COMP-238
Model Applicability Domains: When Can I Use my Model?
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Combining global and local approaches to model domain applicability

Rajarshi Guha, School of Informatics, Indiana University

David T. Stanton, Modeling & Simulations Department, Corporate Research, Procter & Gamble

The Big Picture

- A molecule that is not similar to the TSET is probably going to be poorly predicted
  - We shouldn't rely on such a prediction
- If a molecule is similar to the TSET, it may or may not be well predicted
  - Can we rely on such a prediction?
  - Why should a molecule similar to the TSET be poorly predicted?

Traditional Approaches

- Most approaches to model applicability consider the similarity to TSET
- "Extra" features in a molecule may be invisible to the model descriptors
  - The extra features cause the observed property to differ from that of similar molecules in the TSET
  - We see the effect of this as a large residual

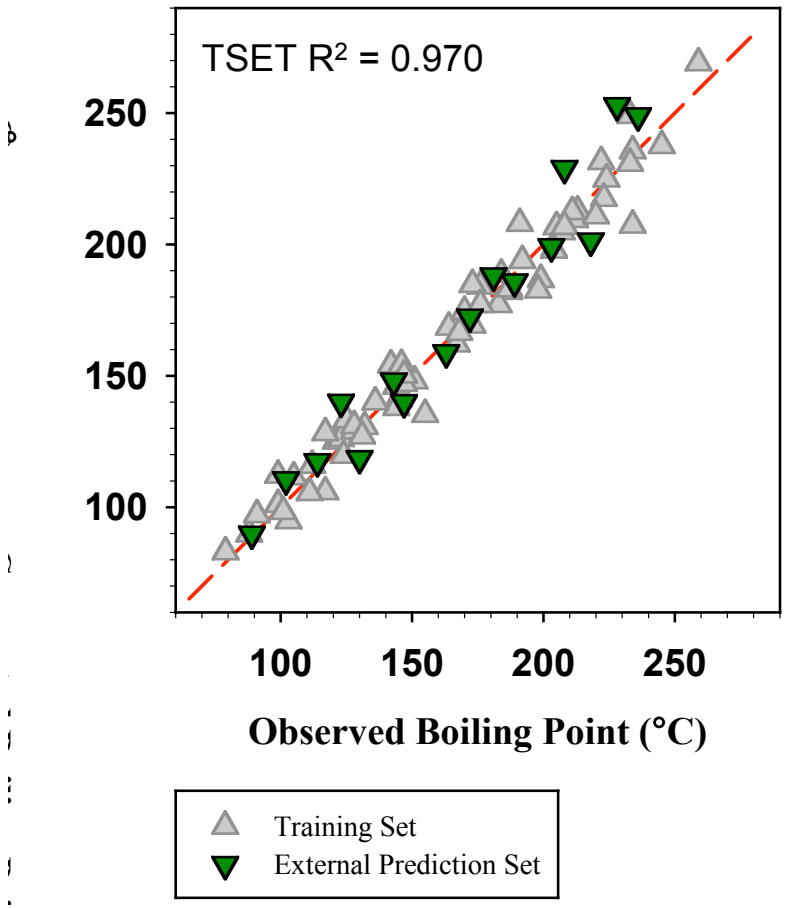
*How do we decide that a molecule, similar to the training set, is **actually** similar to the training set*

Simple Example – Boiling Point Model

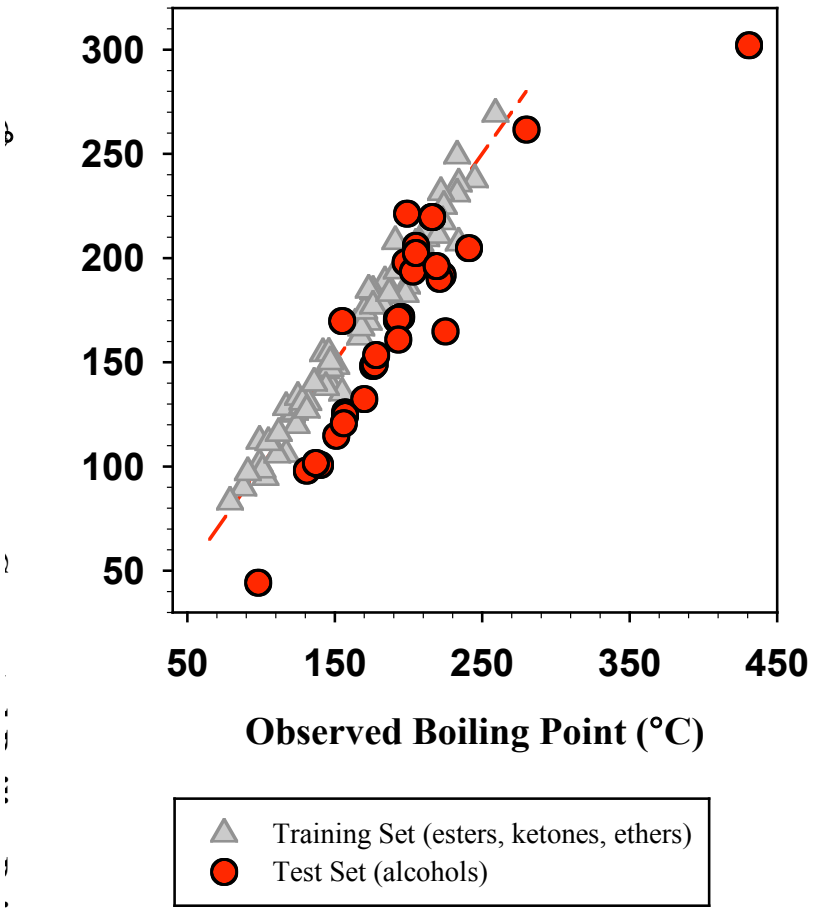
- C_4 – C_{12} Non-aromatic, containing at least 1 oxygen
  - Model development: 80 esters, ethers, ketones
    - 64 in Training set
    - 16 in Validation set
  - New External Prediction Set: 32 alcohols
- 6-variable model
  - R^2 = 0.970
  - Good fit for Validation set (r = 0.973)
- Applied model to predict BP for alcohols

Simple Boiling Point Model - Results

Model Development Results



External Prediction Results



The model under predicts most of the new observations

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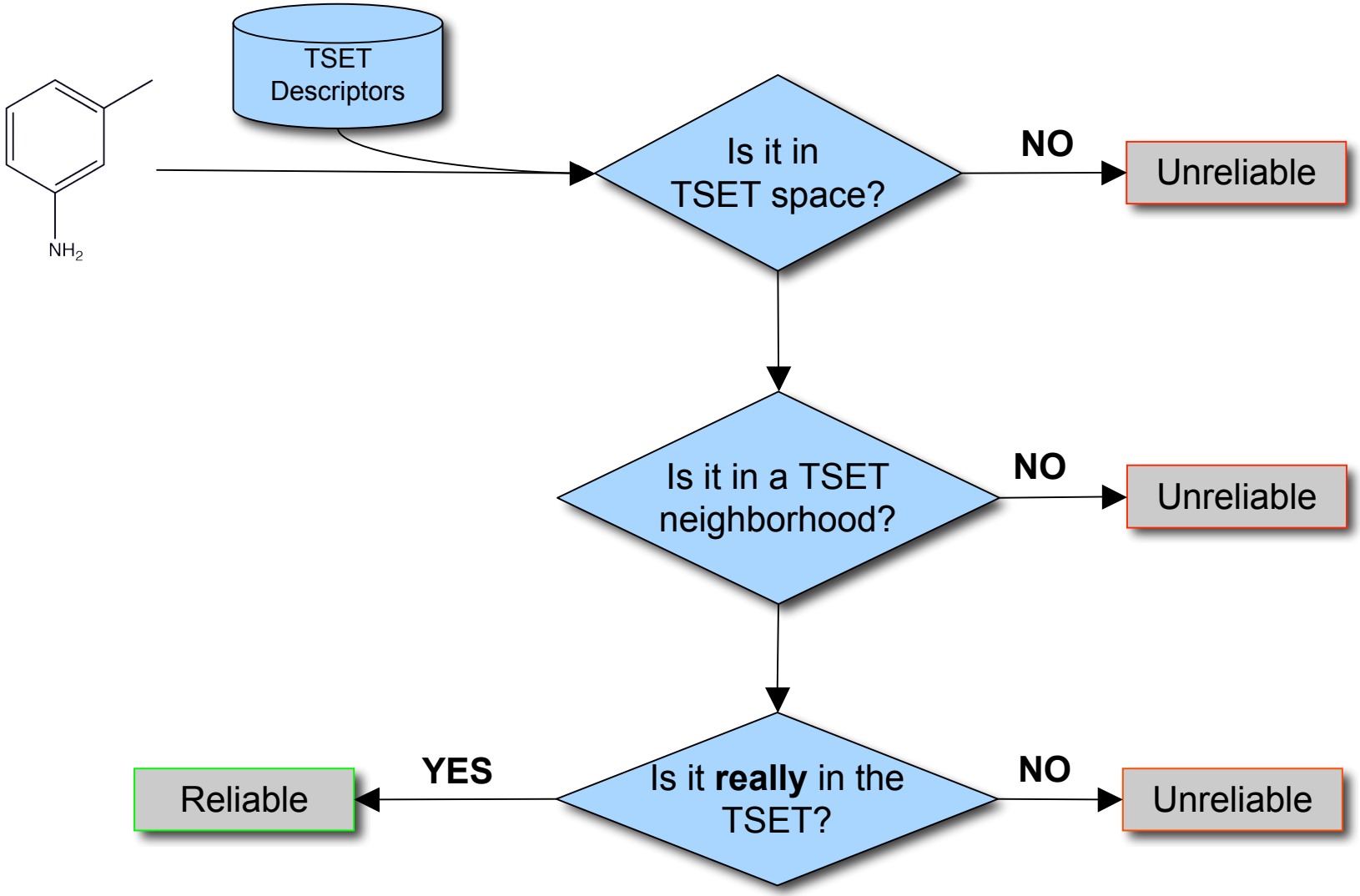
A Hierarchical Strategy



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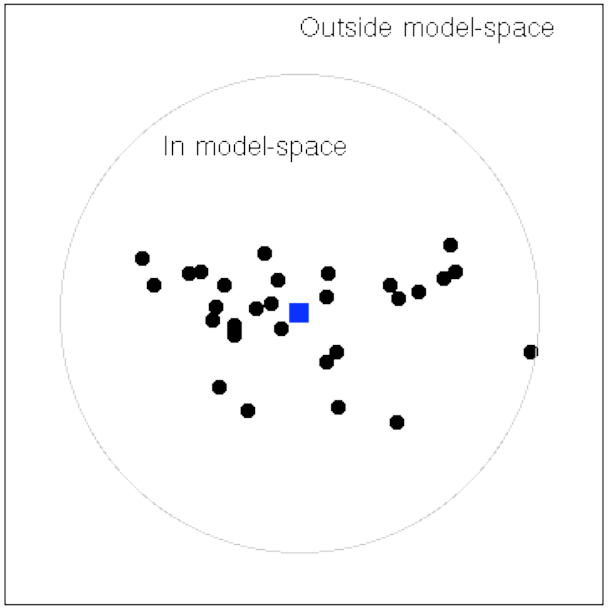
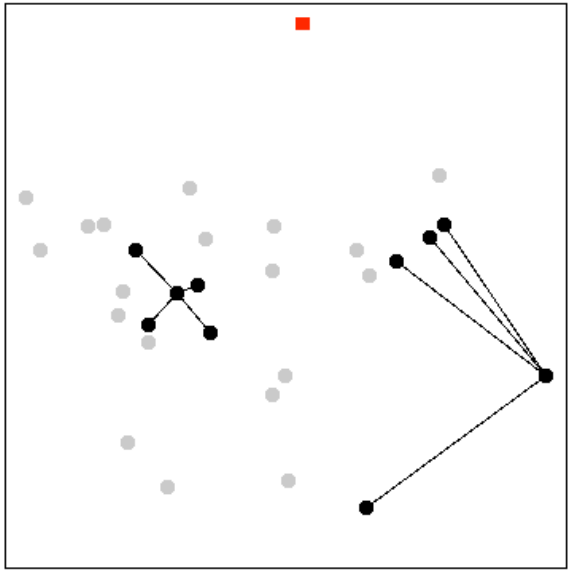
Model-Space Characterization

- Evaluate mean and std dev of the distances of the TSET points to the centroid of the TSET
  - A PSET point is *in model-space* if its distance to the centroid is within 2SD of the mean TSET distances
- Crude classification
- But we can safely ignore points that lie outside model space



Neighborhood Characterization

- Evaluate the average pairwise distance between 5-NN of each TSET point
- Summarize the whole TSET in terms of mean and standard deviation
  - For a PSET point, determine the average 5-NN distance in the TSET
  - Apply a similar classification rule as before
- Isolated TSET points can skew the mean and std dev



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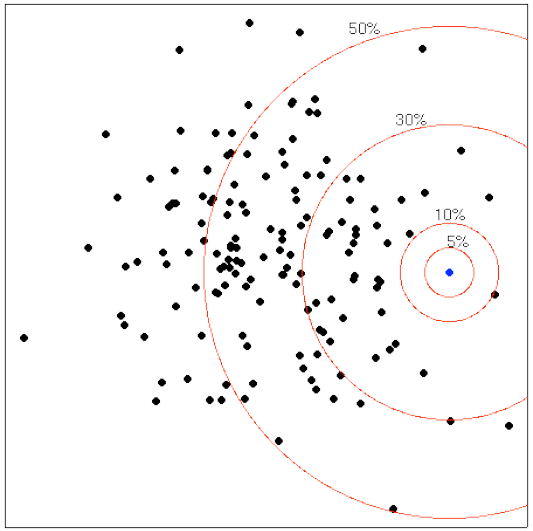
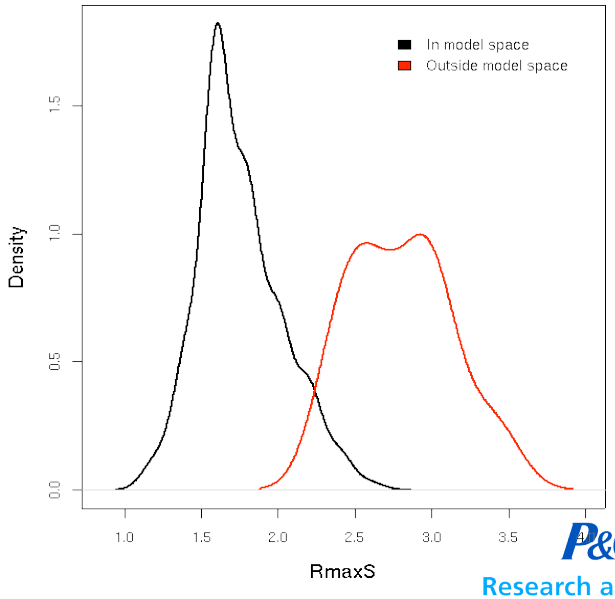
Neighborhood Characterization

- The *R*-NN curve method numerically measures the density of space around a given point
  - The measure is called $R_{max(S)}$ and higher values indicate a more sparse location
  - Makes no assumptions about the spatial distribution of points





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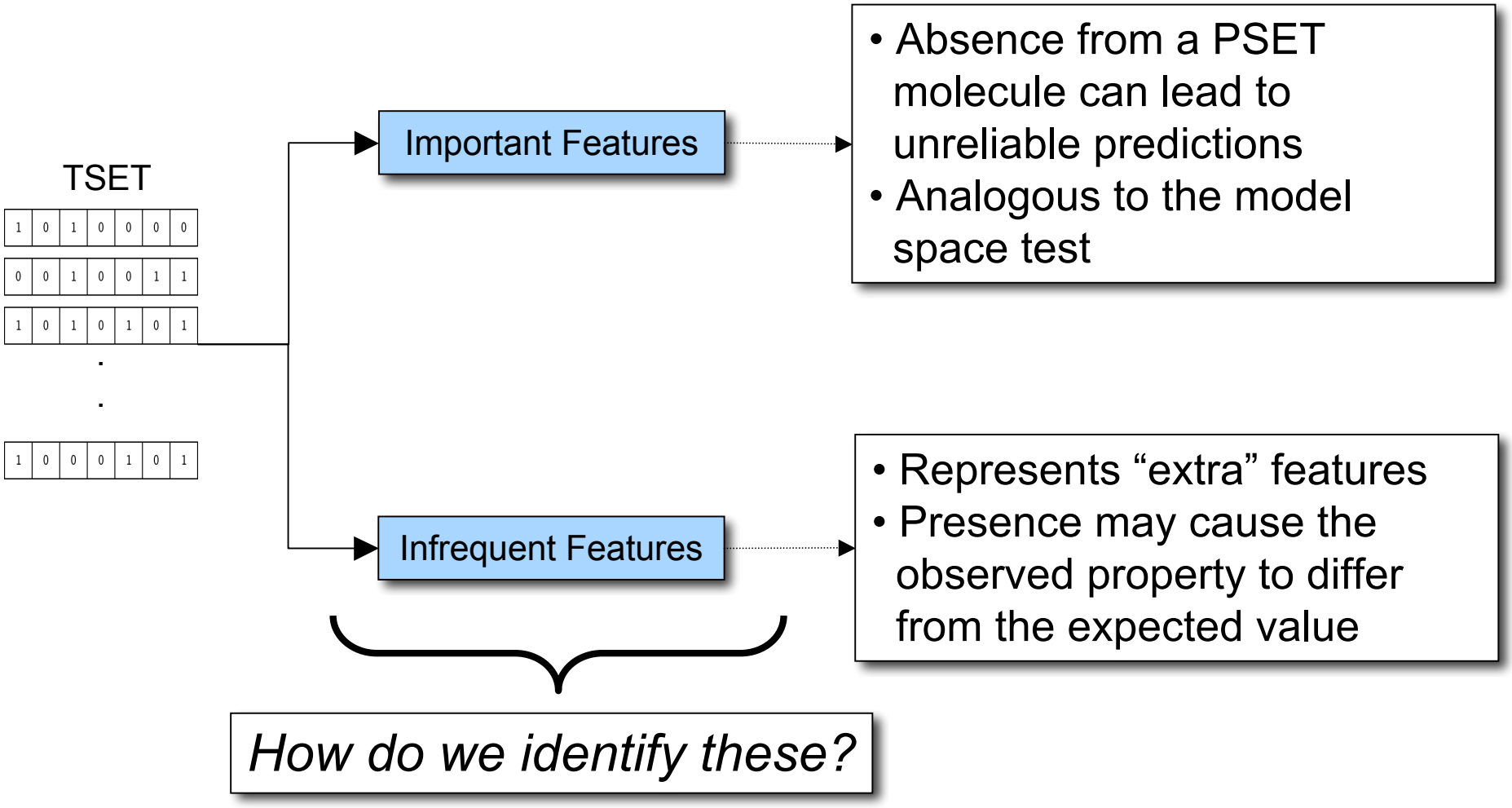
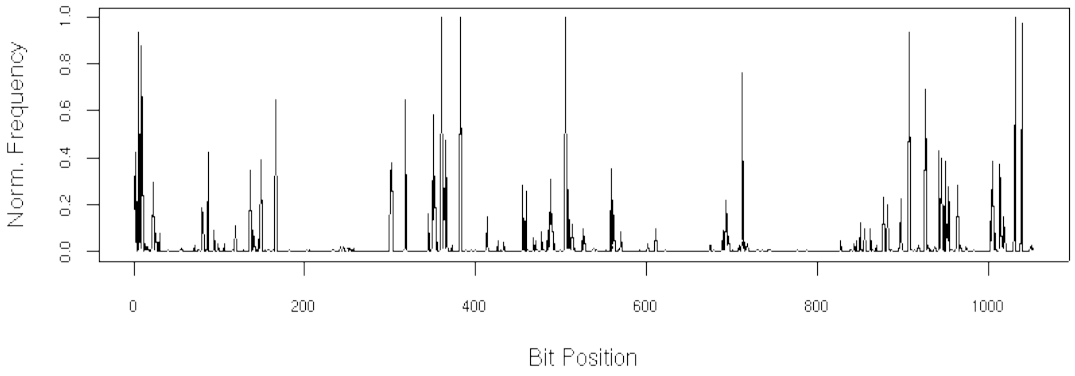
Global Features - Structural Fingerprints

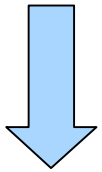


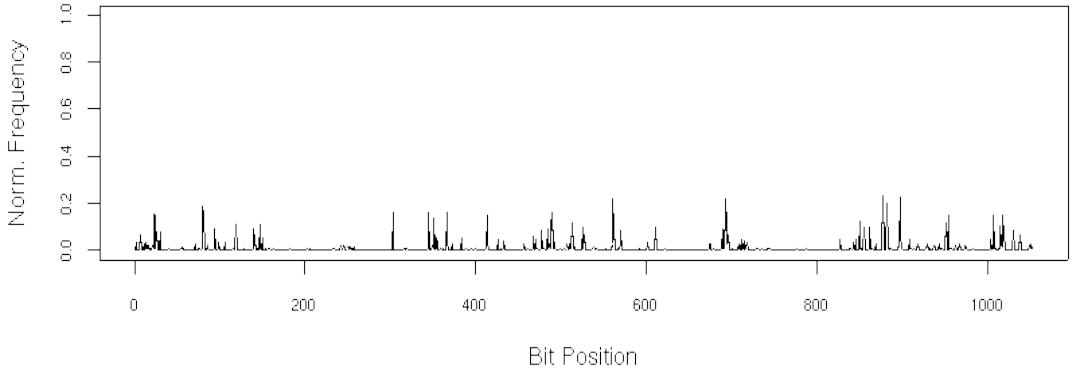
Global Features - Structural Fingerprints

TSET

1	0	1	0	0	0	0
0	0	1	0	0	1	1
1	0	1	0	1	0	1
.						
.						
.						
1	0	0	0	1	0	1







- Summarize the TSET in terms of bit frequencies
- Identify bits that have low frequencies
- Identify bits that have intermediate frequencies

Infrequent Features

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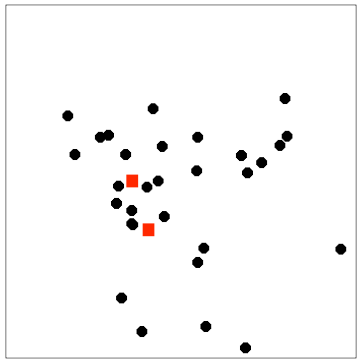
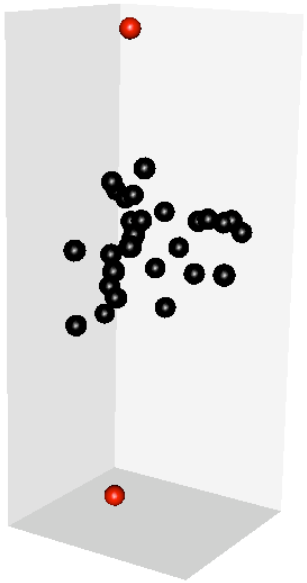
Augmenting Descriptor Spaces

- Is a PSET molecule truly within the TSET?
- Augment the model space with another dimension
  - If the distance and neighborhood classifications don't hold, maybe it really isn't in model space





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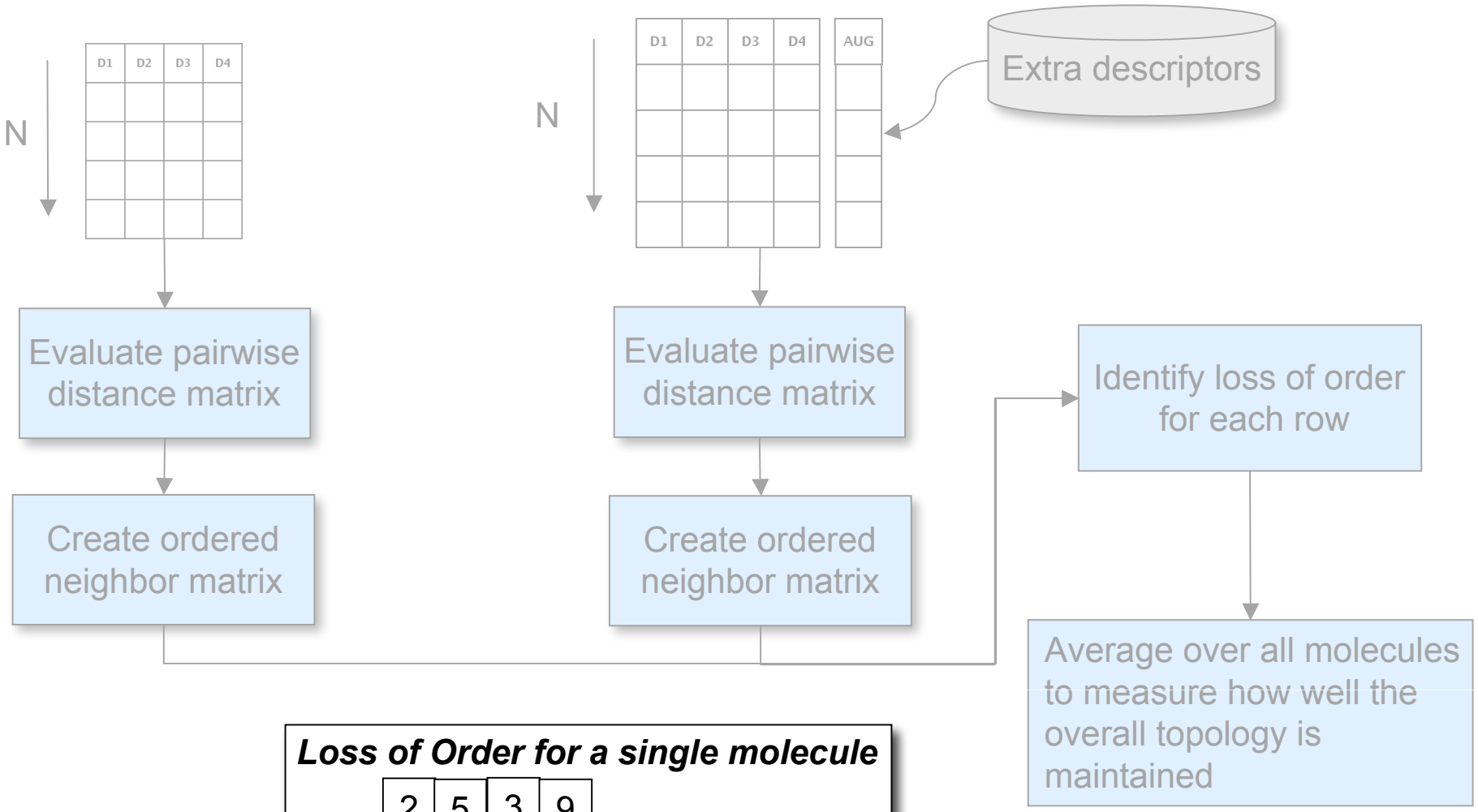
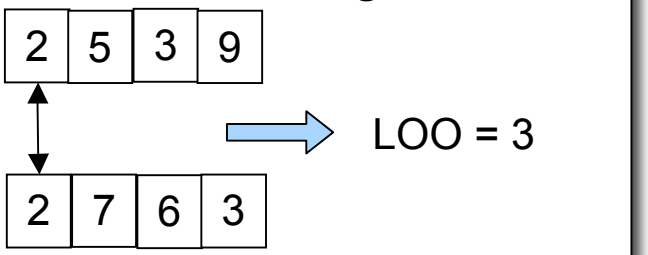
Augmenting Descriptor Spaces

- We don't know what this extra dimension should be
- We might need more than one extra dimension
- But we can provide a few constraints
  - The topology of the TSET should be the same in both spaces
  - The extra dimensions should not be highly correlated to the model descriptors
  - The distributions in the extra dimensions should not be the same for the TSET and PSET

Searching for Suitable Spaces



Loss of Order for a single molecule



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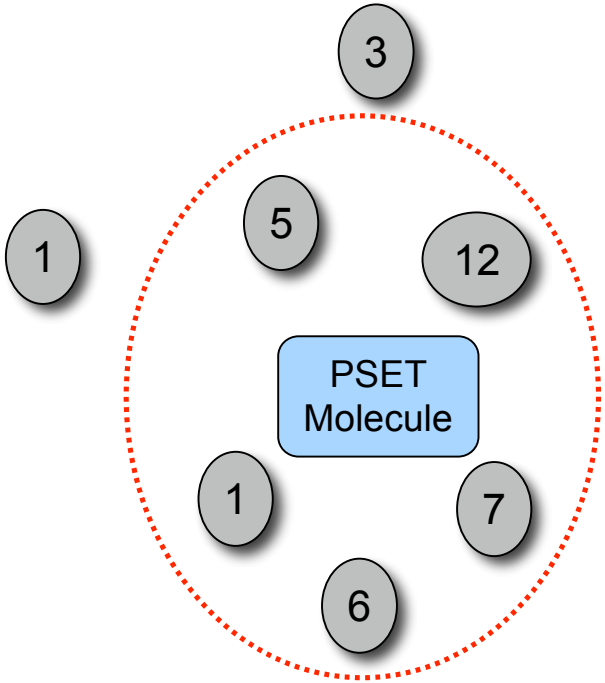
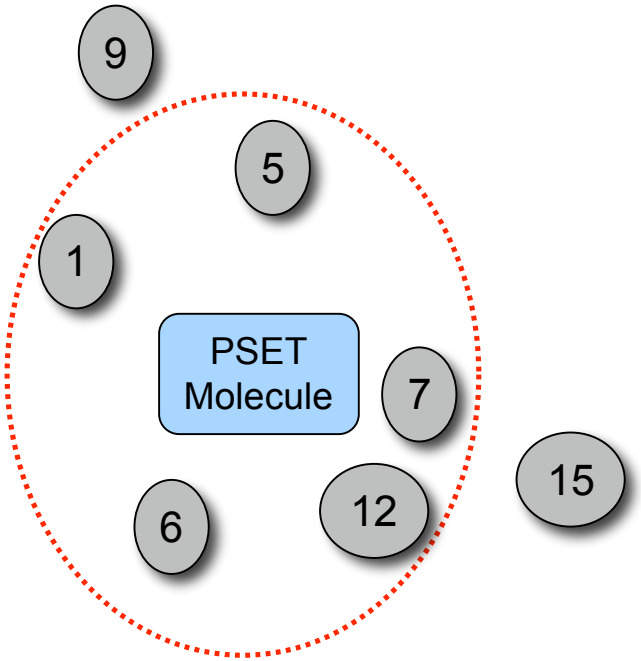
Using Augmented Descriptor Spaces

Original Descriptor Space



Augmented Descriptor Space



- If the nearest neighbors stay the same in the augmented space, the PSET molecule is most likely similar to the TSET

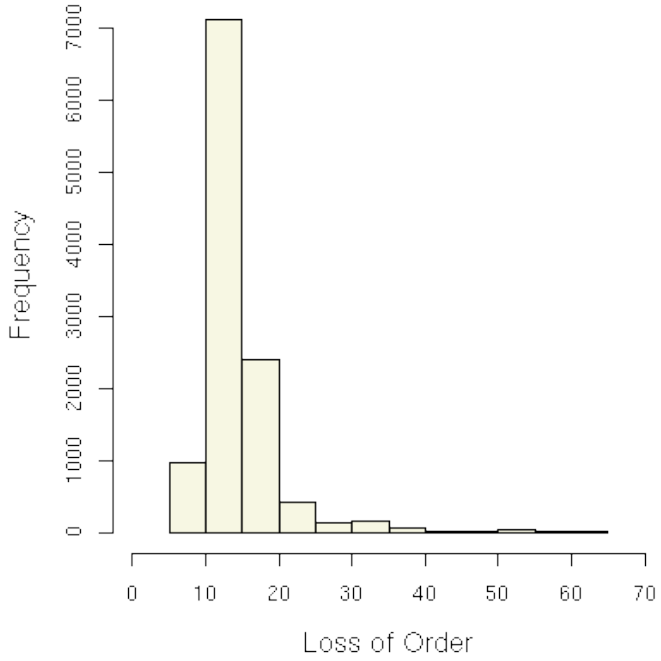
Simple BP Model - Local Assessments

	Local Model IN	*Local Model OUT*
Error IN	6	1
Error OUT	23	2

- Most of the PSET is considered to be within the TSET
- The model descriptors are not capturing molecular features that differentiate the PSET molecules from the TSET

Simple BP Model - Descriptor Augmentation

- Augmented with 2 descriptors
  - Used a brute force method to identify suitable sets
  - Most sets cause relatively low loss of order



- Chose two H-bonding descriptors
  - RPCS, RNCS
  - Very low correlation to the model descriptors
  - Non-zero values in the TSET and PSET

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Simple BP Model - Global Assessments

	Local Model IN	Local Model OUT
Error IN	6	1
Error OUT	23	2

25% Correct Assessment

True Positives

	Global Model IN	Global Model OUT
Error IN	0	6
Error OUT	0	0

False Positives

	Global Model IN	Global Model OUT
Error IN	0	0
Error OUT	0	23

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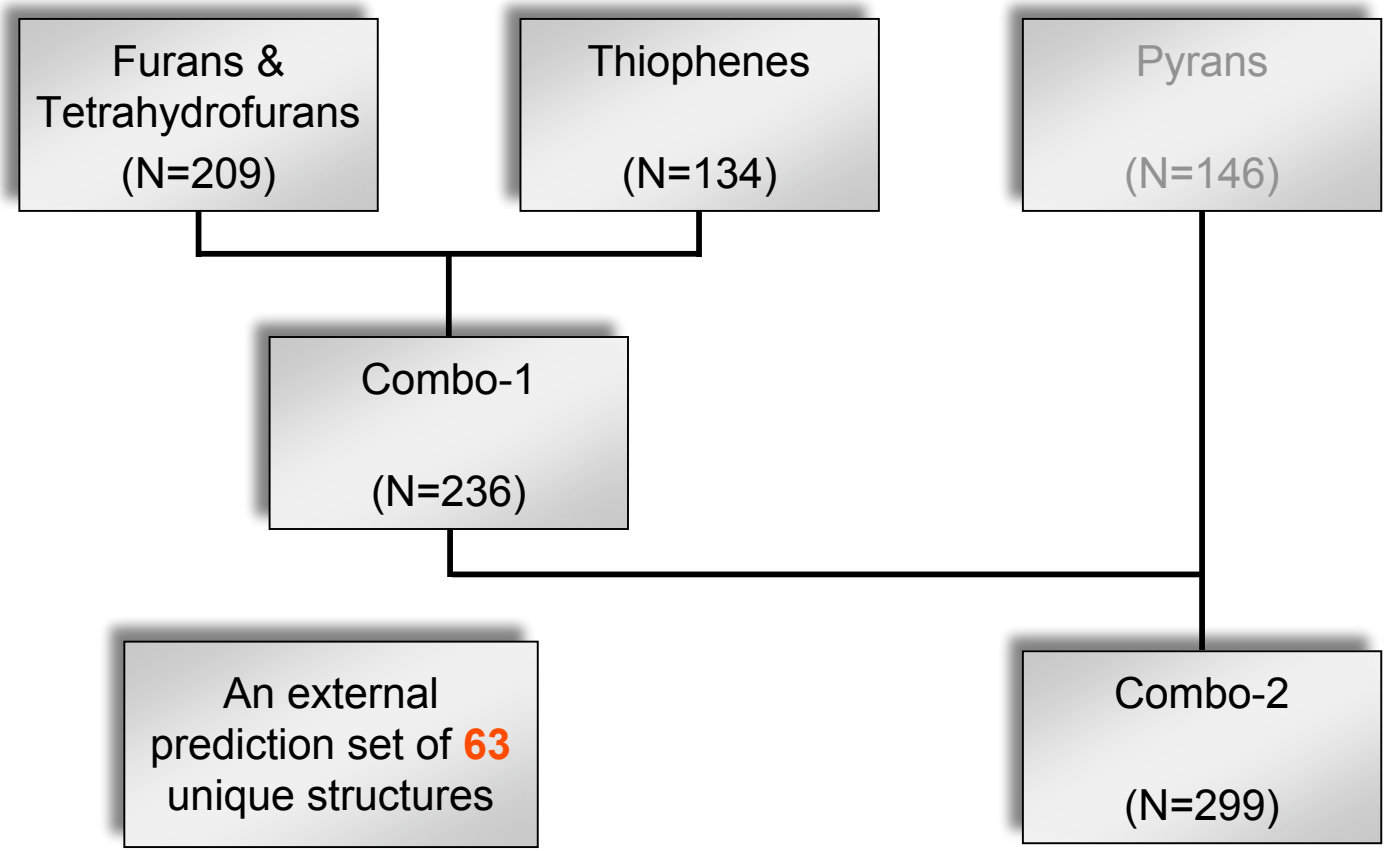
Beilstein Data Set BP Models

- Published boiling point models*
  - Four very diverse training sets



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* *J. Chem. Inf. Comput. Sci.*, **1991**, *31*, 301-310
J. Chem. Inf. Comput. Sci., **1992**, *32*, 306-316

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Beilstein BP Models - Local Assessments

Furan / Tetrahydrofuran Model

	Local Model IN	*Local Model OUT*
Error IN	24	1
Error OUT	35	3

42.8% Correct Assessment

Combo-2 Model

	Local Model IN	*Local Model OUT*
Error IN	63	0
Error OUT	0	0

100% Correct Assessment

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Beilstein BP Models - Global Assessments

Furan / Tetrahydrofuran Model

	Local Model IN	*Local Model OUT*
Error IN	24	1
Error OUT	35	3

42.8% Correct Assessment

True Positives

	Global Model IN	*Global Model OUT*
Error IN	20	4
Error OUT	0	0

False Positives

	Global Model IN	*Global Model OUT*
Error IN	0	0
Error OUT	30	5

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Beilstein BP Models - Global Assessments

Combo-2 Model

	Local Model IN	*Local Model OUT*
Error IN	63	0
Error OUT	0	0

100% Correct Assessment

True Positives

	Global Model IN	*Global Model OUT*
Error IN	42	21
Error OUT	0	0

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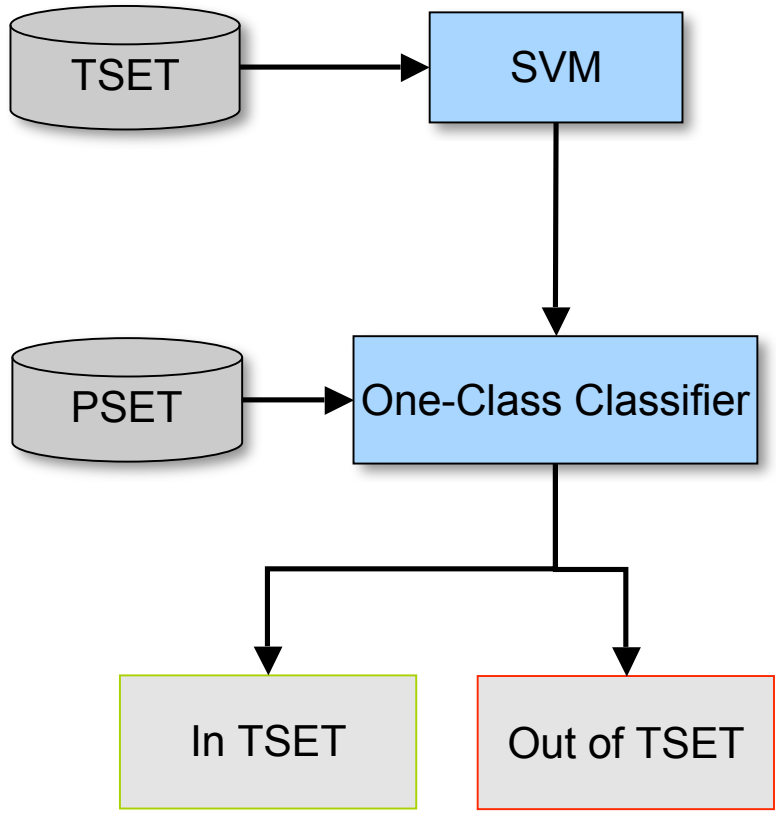
More Sophistication?

- Model applicability is equivalent to novelty detection
- Augmented spaces are conceptually similar to the theory of SVM's
  - Go to a high-D space, to get better separation



The original problem remains - what is a set of suitable descriptors?

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Scholkopf, B. et al, *Adv. Neural Inf. Proc.*, **2000**, *12*

Summary

- It's not enough to just consider the model space
- So what is a good global space?
  - Augmented space approach is intuitive
  - Molecular diversity
  - Probably more important than methodology
- Fix the false positives, leave the true positives
- Becomes much harder when applied to diverse training sets

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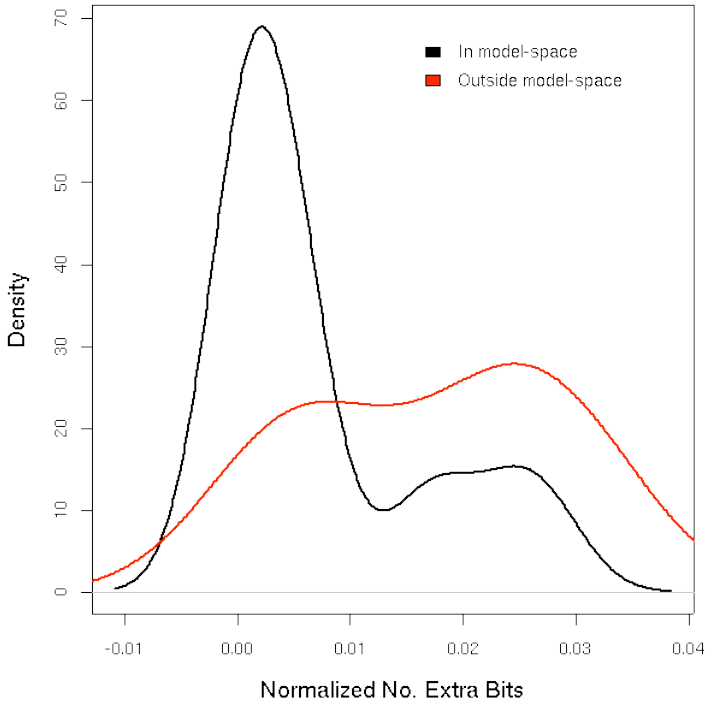
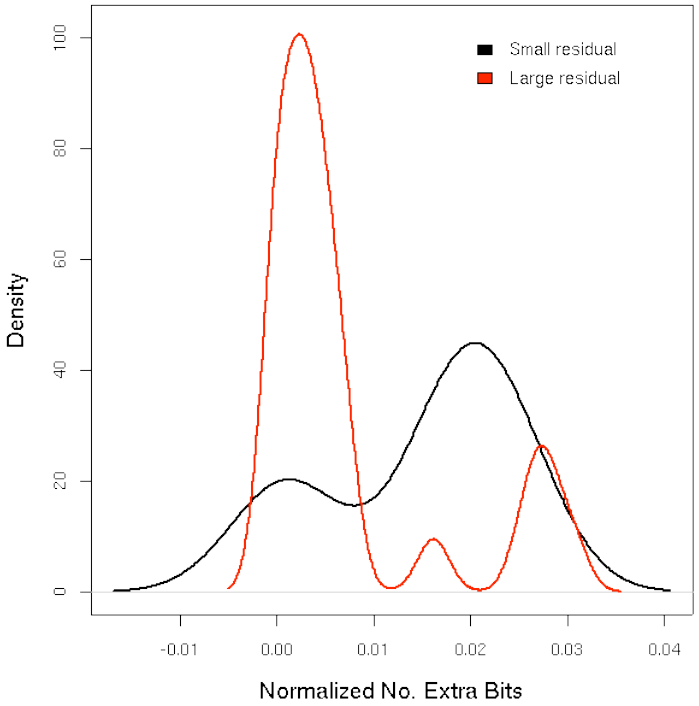
Simple BP Model - Fingerprint Classification

- Molecules that are similar to the TSET by distance have very few “extra” features





- This does not correspond well with residual classes
- Molecules with no “extra” features may still have a high residual

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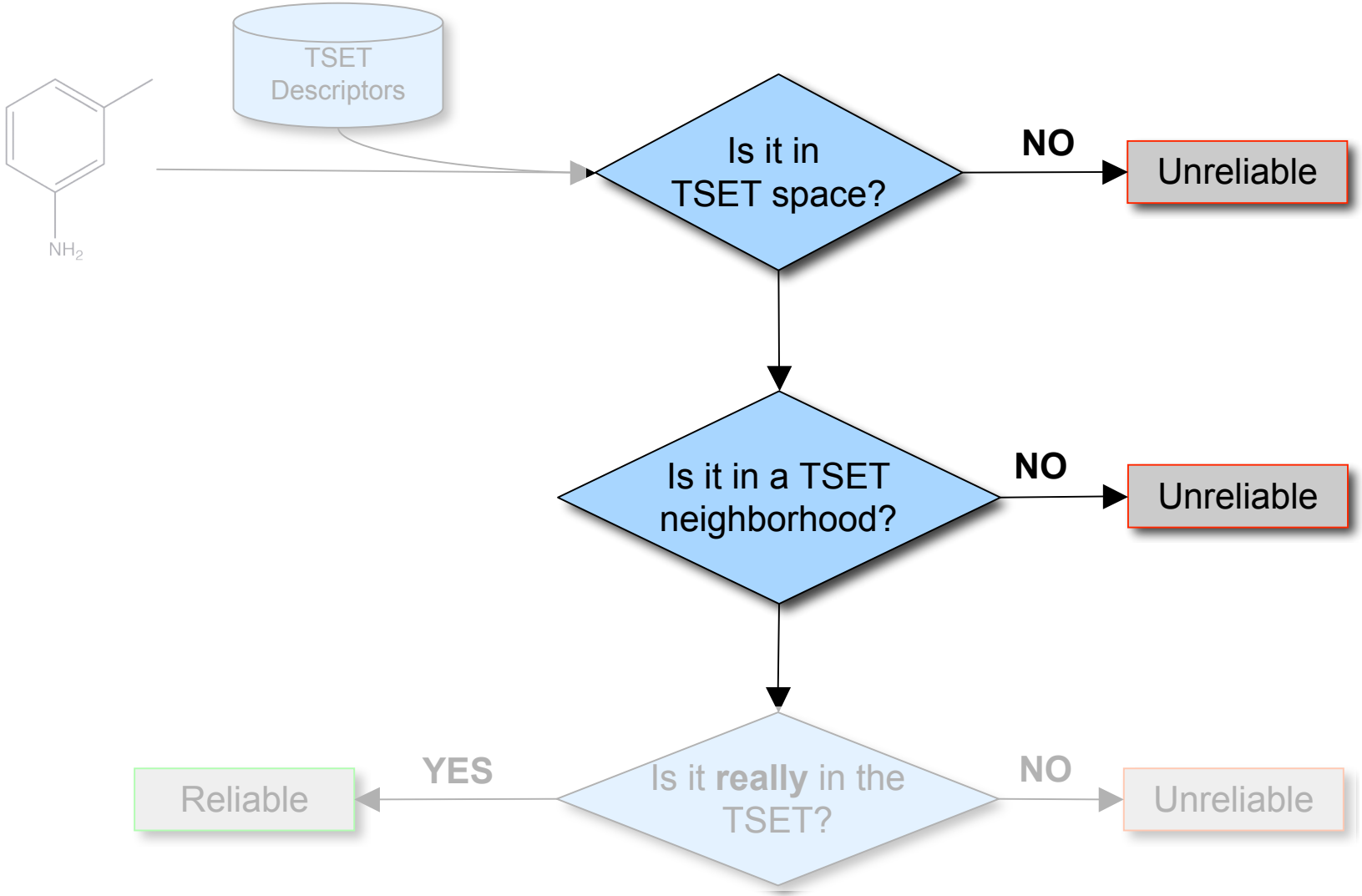
A Hierarchical Strategy - Local Information



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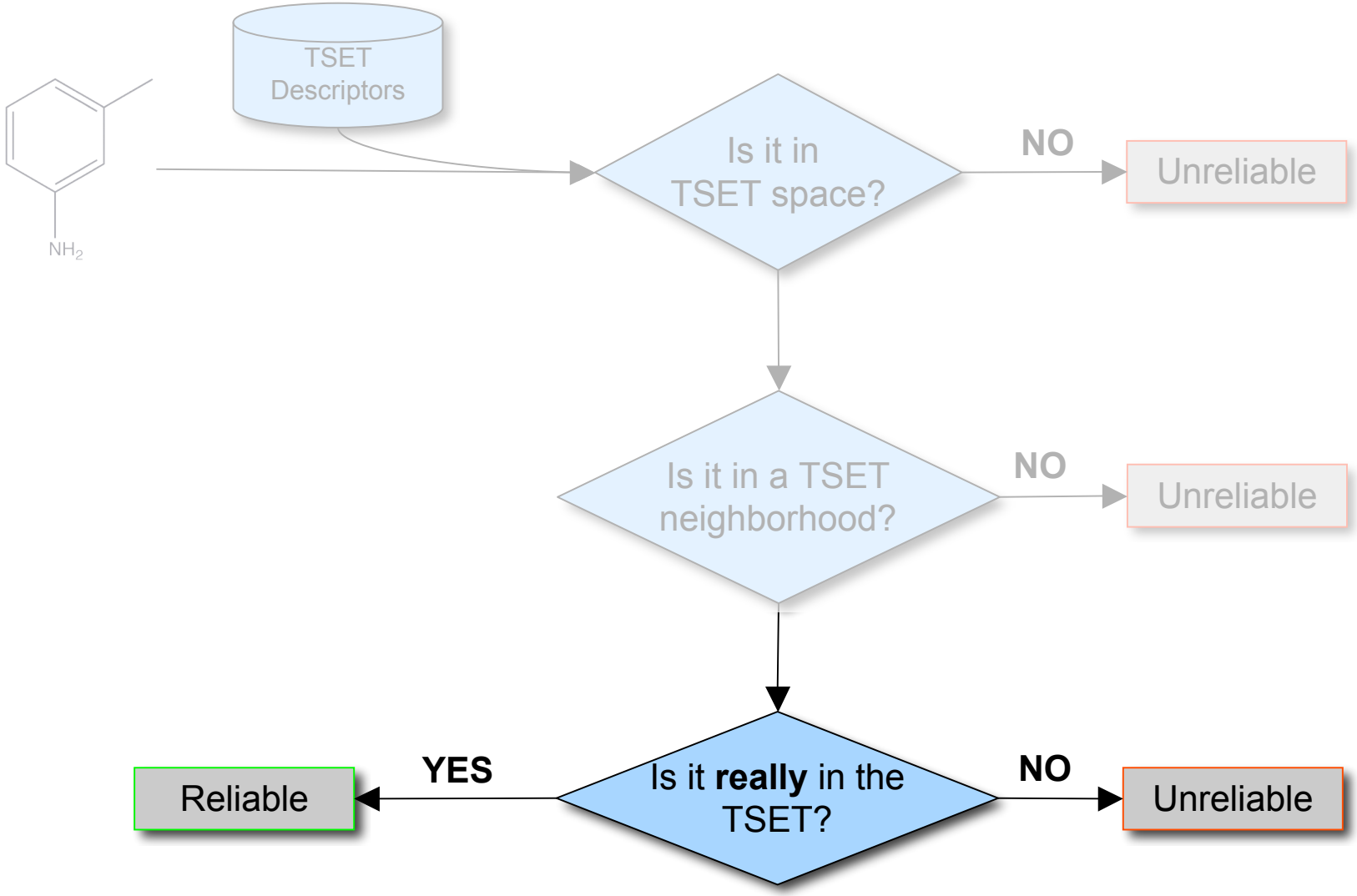
A Hierarchical Strategy - Global Information



Simple BP Model - Descriptor Augmentation

- From a pool of 160 descriptors, we identified 3 descriptors
  - Maintained the topology of the TSET perfectly
- They were all H-bonding descriptors
  - Values for the TSET were 0, non-zero for the PSET molecules
- We consider SSAH as the augmenting descriptor

Simple BP Model - Descriptor Augmentation

- In terms of the distance to centroid class
  - All PSET molecules are outside of model space in the augmented space
- In terms of the number of common nearest neighbors
  - All PSET molecules have the same neighborhood in both spaces