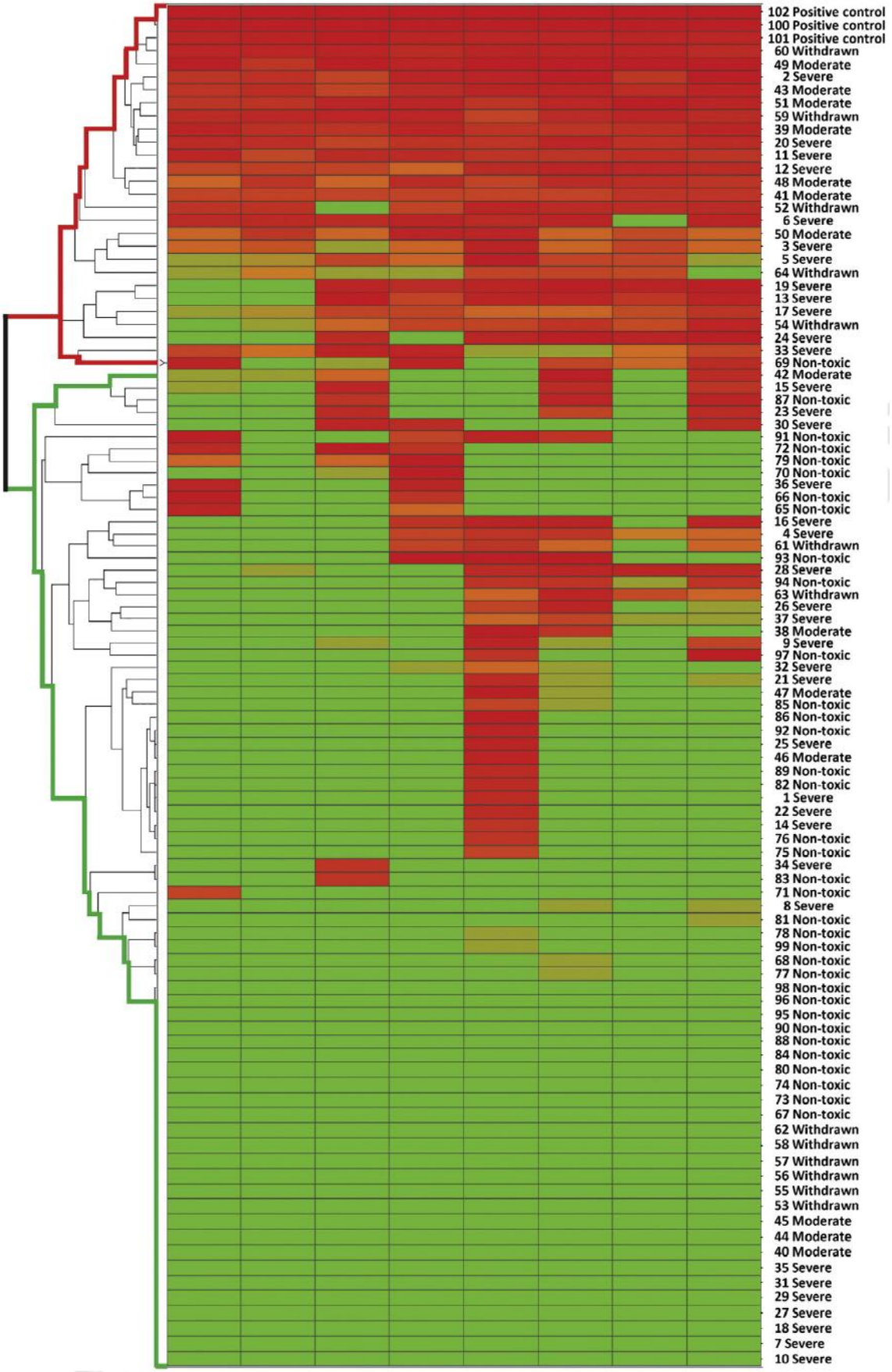
Potential Improvements Enlarge the Experimental Space



Study Guidelines

- Define Relevant Use Case
- Map Use Case to available dataset
  - One measurement -> one assay
- Run simulations with different selection methods as if experiments were being executed as directed rather than looking at the whole dataset at once
- Measure success (accuracy) after each batch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100 Positive control
101 Positive control
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2 Severe
43 Moderate
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20 Severe
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41 Moderate
52 Withdrawn
6 Severe
50 Moderate
3 Severe
5 Severe
64 Withdrawn
19 Severe
13 Severe
17 Severe
54 Withdrawn
24 Severe
33 Severe
69 Non-toxic
42 Moderate
15 Severe
87 Non-toxic
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36 Severe
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16 Severe
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28 Severe
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26 Severe
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9 Severe
97 Non-toxic
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25 Severe
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73 Non-toxic
67 Non-toxic
62 Withdrawn
58 Withdrawn
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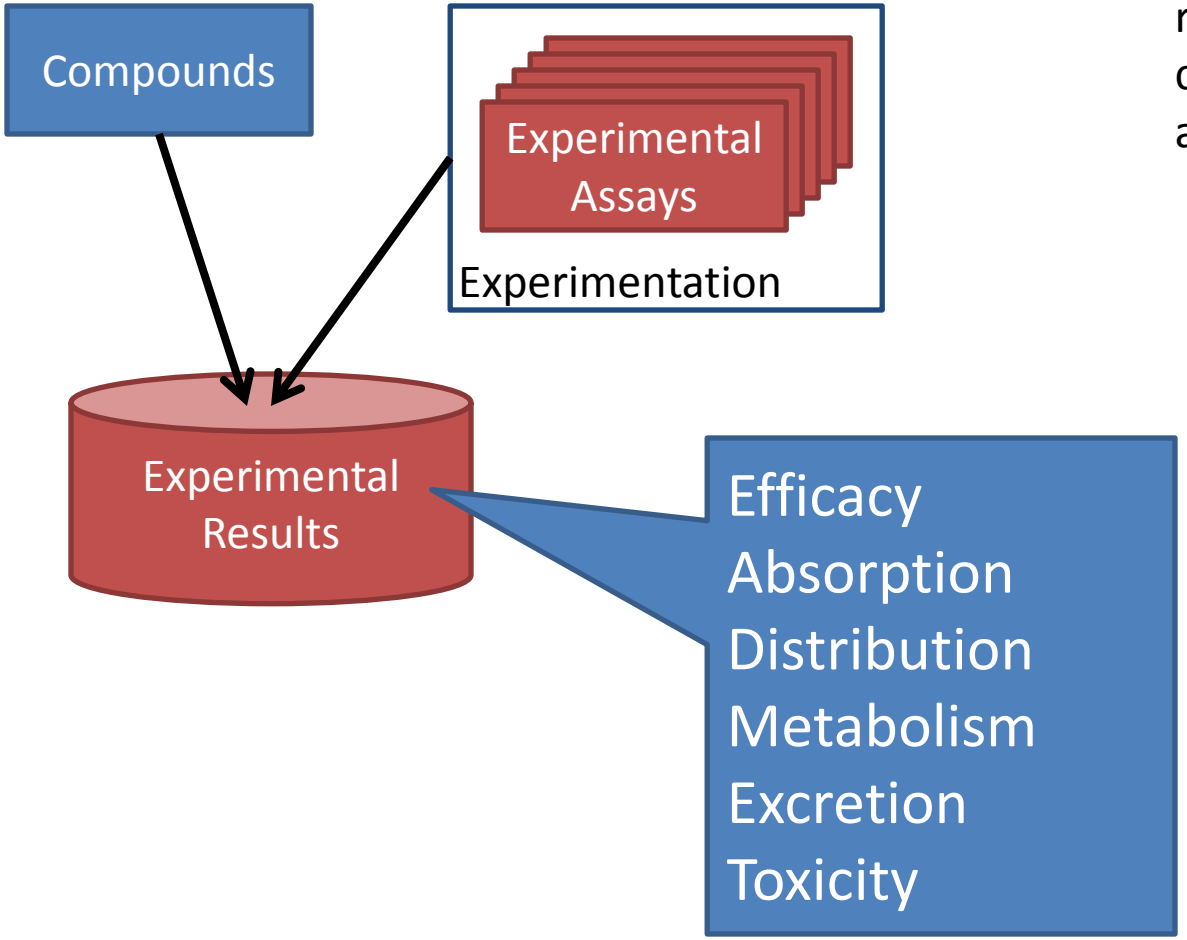
Current Experimental Approach

1. Select a set of compounds of interest (2 – 10^6 total).

Compounds

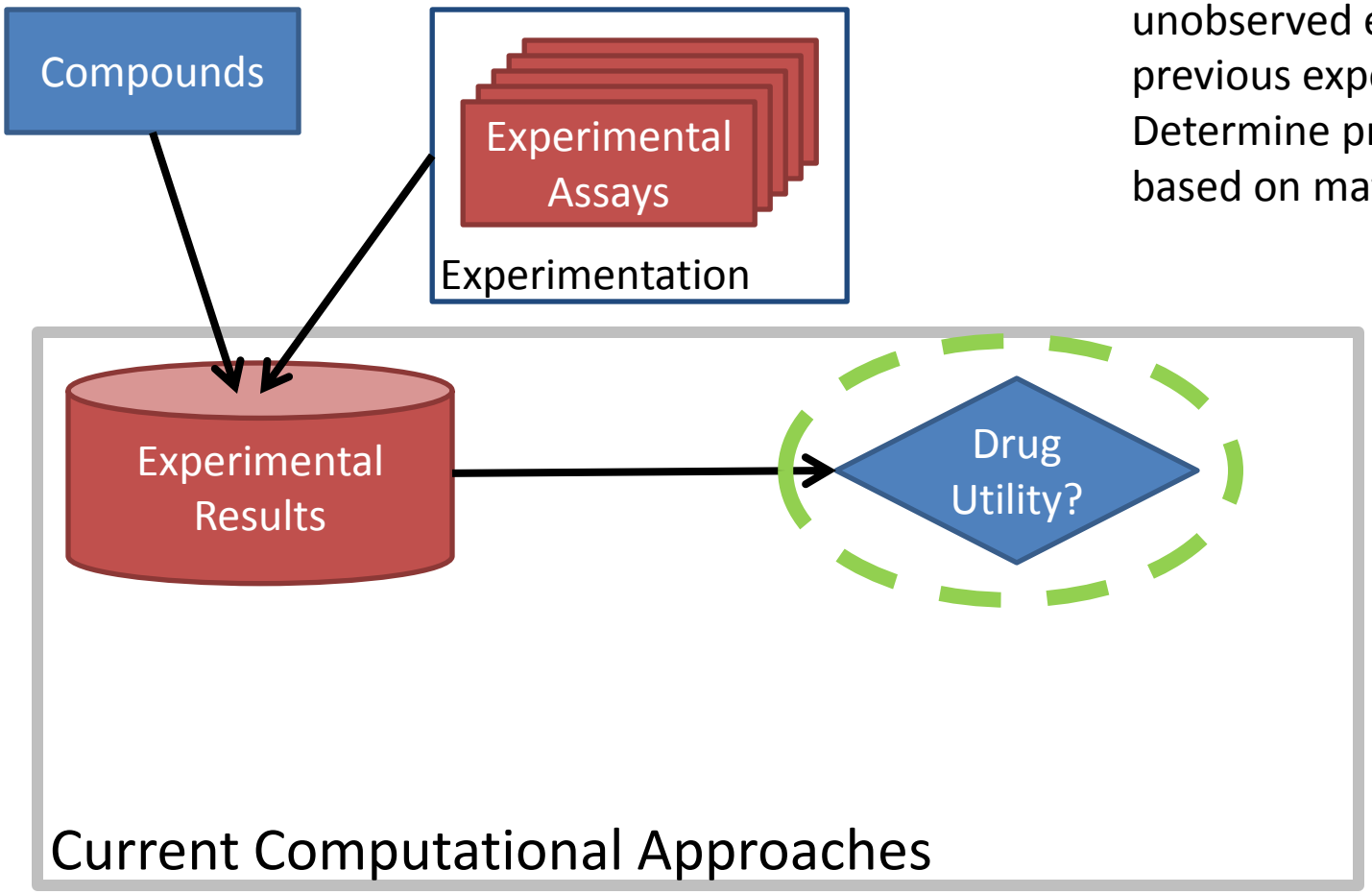
Current Computational Approach



2. For a set of relevant assays, gather all available experimental results from running those compounds against those assays (1-10^2).

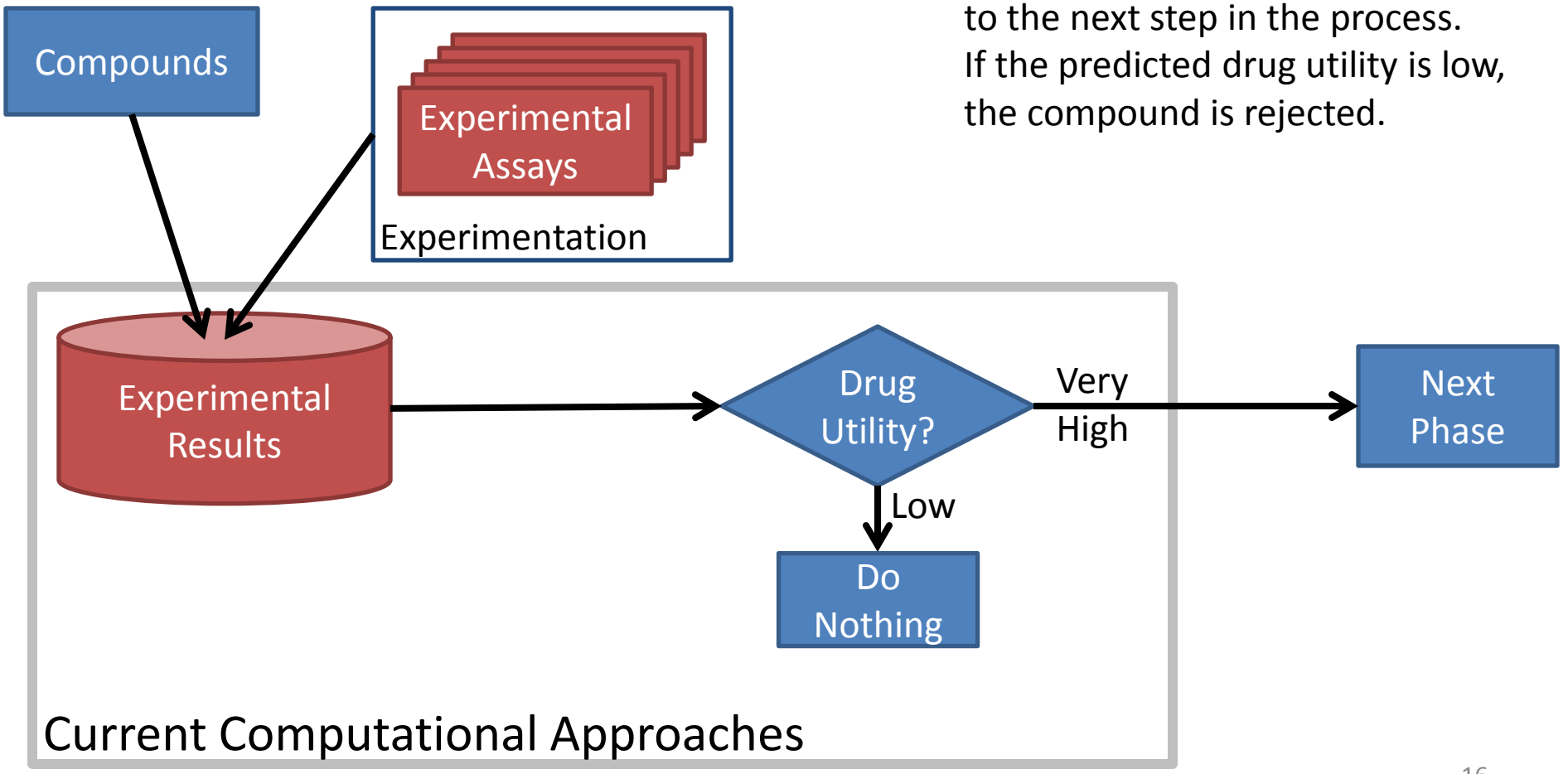
Current Computational Approach

3. Use computational methods to predict the results for all unobserved experiments based on previous experimental results. Determine predicted “drug utility” based on match to a desired profile.



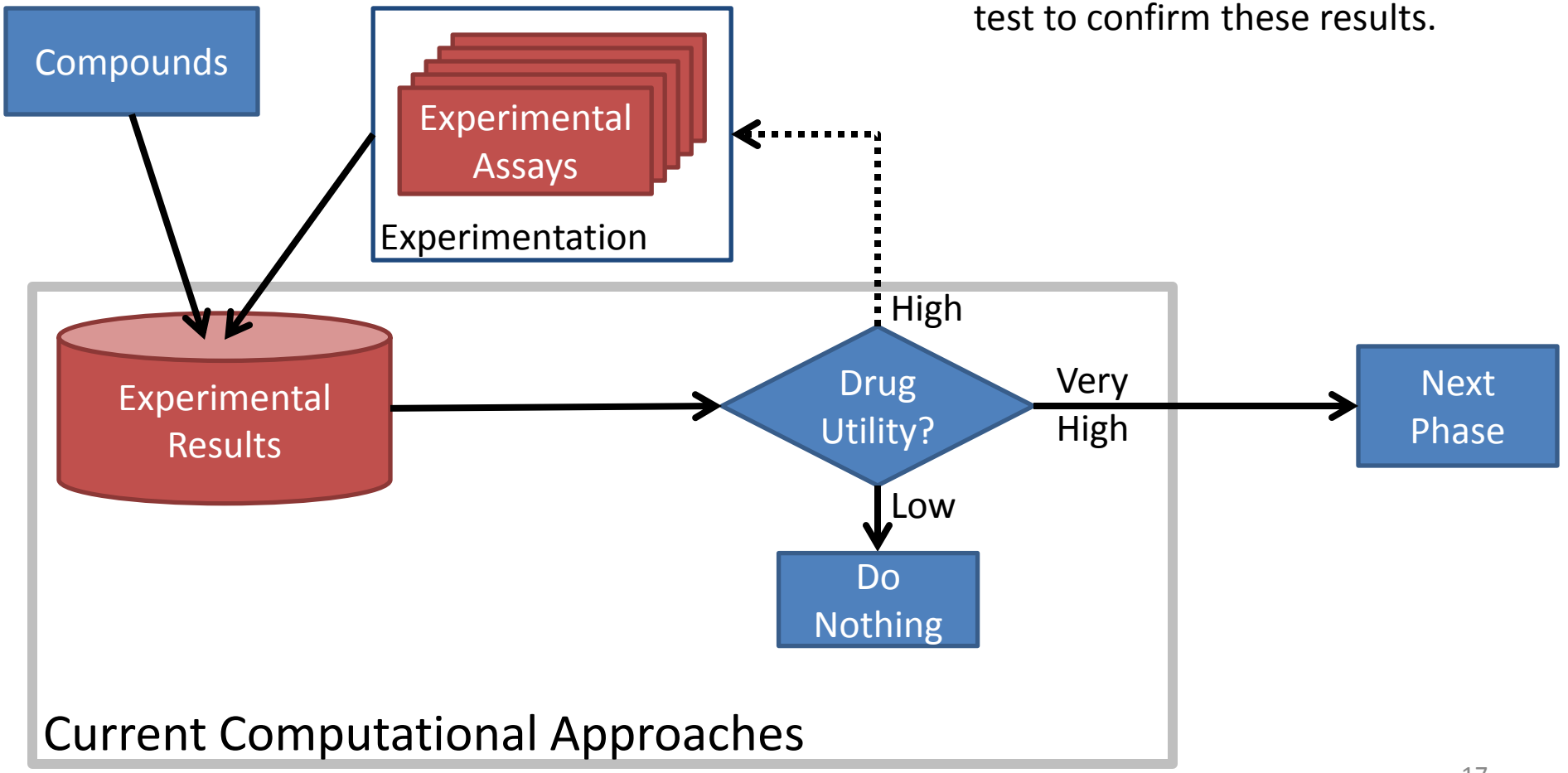
Current Computational Approach

4. If the predicted drug utility is very high, the compound can be moved to the next step in the process. If the predicted drug utility is low, the compound is rejected.

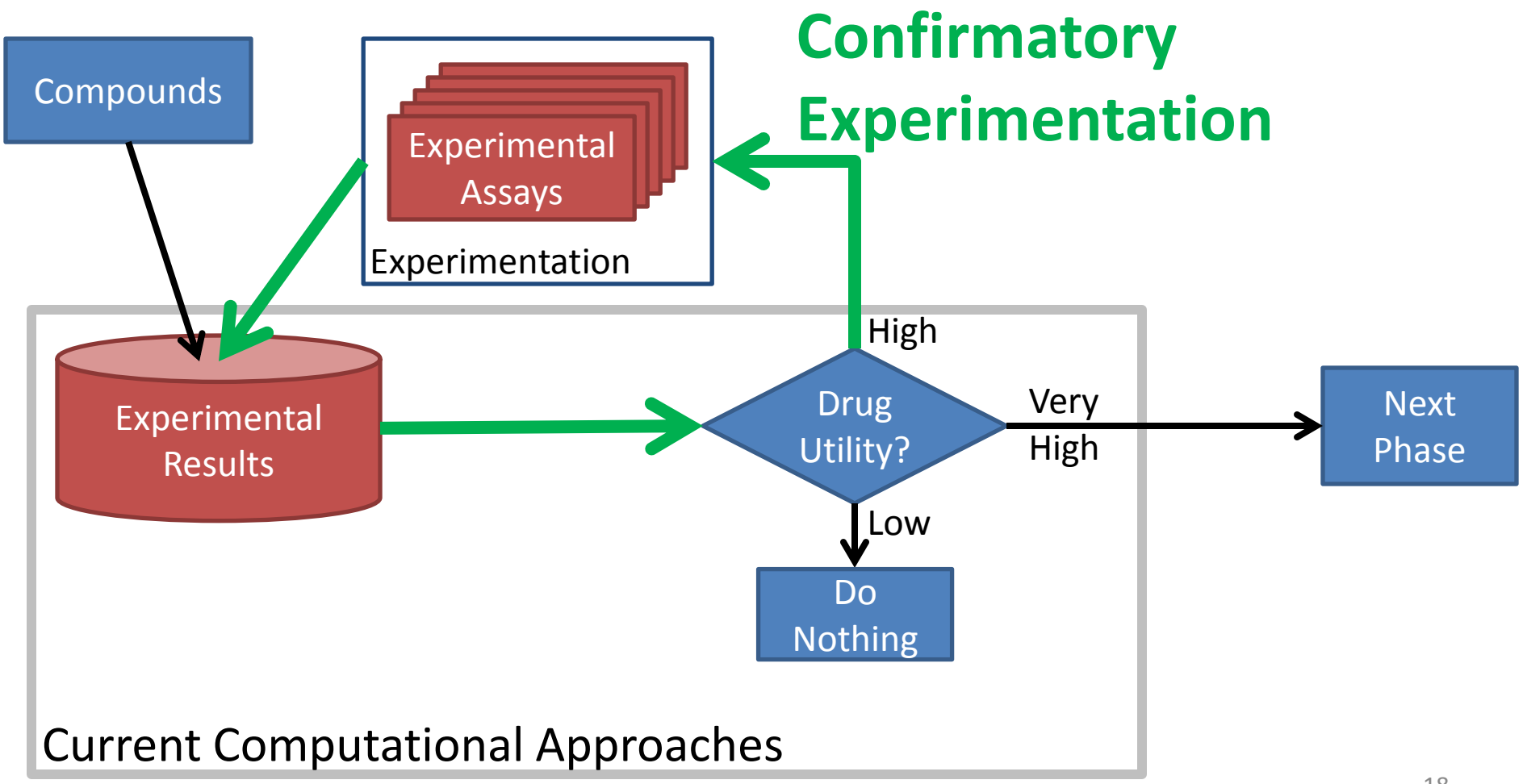


Current Computational Approach

5. If the there is a high predicted drug utility, one might run more test to confirm these results.



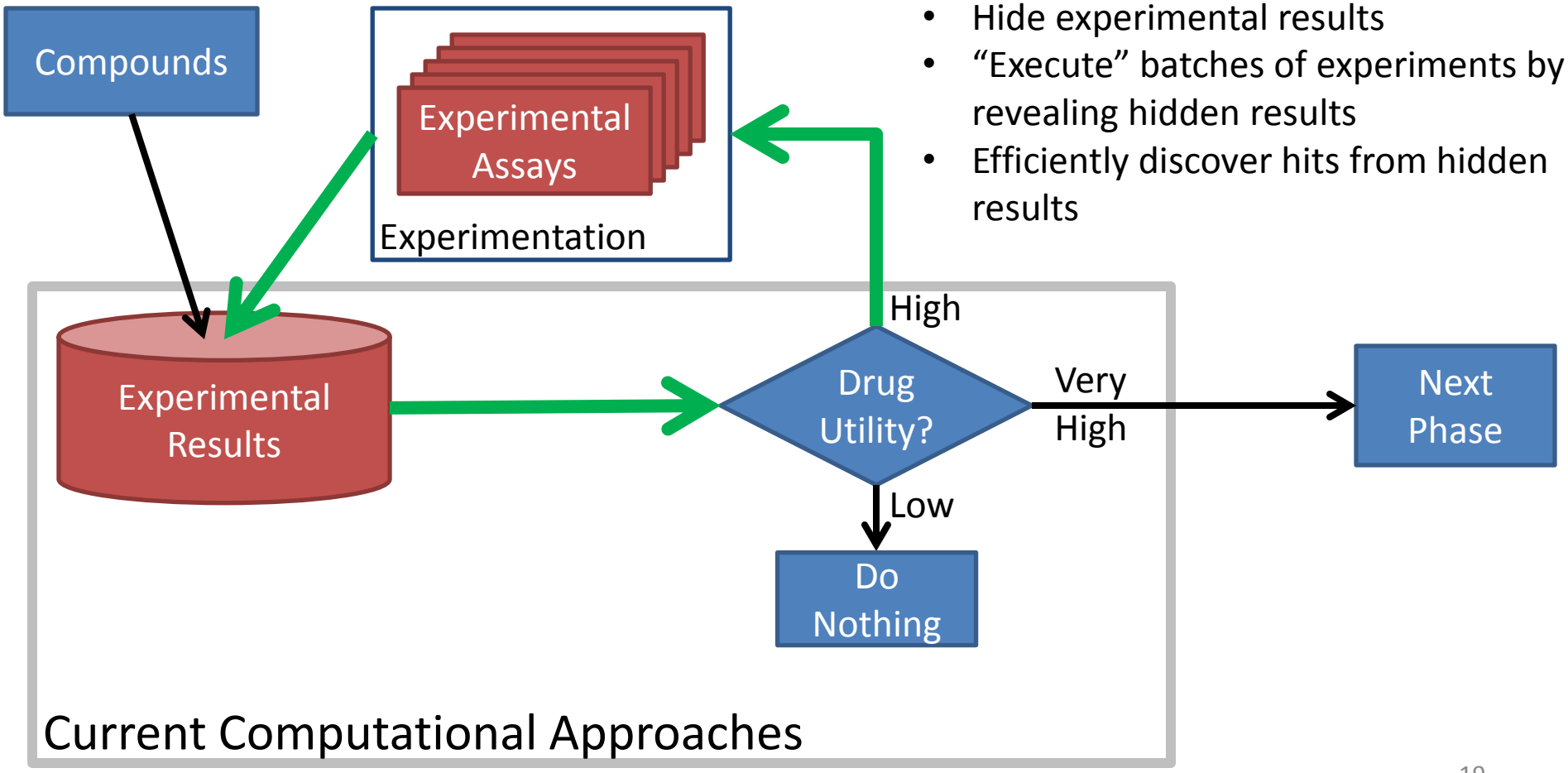
Current Computational Approach



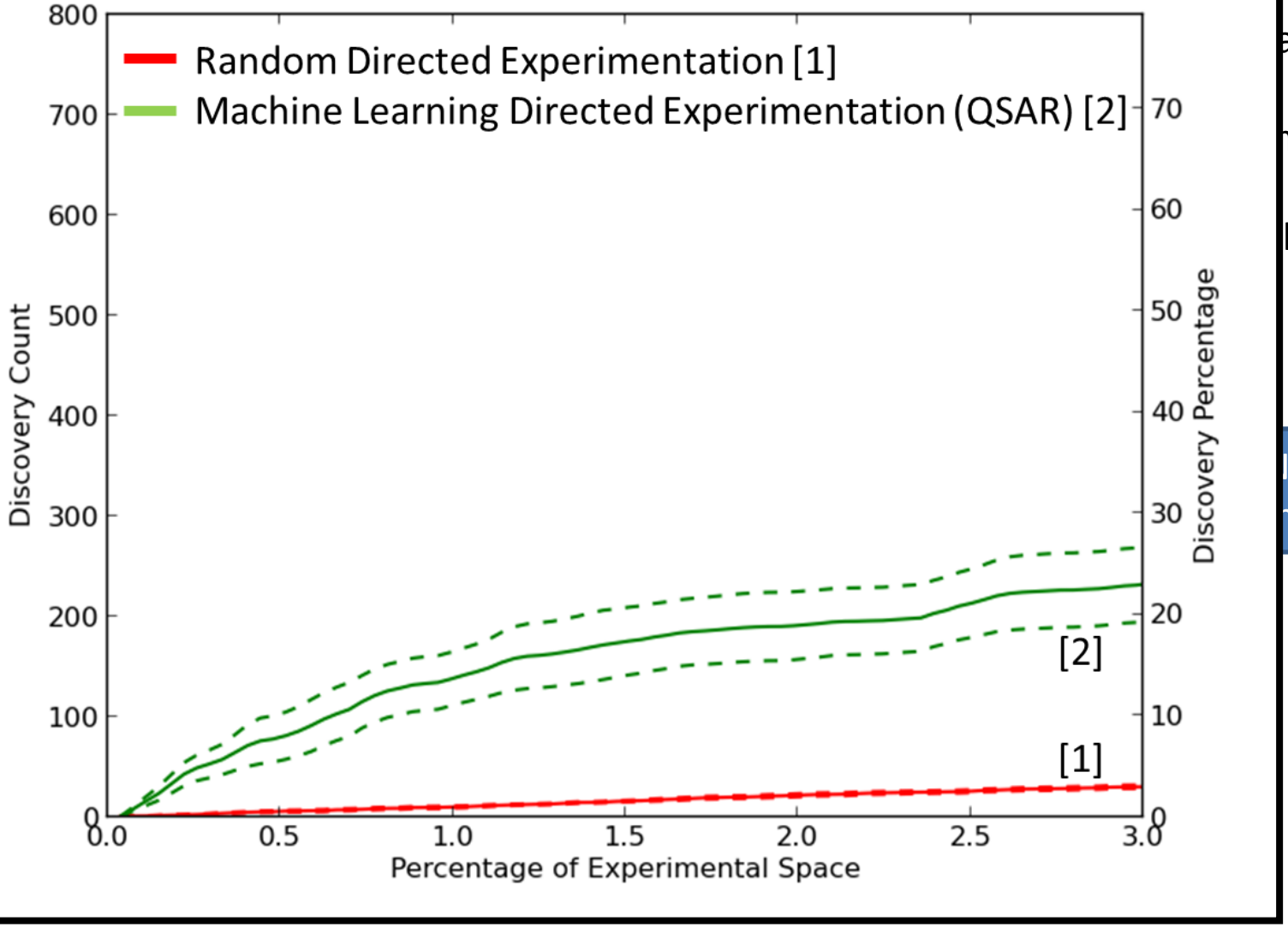
Current Computational Approach

PubChem Simulation:

- 20,000 compounds and 177 assays
- Hide experimental results
- "Execute" batches of experiments by revealing hidden results
- Efficiently discover hits from hidden results

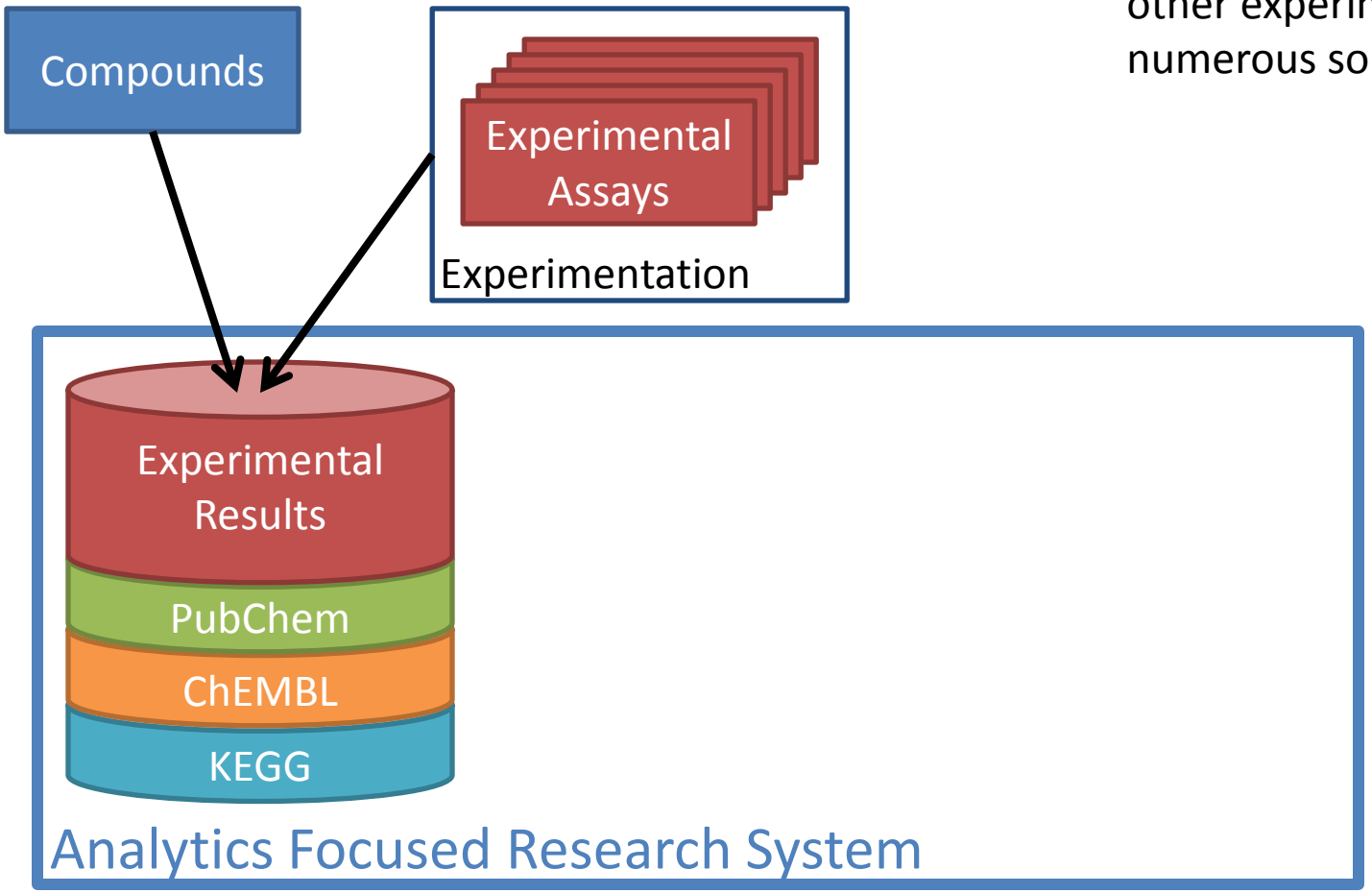


Current Computational Approach



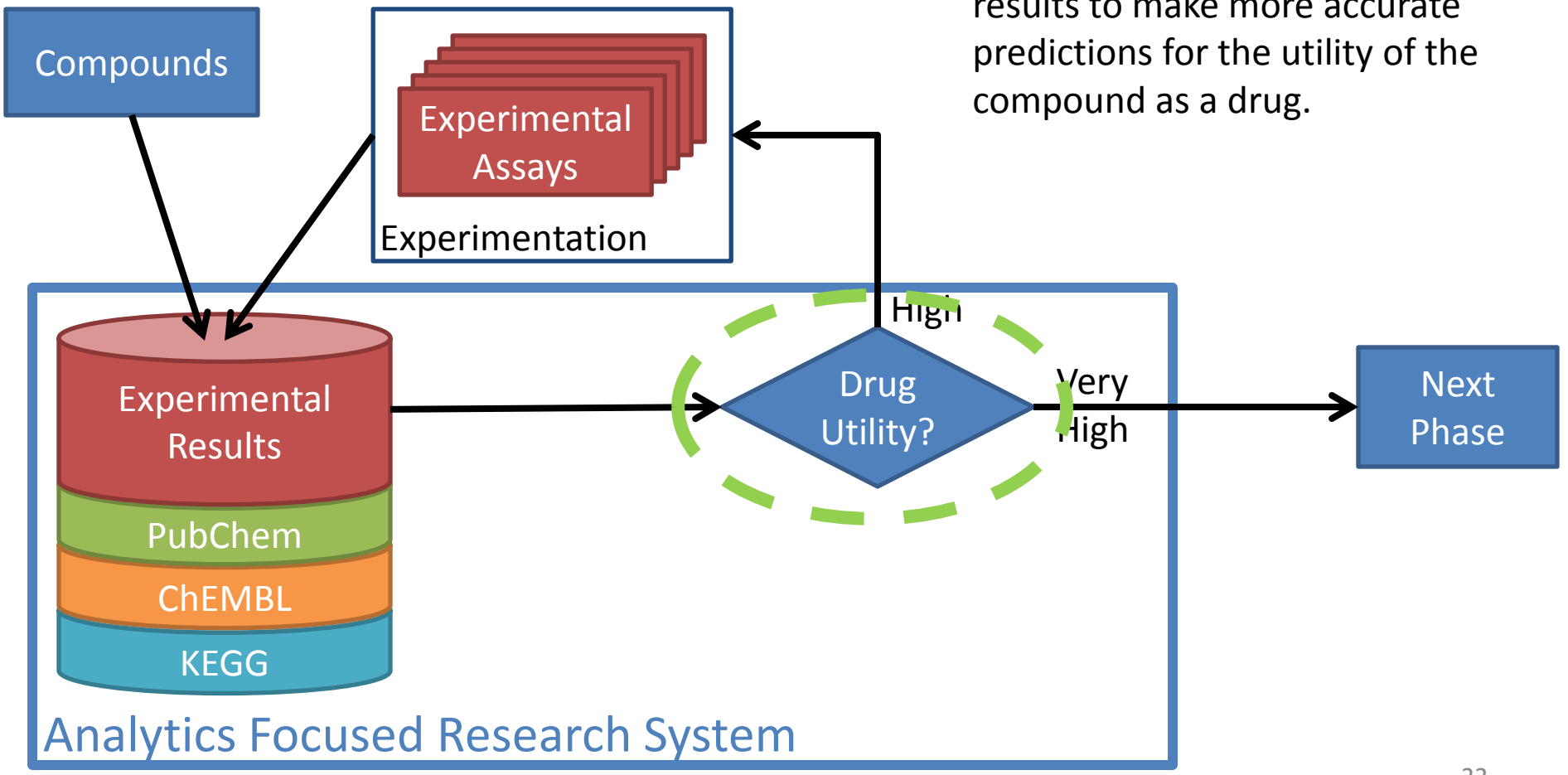
AFRS Approach For Efficient Experimentation

1. We combine experimental results with a large knowledge base of other experimental results from numerous sources.



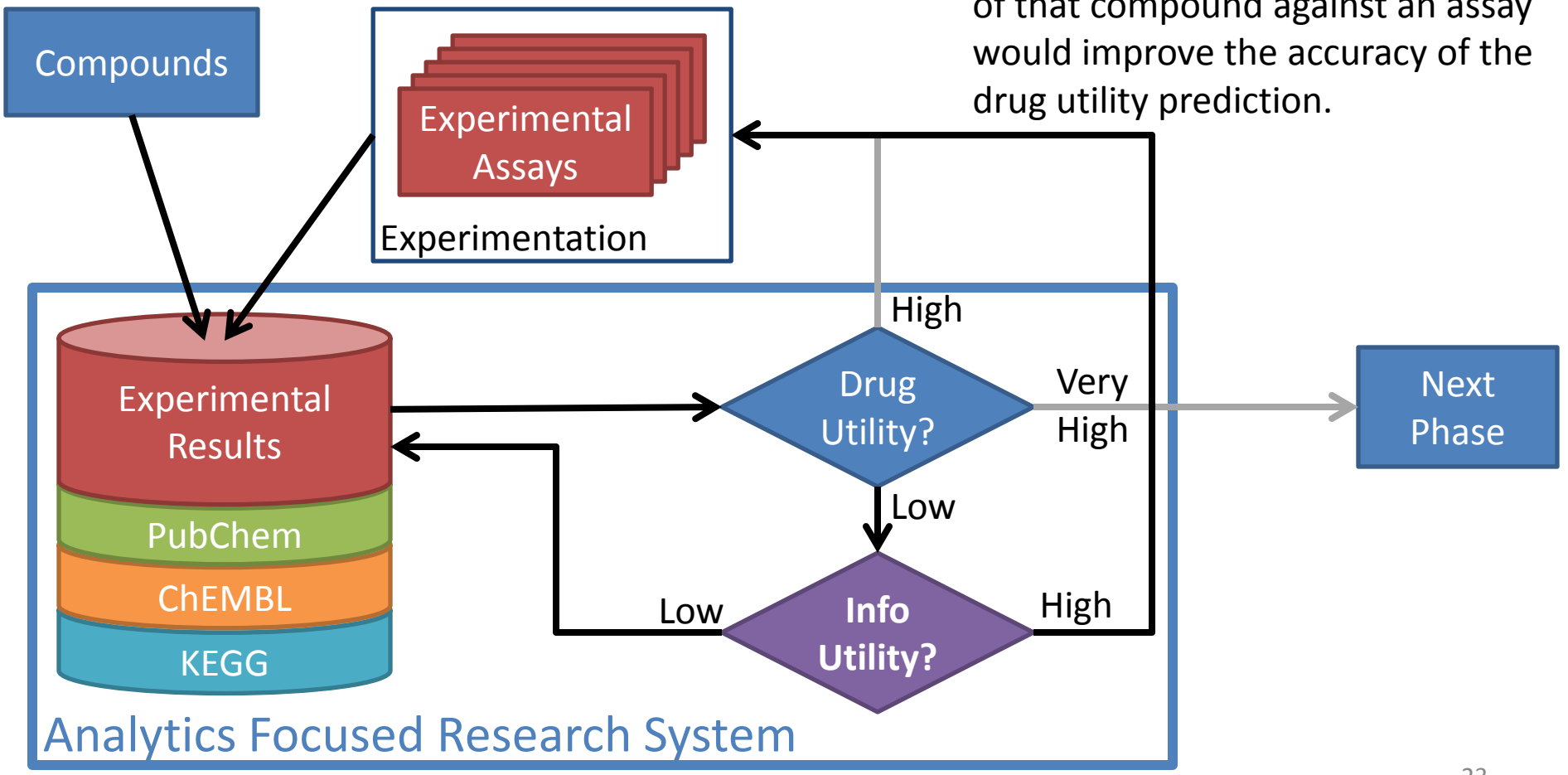
AFRS Approach For Efficient Experimentation

2. We use our vast sources of information as well as experimental results to make more accurate predictions for the utility of the compound as a drug.



AFRS Approach For Efficient Experimentation

3. If a compound has low predicted drug utility, we predict if the results of that compound against an assay would improve the accuracy of the drug utility prediction.



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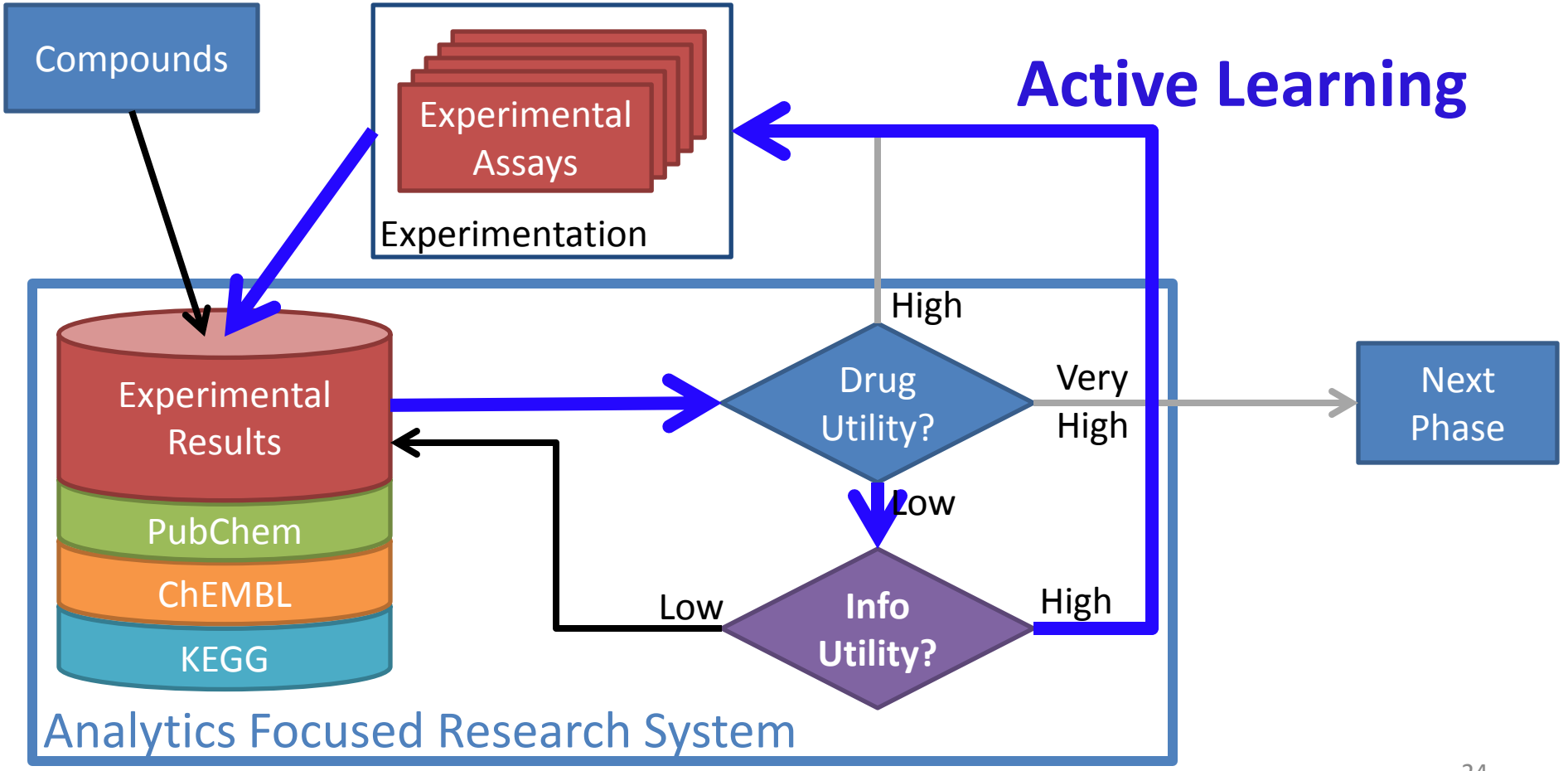

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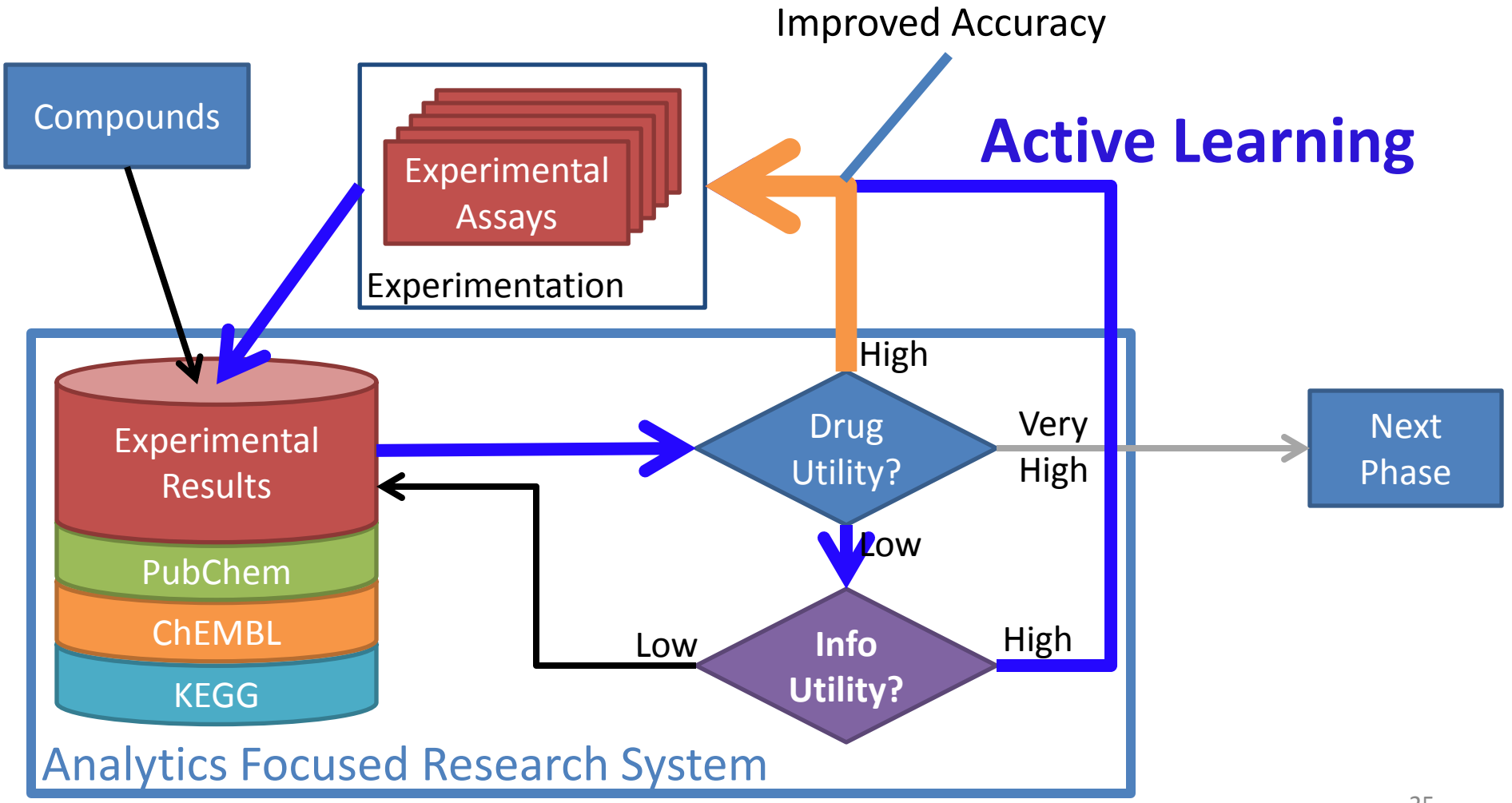
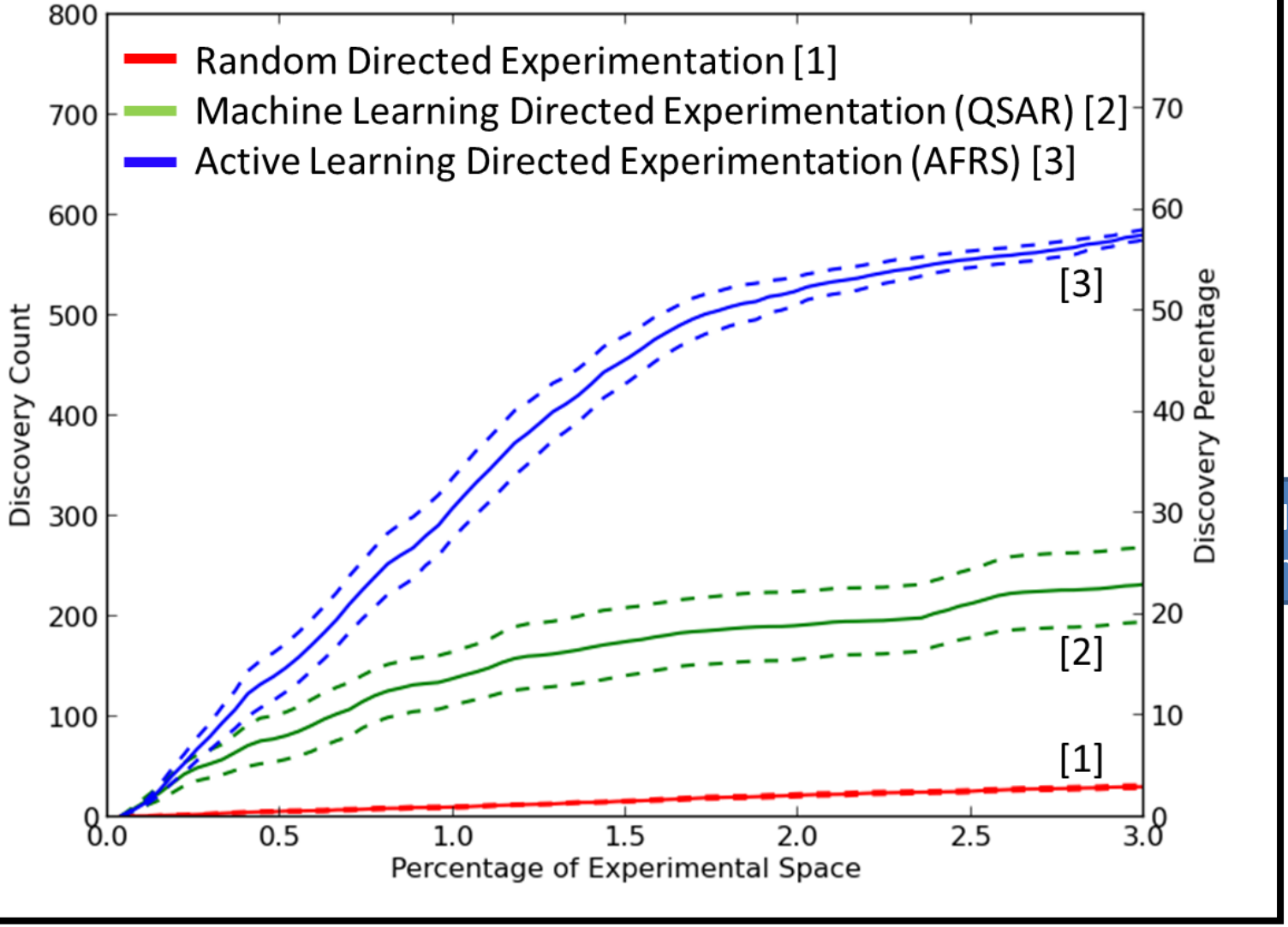


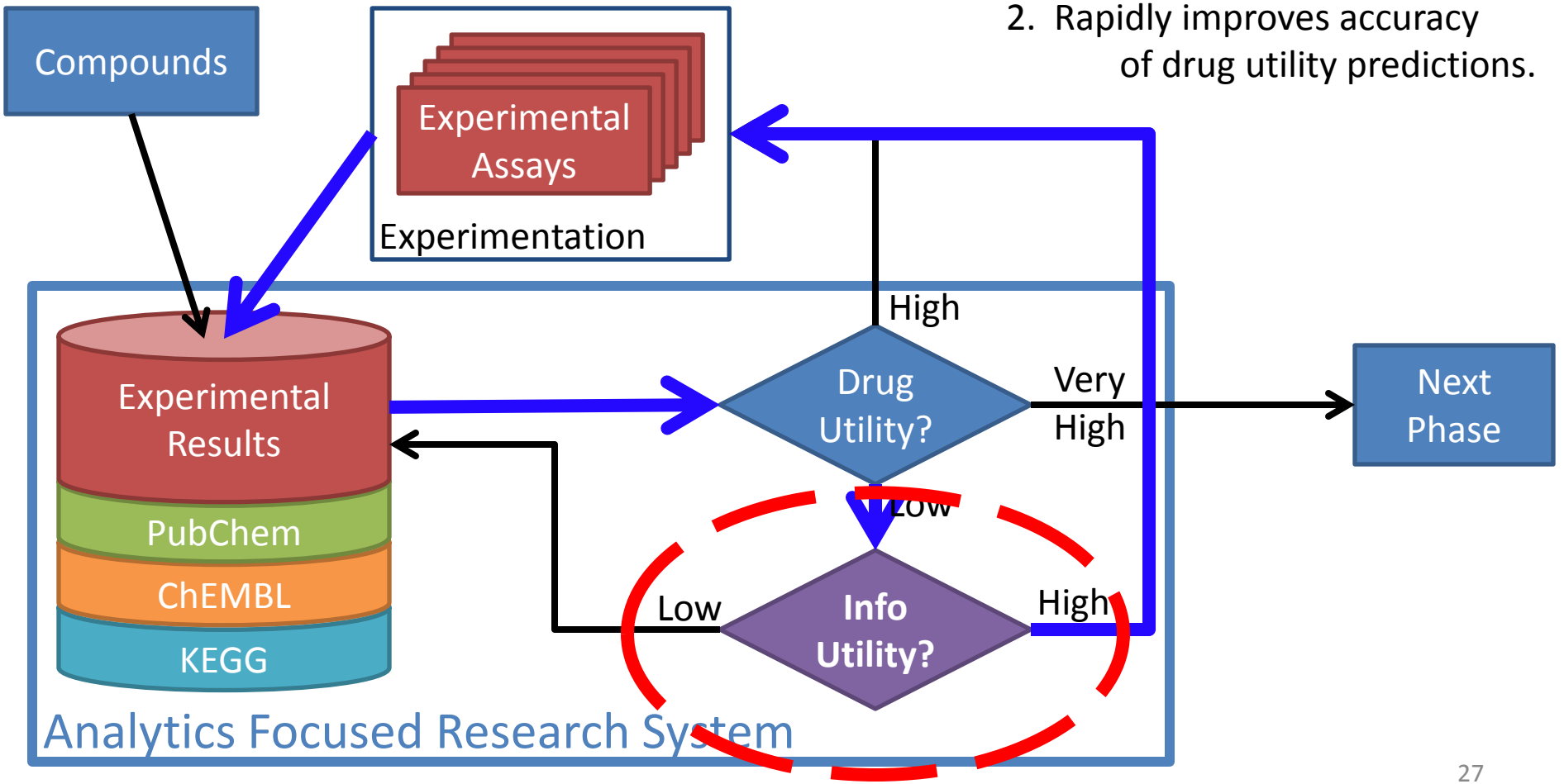
AFRS Approach For Efficient



AFRS Approach For Efficient Experimentation

Running this path:

1. Reduces experimentation
2. Rapidly improves accuracy of drug utility predictions.



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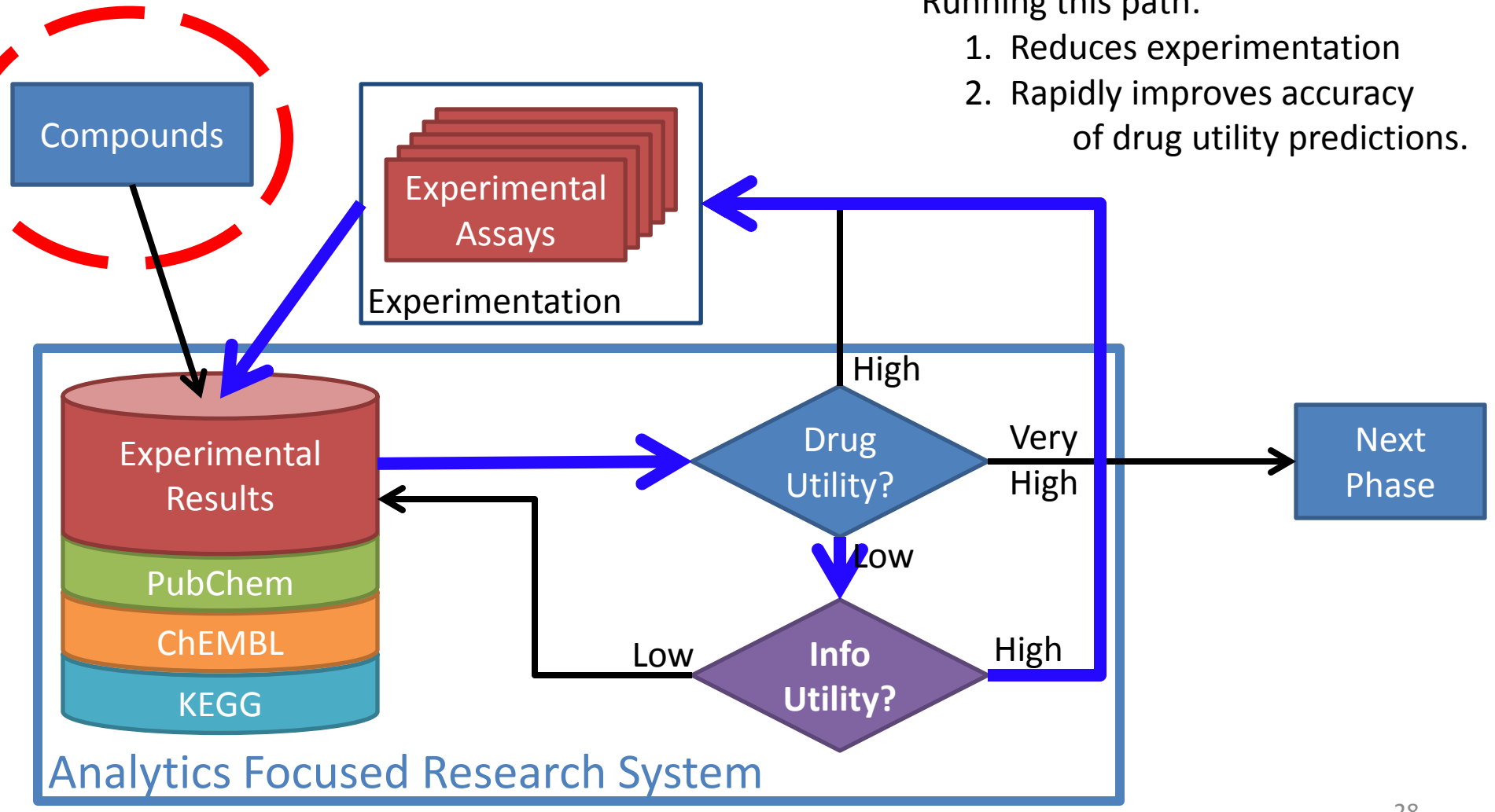

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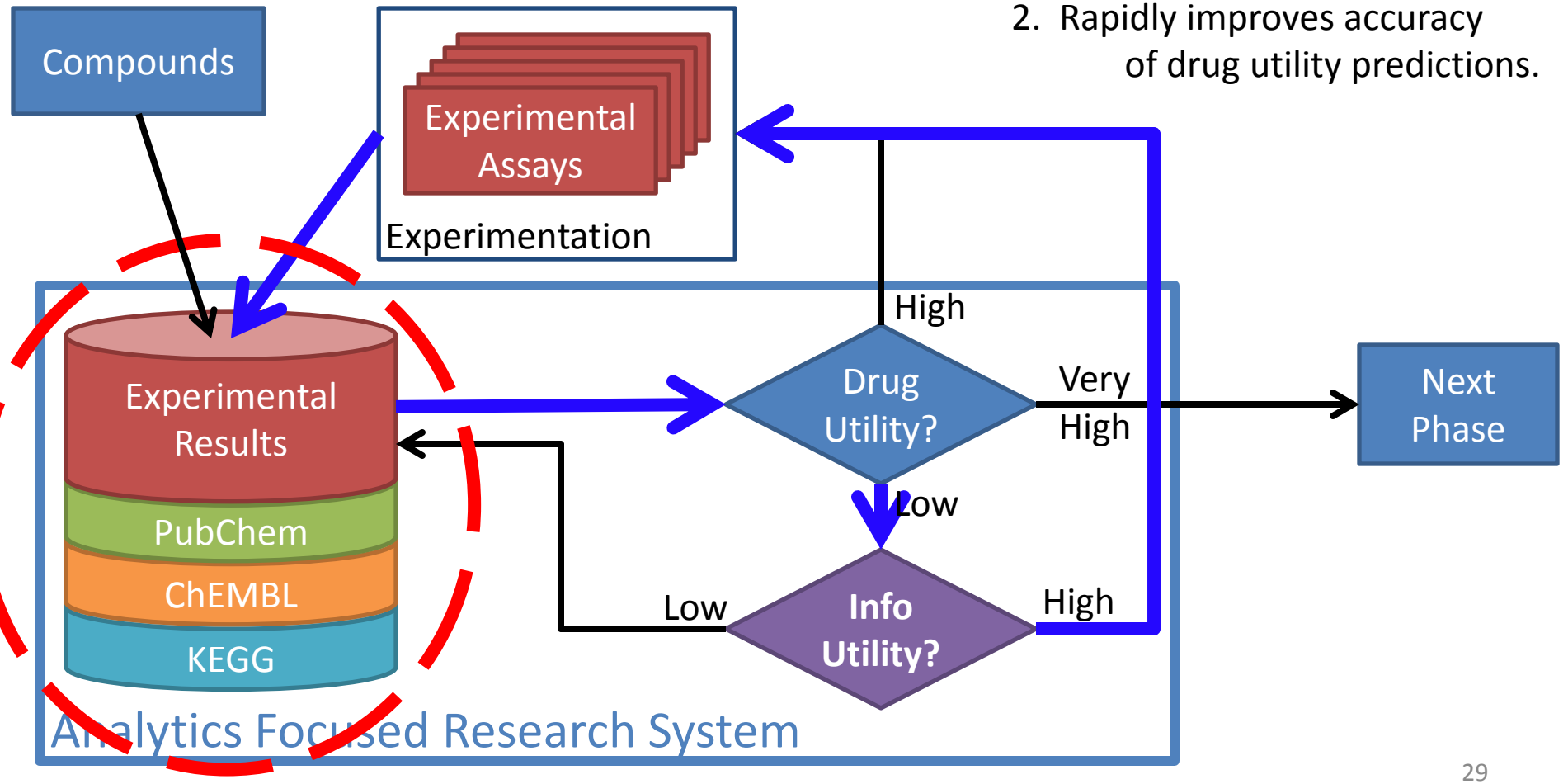

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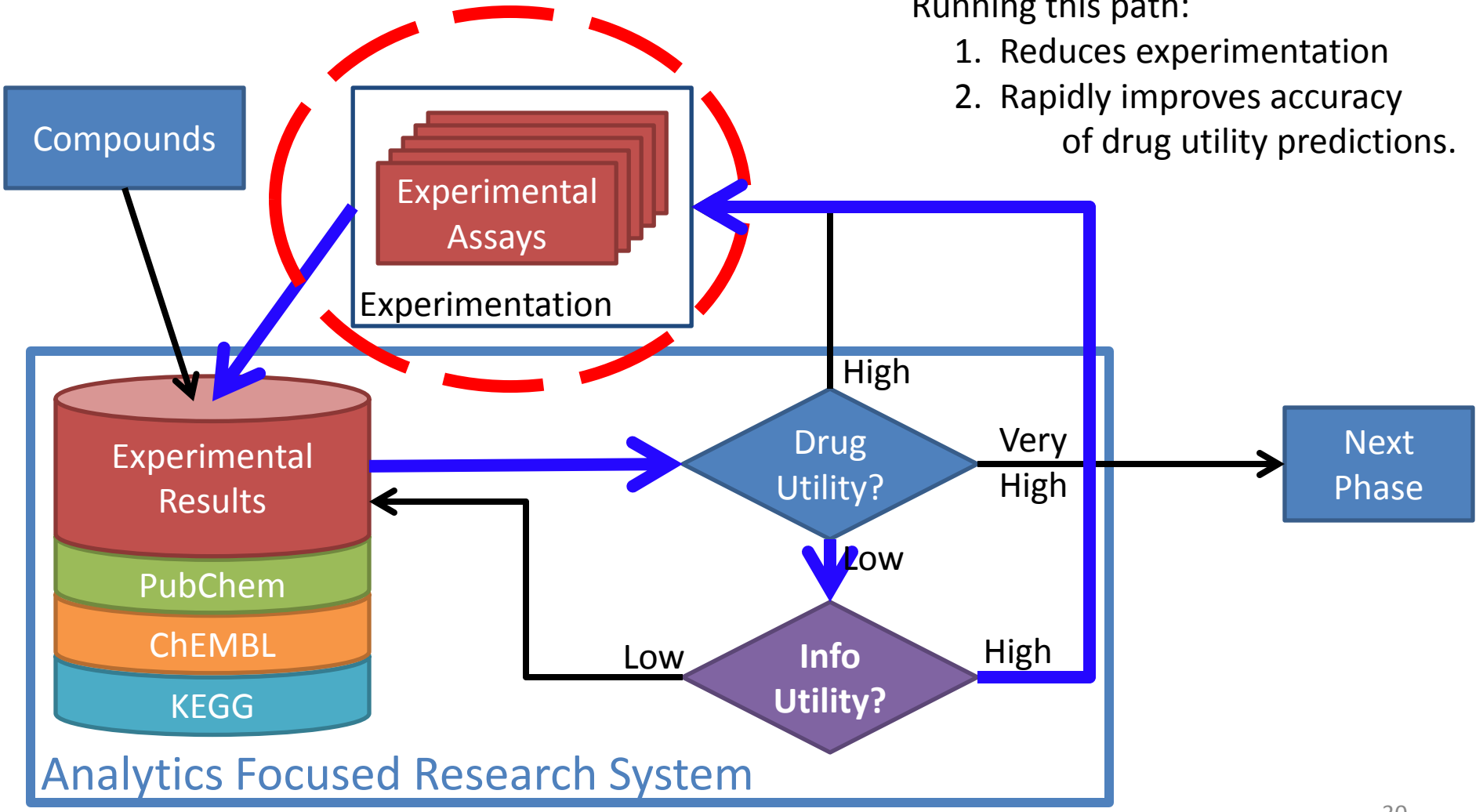
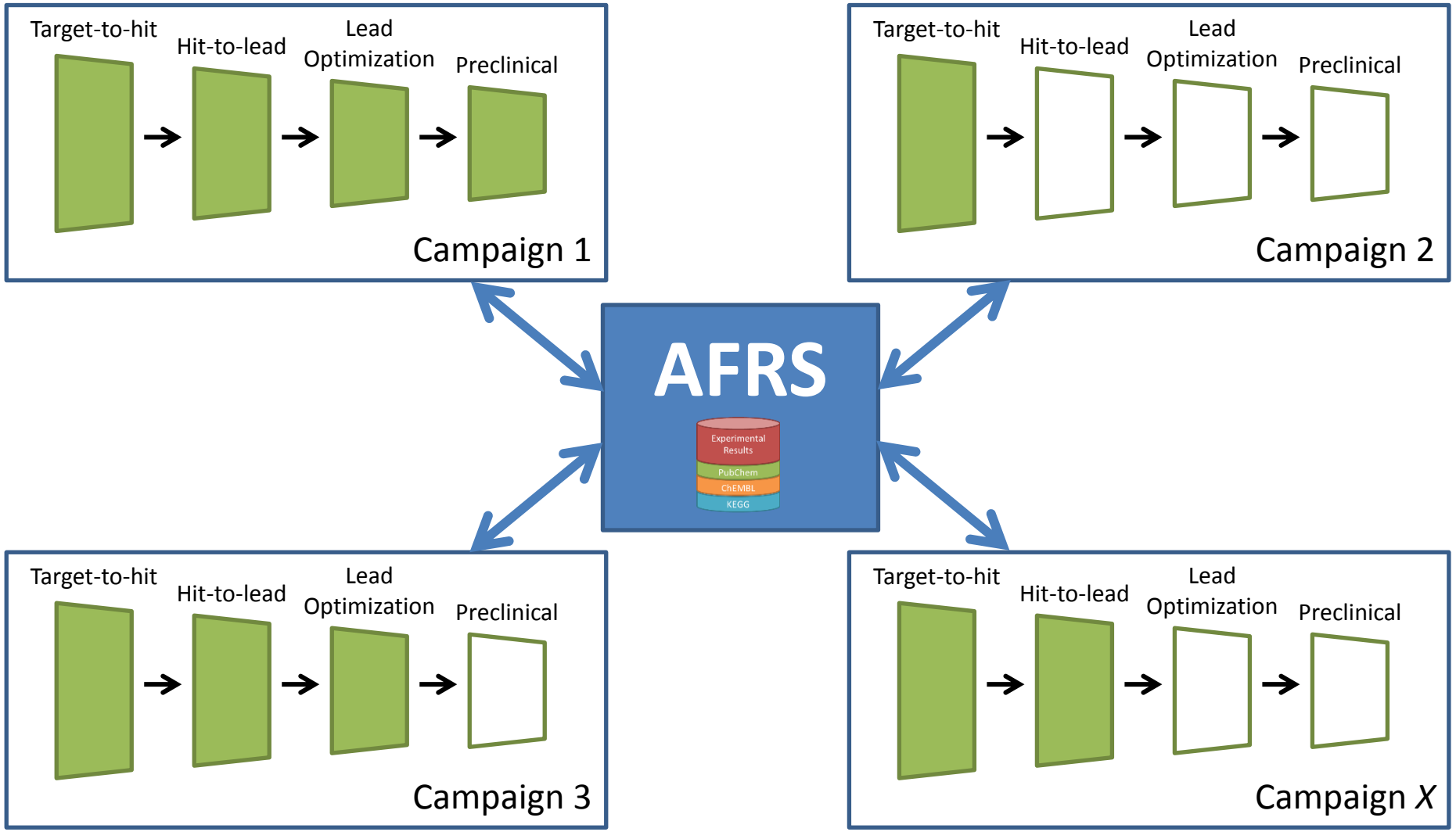
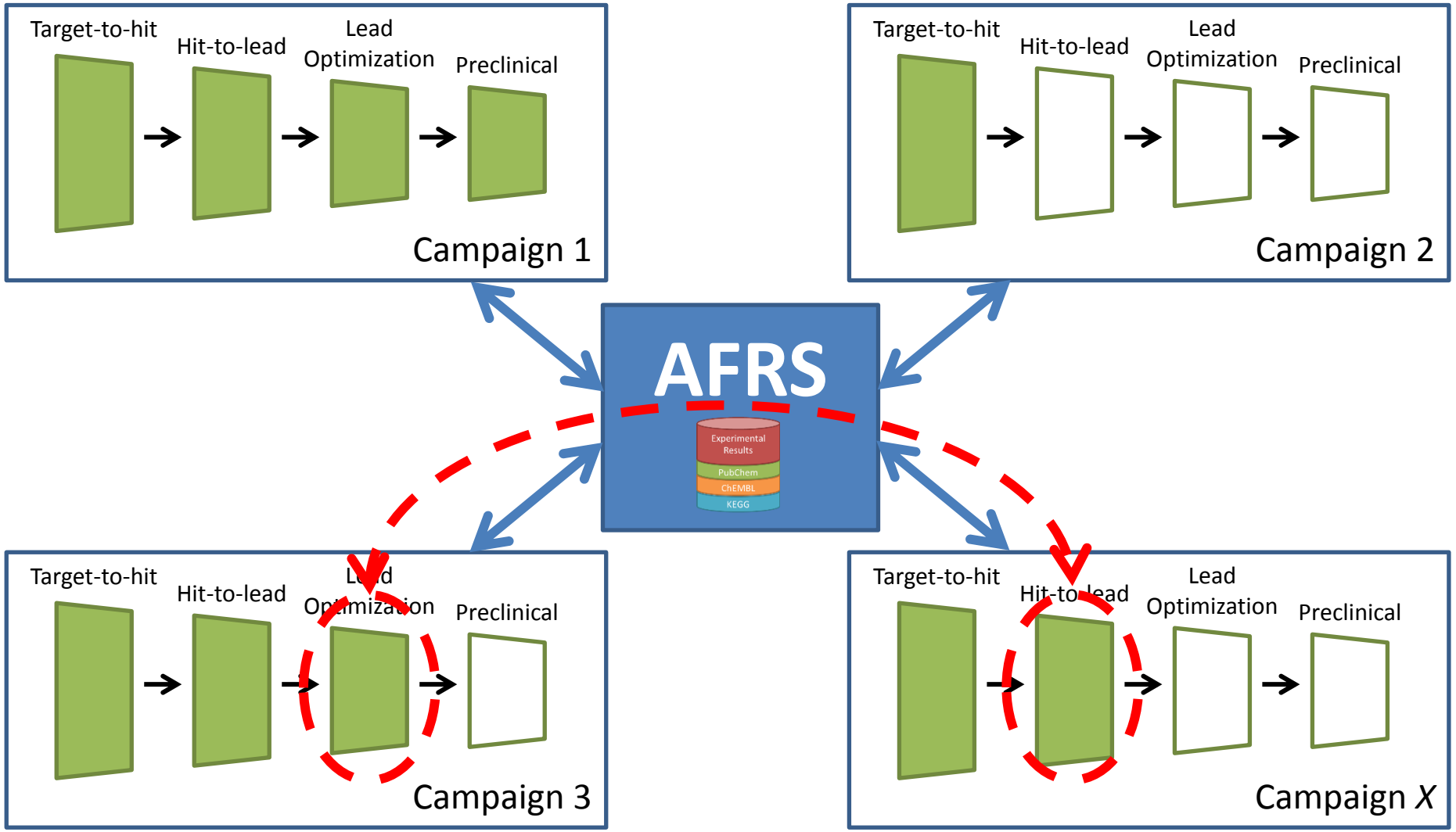


AFRS Approach Across Campaigns



AFRS Approach Across Campaigns



AFRS Approach For Efficient Experimentation

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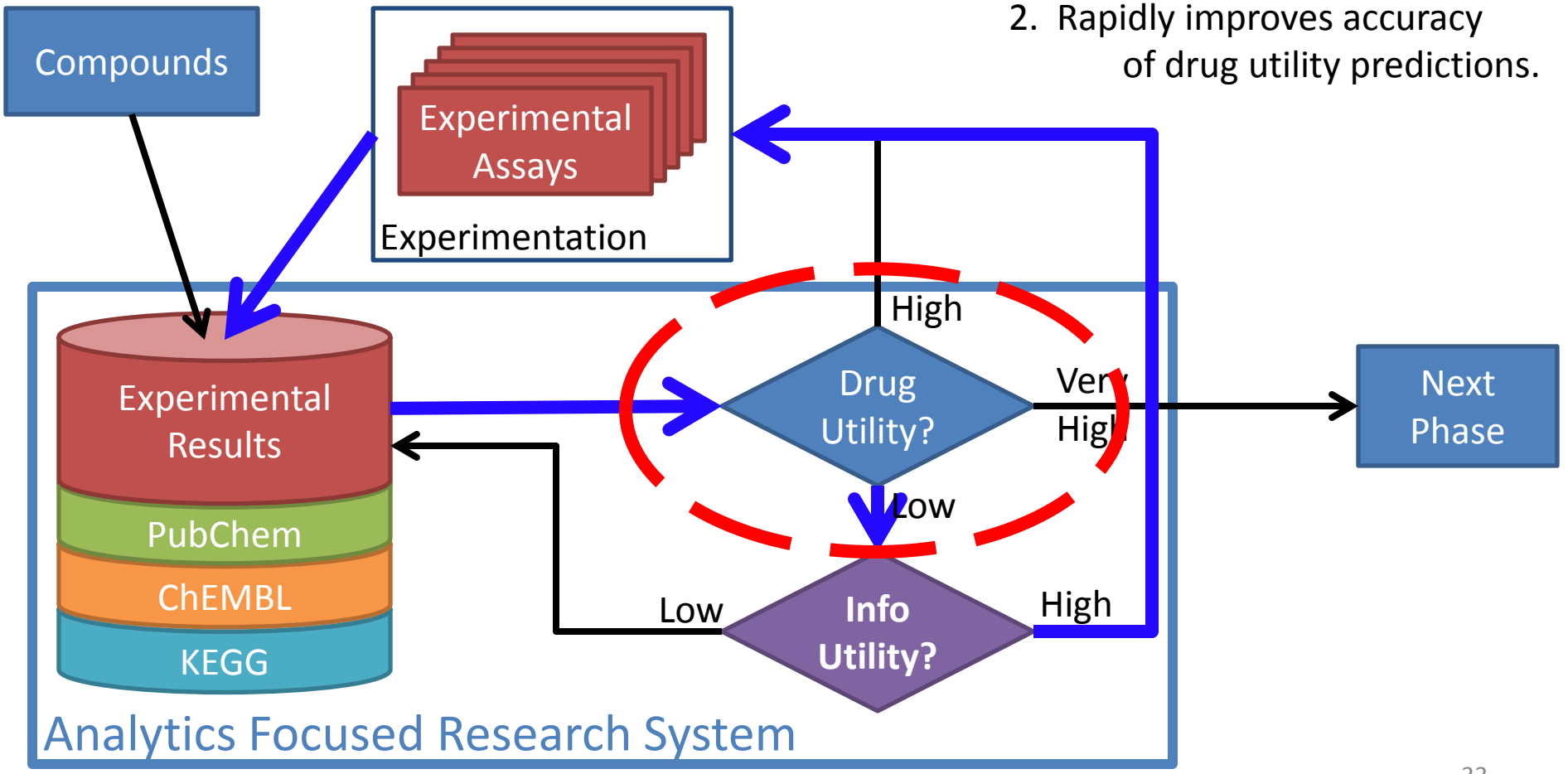

Synopsis

- Integrated system designed to enable these parts to interoperate:
  - Compound libraries
  - Diverse Experimentation methods
  - Extensive knowledge bases
  - Active machine learning-based predictions
- Synergistic relationship between all system components

Benefits

- Immediate Benefits:
  - Less experimentation to yield the same or better results - reduced time, lower cost
  - “Drug Utility” predictive accuracy improves every iteration within the campaign
- Long Term Benefits:
  - Combines and directs experimentation from many diverse modalities
  - Builds more informative corporate dataset for future studies
  - Continually building more accurate predictive models
  - Reduced attrition compared with using less predictive models learned from inadequate data

Use Case

Situation: We have developed an assay which is costly to run. We desire to run this assay on 1,000 compounds and build a predictive model for that assay to reduce the need to run the assay in the future.

Use Case

Action:

- **Standard Approach:** Choose diverse set of 1,000 compounds from compound library and test them all using the assay. Learn a predictive model from those results.
- **AFRS Approach:** Use the AFRS to select 200 compounds from the corporate library for testing using this assay in batches of 10-40 compounds.

Use Case

Results:

- **Standard Approach:** A model is built with a predictive accuracy of X% after running 1,000 compounds.
- **AFRS Approach:** A model is built with a predictive accuracy comparable to or better than X% after running only 200 compounds.

Potential ToxCast Studies

Study Guidelines

- Define Relevant Use Case
- Map Use Case to ToxCast dataset
  - One ToxCast measurement -> one Toxicology Assay
- Run simulations with different selection methods as if ToxCast experiments were being executed as directed rather than looking at the whole dataset at once
- Measure success after each batch

One possible study…

- Use Case – build accurate predictive model for toxicological assay
- For this project:
  - 1 measurement -> 1 assay
- Hide all results from one assay as if it had never been executed
- Loop until assay fully explored
  - Select next batch of experiments
  - Reveal experimental result to model
  - Measure success characteristic(s)

Success Characteristics

- Measure all as a function of the fraction of experiments executed:
  - Accuracy
  - Fraction of hits discovered
  - Fraction of compounds with ideal profile confirmed
  - Others?

Selection Methods to be Compared

- Select Randomly
- Select on Drug Utility Prediction ***only***
- Select using AFRS
- Others?

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