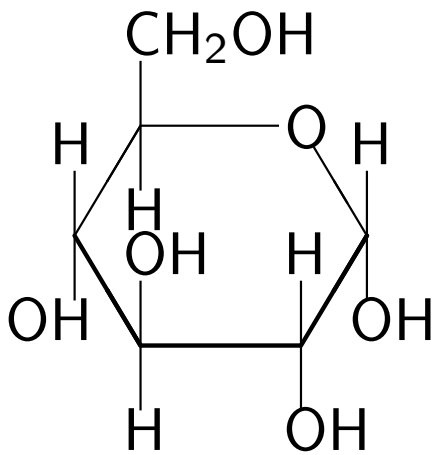
A Pattern Recognition Based Model for Characterizing and Predicting Glucose-Binding Sites

Houssam Nassif

June 7, 2006



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Goal

Identify glucose-binding sites.

Biochemical Background

A glucose-binding site involves:

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1. A glucose molecule.

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2. A protein.

Biochemical Background

A glucose-binding site involves:

1. A glucose molecule.
2. A protein.
3. Their interaction.

Glucose Structure

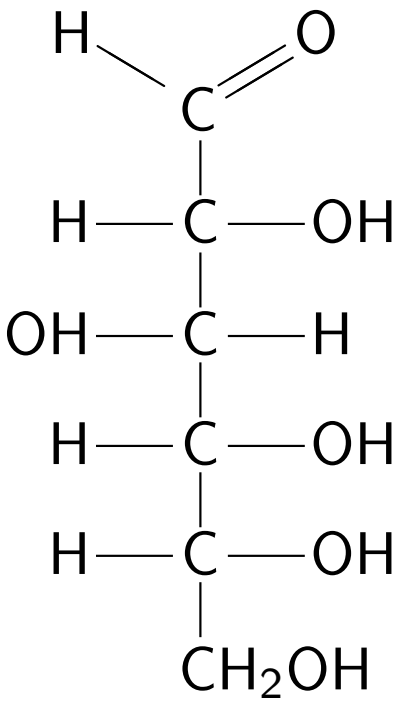

Figure: Glucose

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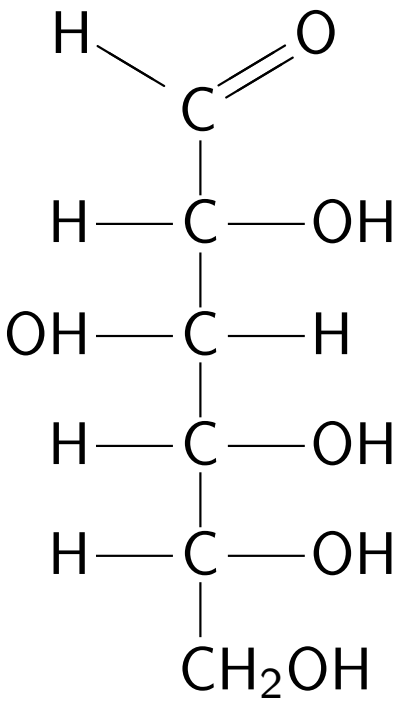

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- Glucose is a 6-carbon sugar.
- It contains two functional groups.

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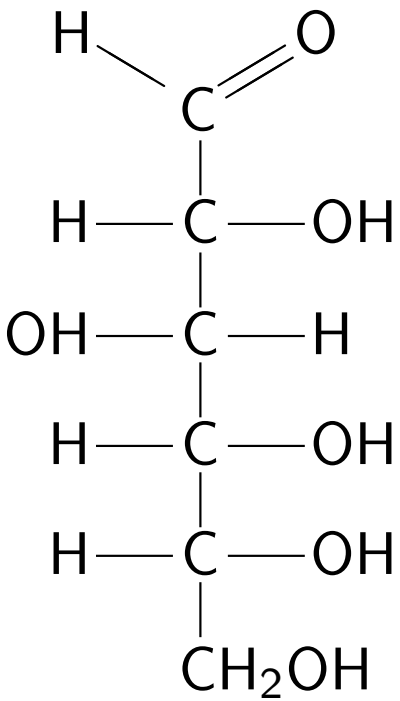

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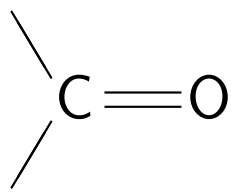
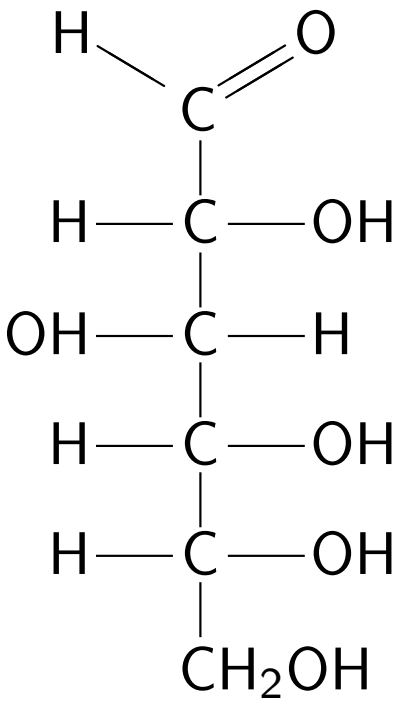


(a)
Carbonyl

Glucose Structure



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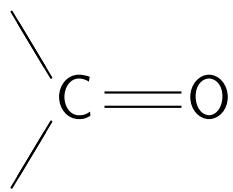

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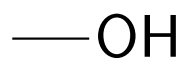

(b)
Hydroxyl

Glucose Structure

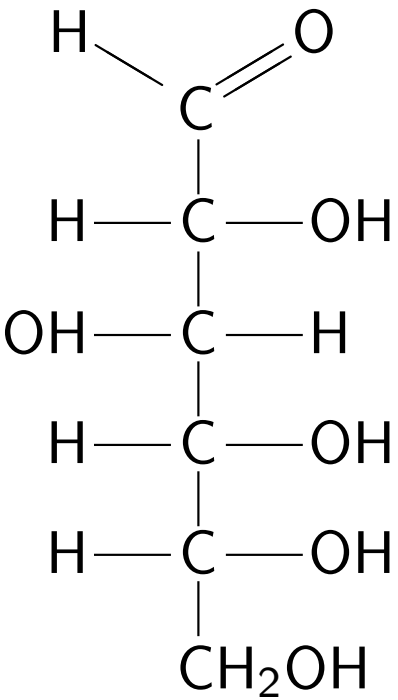

Figure: Glucose

- Glucose is a 6-carbon sugar.
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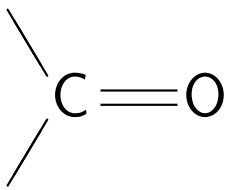
- Both groups can interact together.



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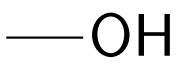

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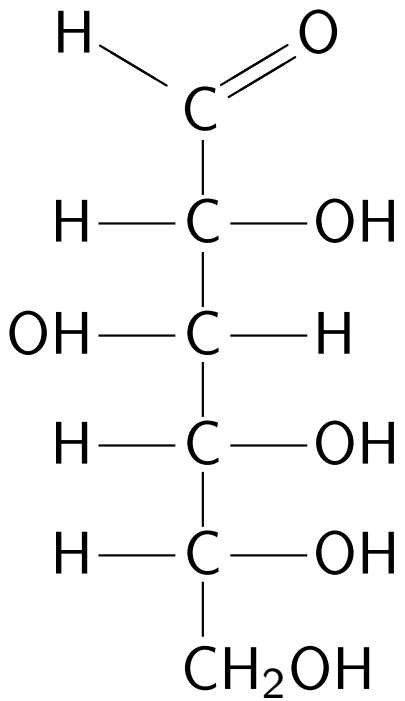
Glucose Cyclization

- The molecule folds on itself and forms a *pyranose* ring.



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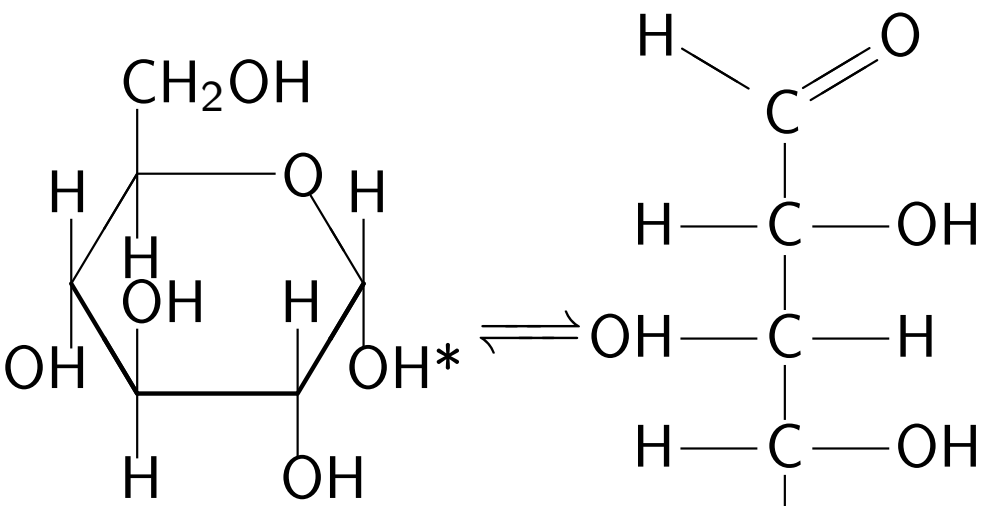
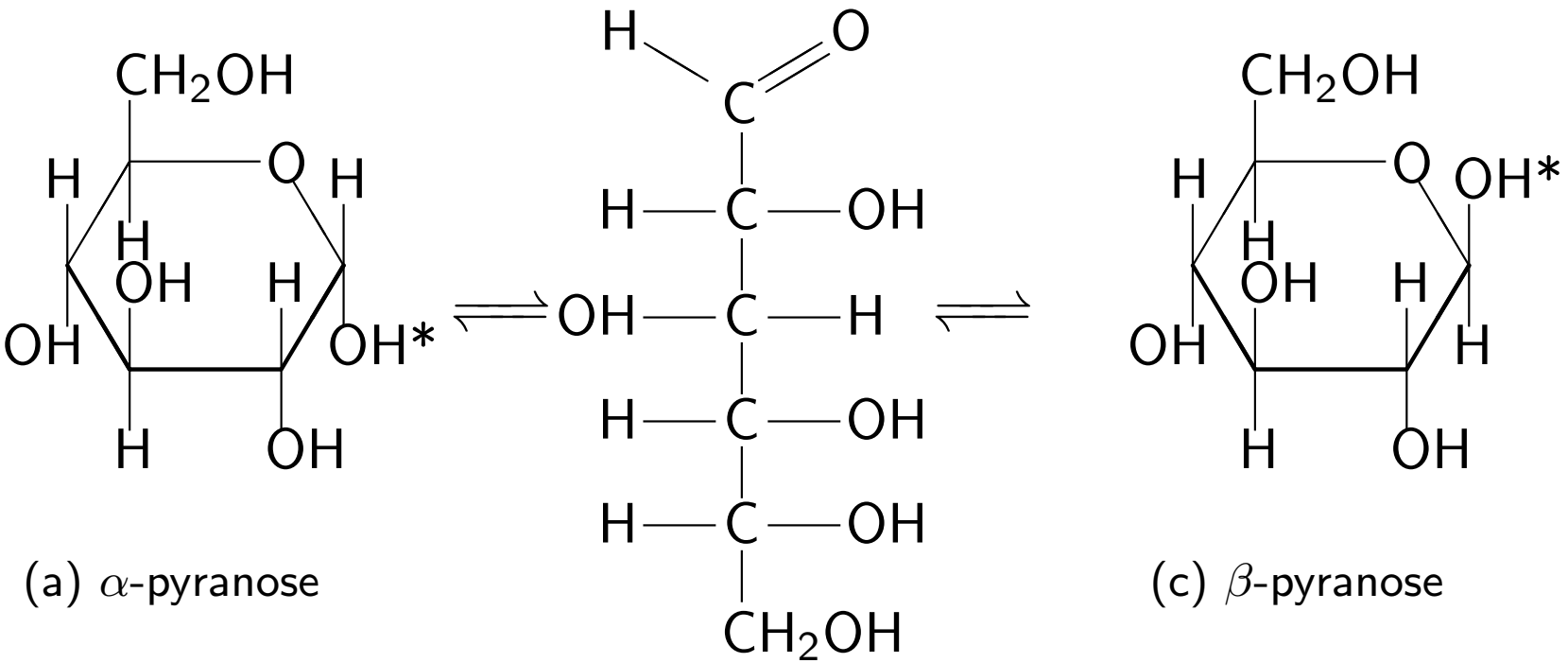


(a) α-pyranose

(b) Open chain

Glucose Cyclization

- The molecule folds on itself and forms a *pyranose* ring.
- In two different ways. Watch the star!



(a) α-pyranose

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(c) β-pyranose

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  - 36% α-pyranose
  - 64% β-pyranose

Amino Acid Structure

- An amino acid consists of:

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  - a central carbon atom C, bonded to:

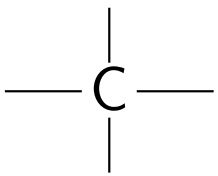
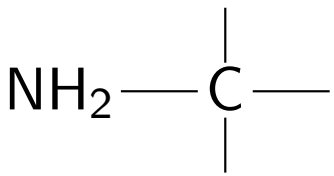


Figure: Amino acid

Amino Acid Structure



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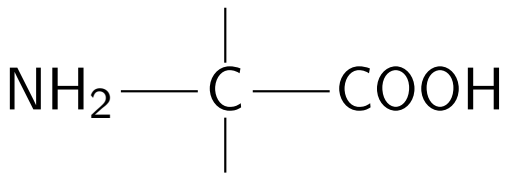

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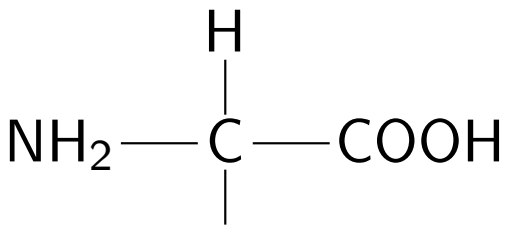

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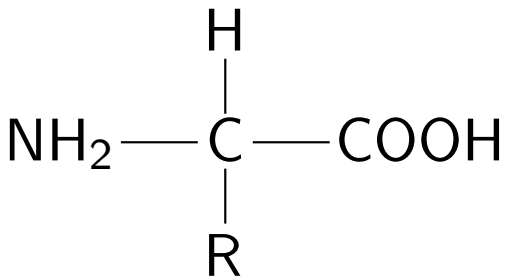

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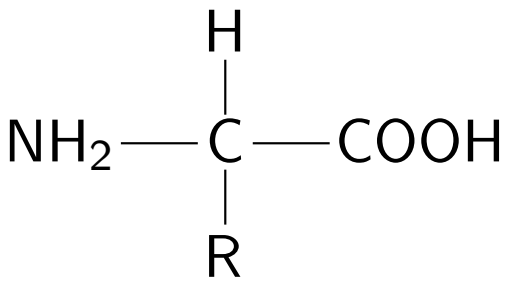

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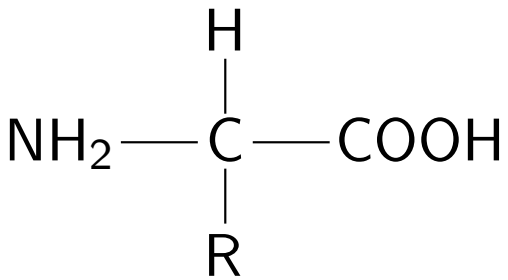

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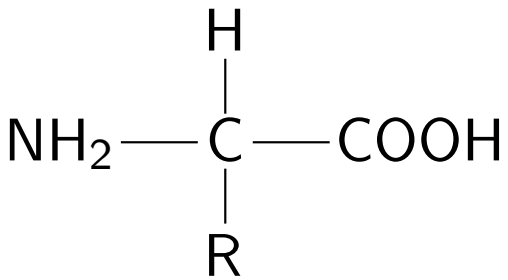

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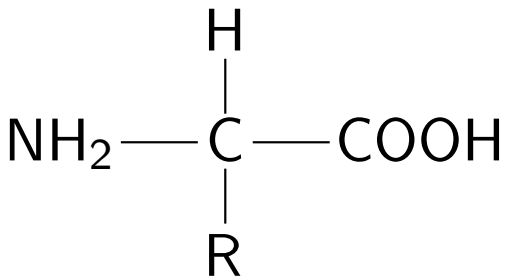

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Amino acid properties

Similar R $\Leftrightarrow$ similar properties. Different R $\Leftrightarrow$ different properties.

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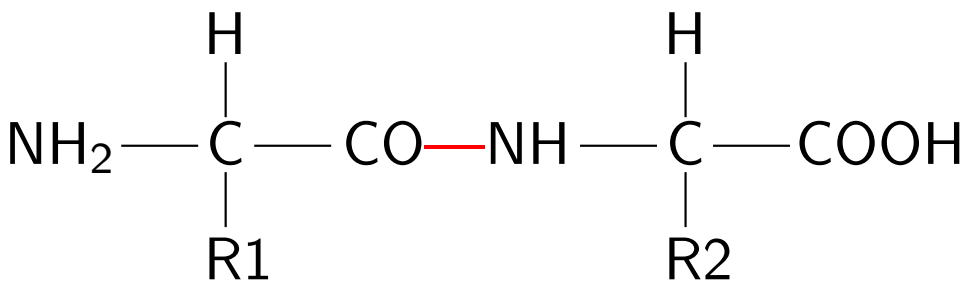

Figure: Linked residues

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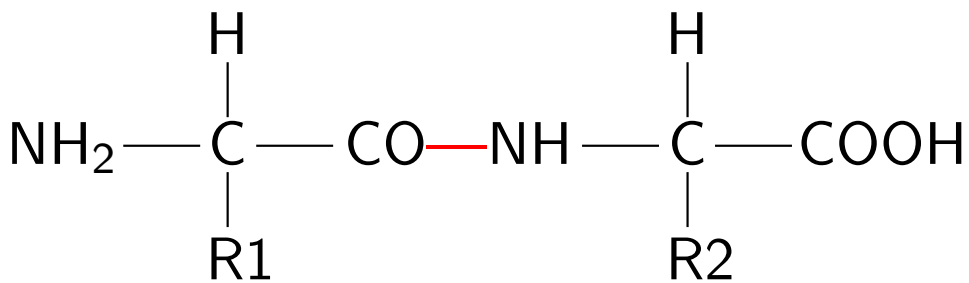

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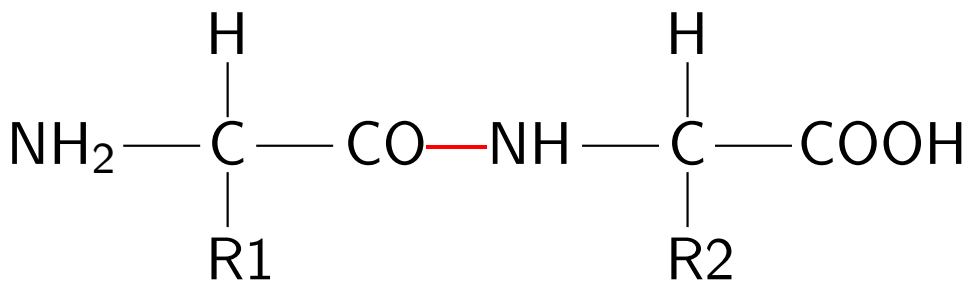

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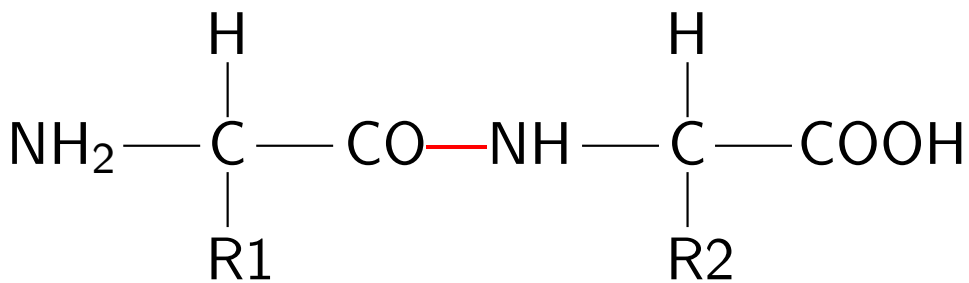

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Important Fact

Similar residues can be easily interchanged in a protein.

Atomic Interactions

Atoms interact together through:

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1. Chemical bonds

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   1. Van der Waals Forces

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   1. Van der Waals Forces
   2. Hydrophobic Interactions

Covalent Bonds

- Close and strong interaction.

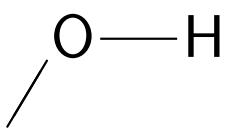
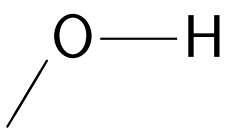


Figure: Covalent bond

Covalent Bonds



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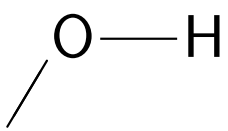

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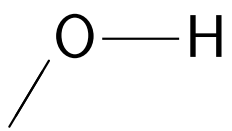

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- Close and strong interaction.
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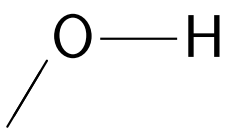
Definition

Electronegativity: A measure of an atom's attraction for electrons

Covalent Bonds



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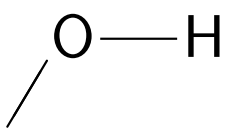

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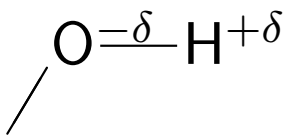

Figure: Covalent polar bond

- Close and strong interaction.
- Form a molecule.
- Atoms share electrons.
- Electronegativity.
  - Equal $\Rightarrow$ nonpolar
  - Different $\Rightarrow$ polar
- Partial charges.

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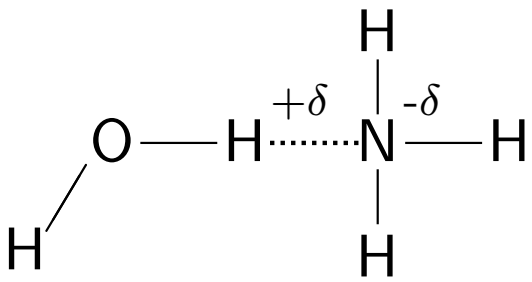
Hydrogen Bonds

- The most relevant in protein interaction.

Hydrogen Bonds



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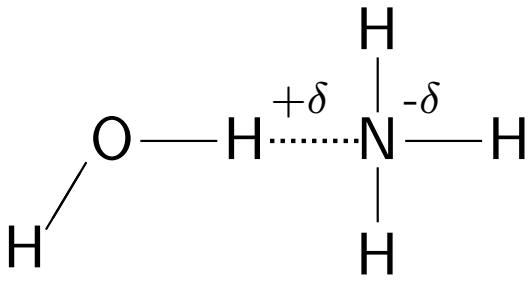

Figure: Hydrogen bond

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- Attraction between a positively charged H and a negatively charged atoms.
- Glucose attaches to the protein using hydrogen bonds.

Forces and Interactions

1. Van der Waals Forces

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Characteristics

Weak electrostatic attraction and repulsion forces.

Forces and Interactions

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Definition

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Characteristics

$\Rightarrow$ attracted by hydrophobic residues

Pattern Recognition

Pattern recognition

Definition

Pattern recognition: The computer learns how to correctly classify an object.

Pattern Recognition

Pattern recognition includes:

1. Classifier

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Classifier phases

- *Training phase*: Learns how to partition the feature space.

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Pattern Recognition

Pattern recognition includes:

1. Classifier
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   - Support Vector Machines (SVM)
2. Feature selection

Classifier phases

- *Training phase*: Learns how to partition the feature space.
- *Testing phase*: Predicts the class of an unknown data.

Pattern Recognition

Pattern recognition includes:

1. Classifier
   - k-Nearest-Neighbor (kNN)
   - Support Vector Machines (SVM)
2. Feature selection
   - Random Forest (RF)

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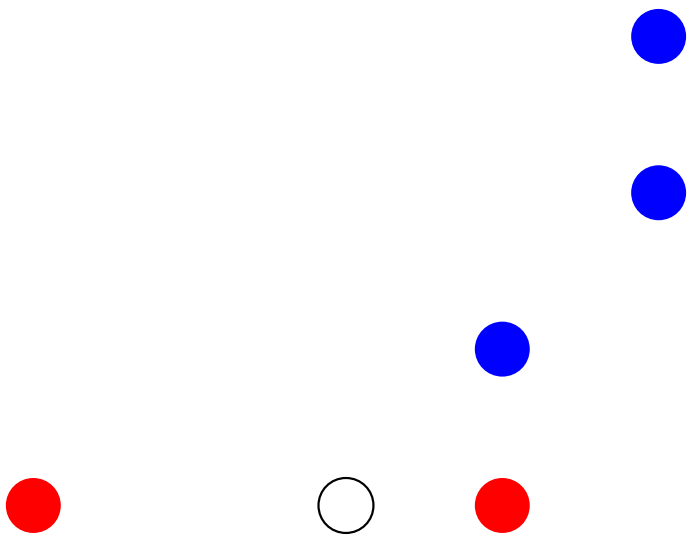
Simple kNN technique



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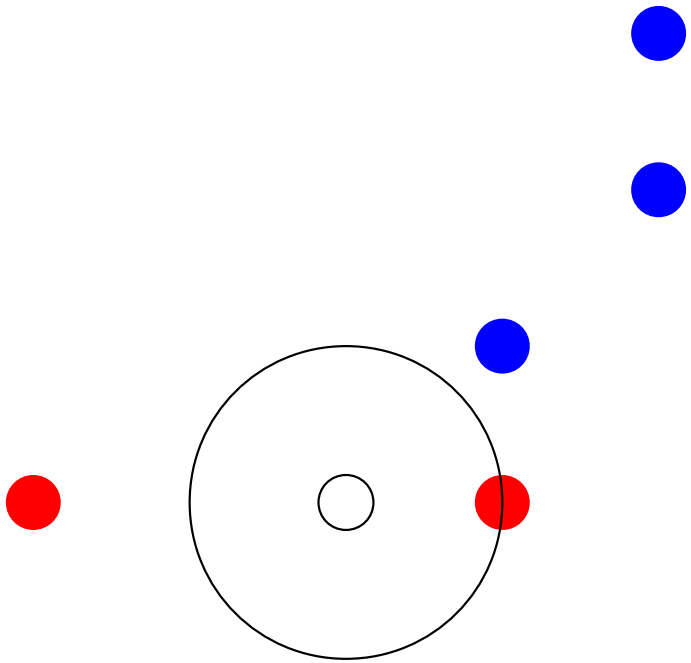
Simple kNN technique, $k = 1$



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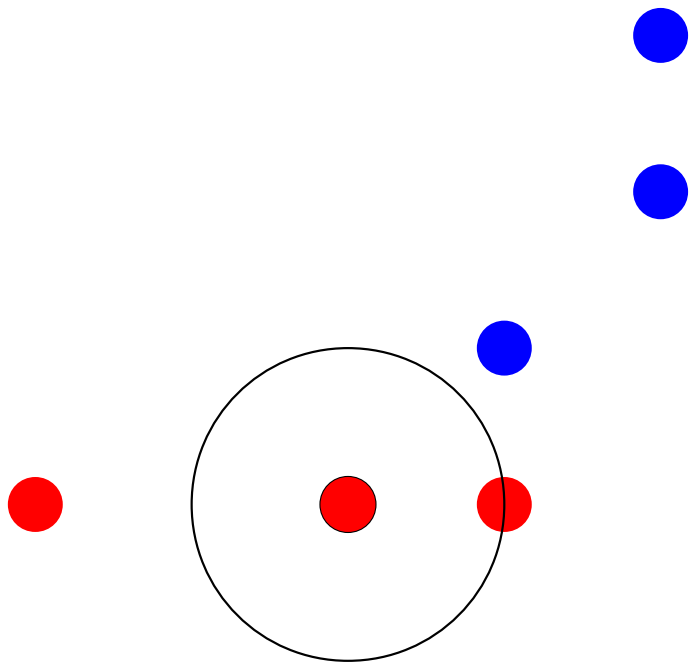

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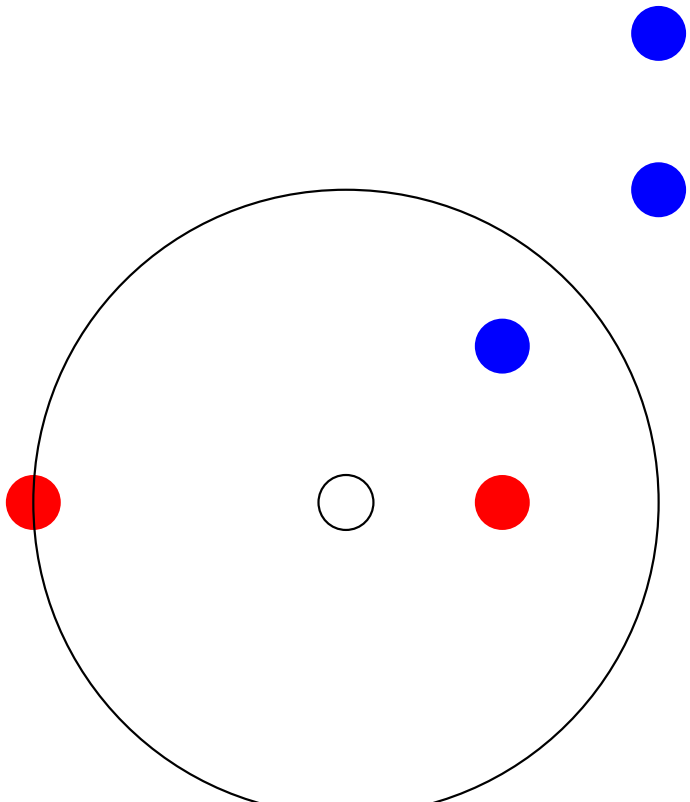
Simple kNN technique, $k = 3$



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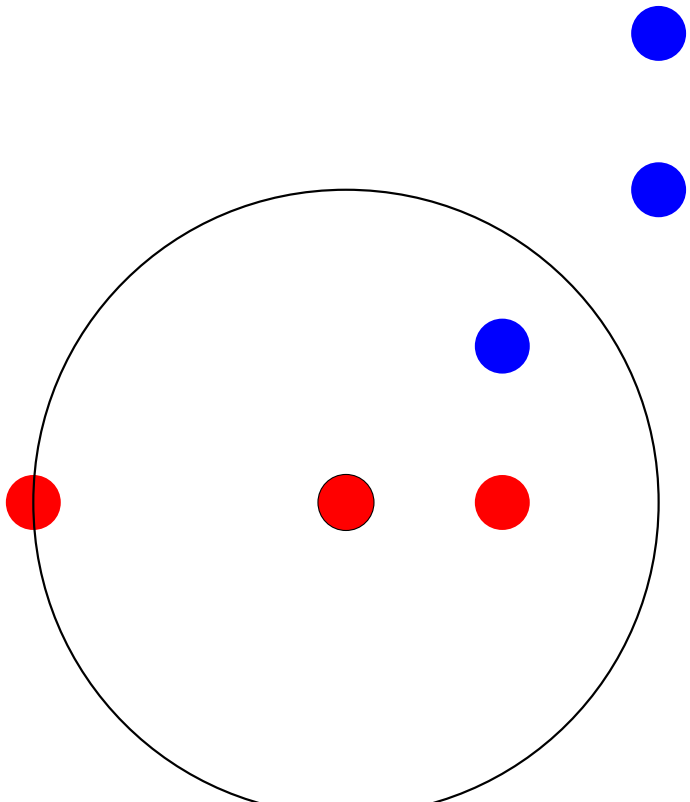

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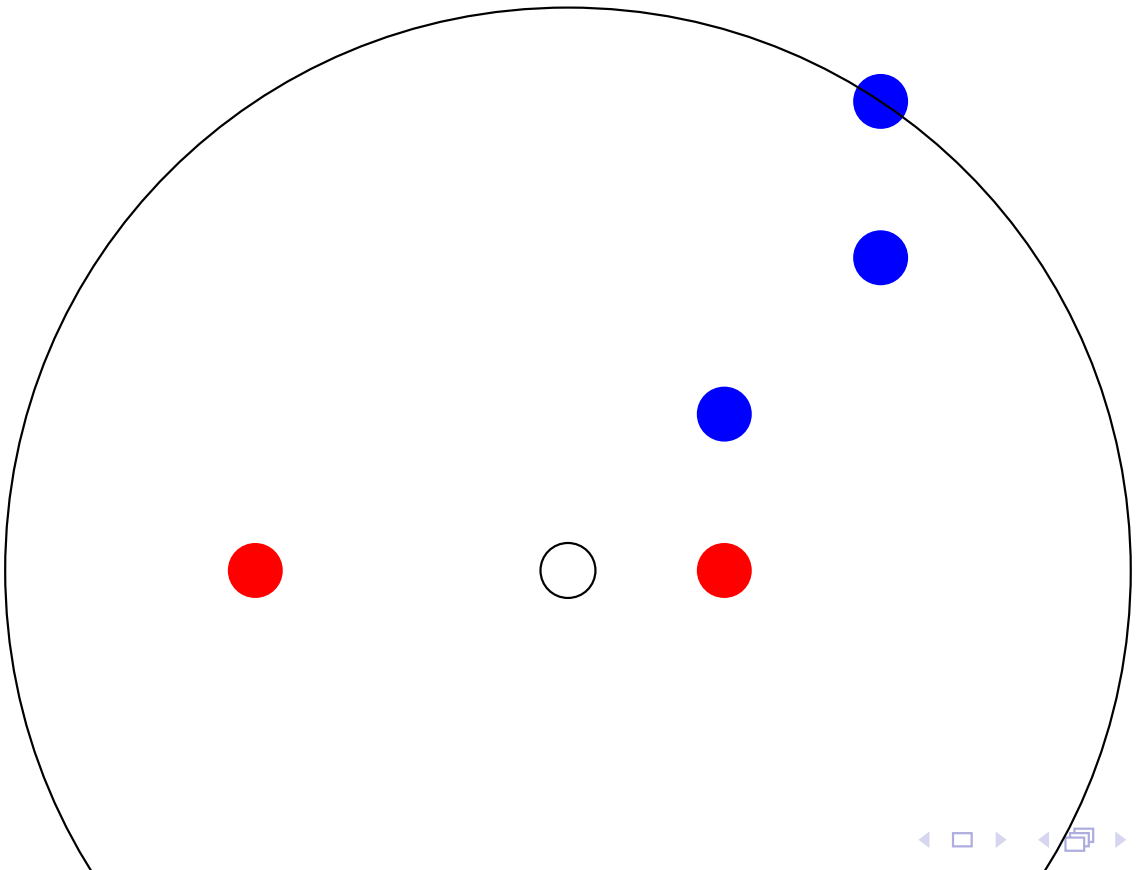
Simple kNN technique, $k = 5$



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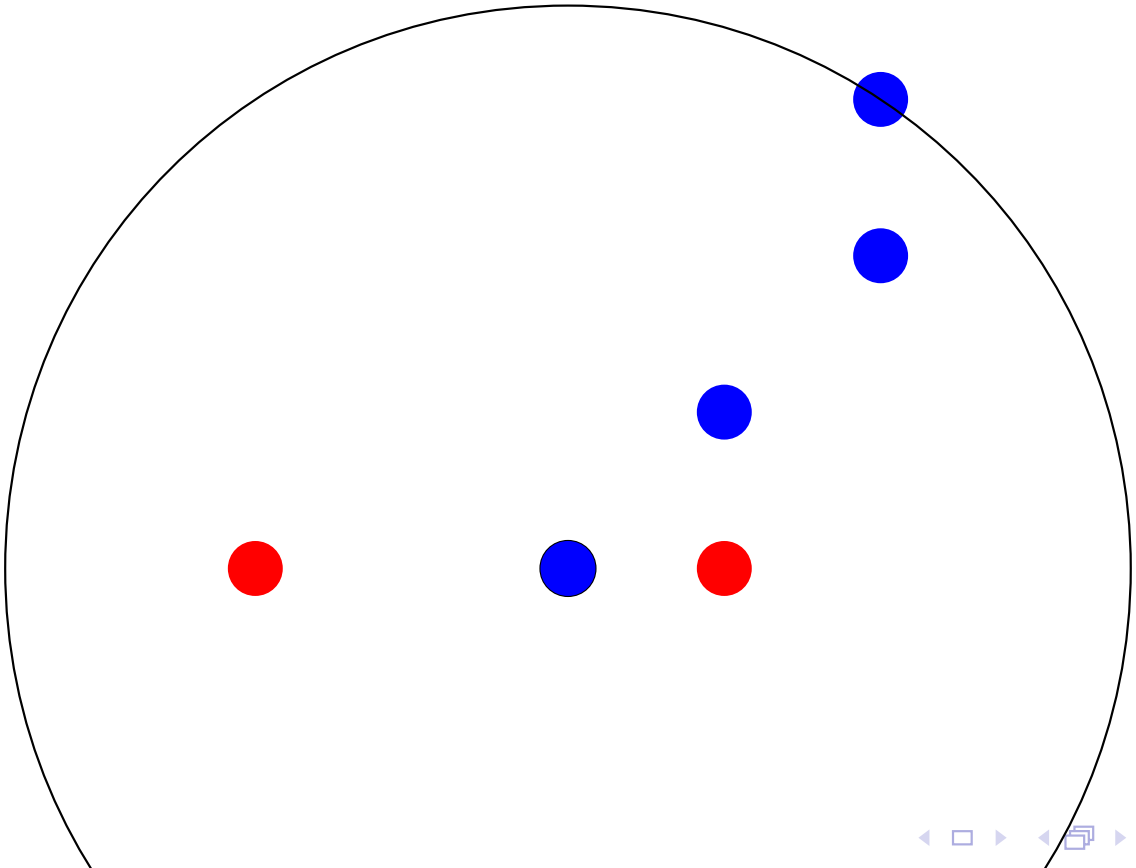

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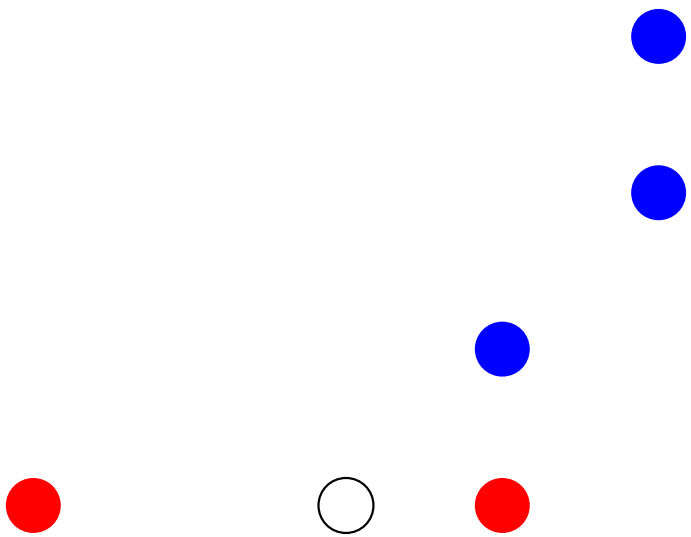

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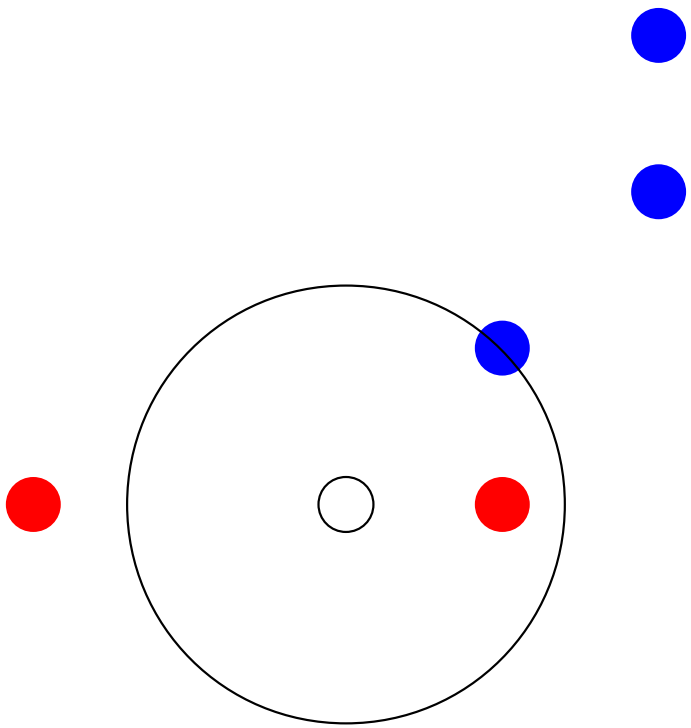

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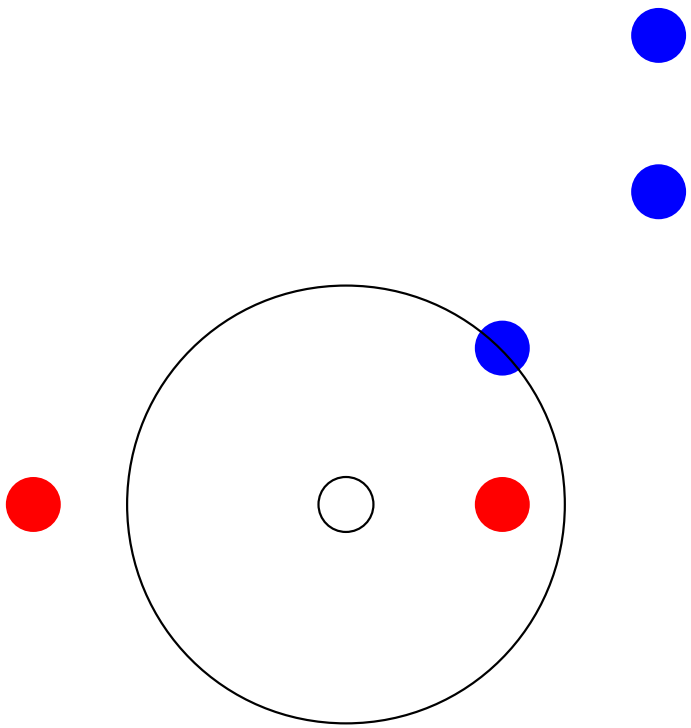
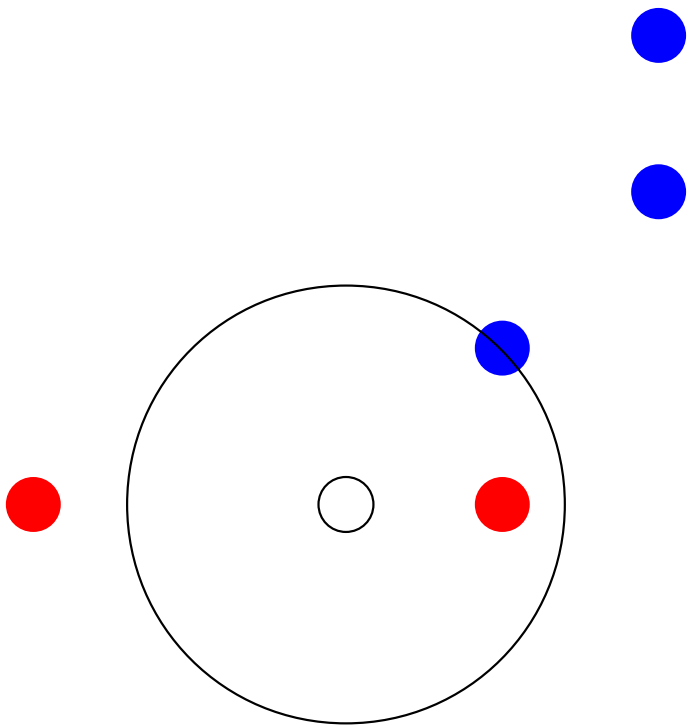


k-Nearest-Neighbors (kNN)

Solution: Weighted kNN



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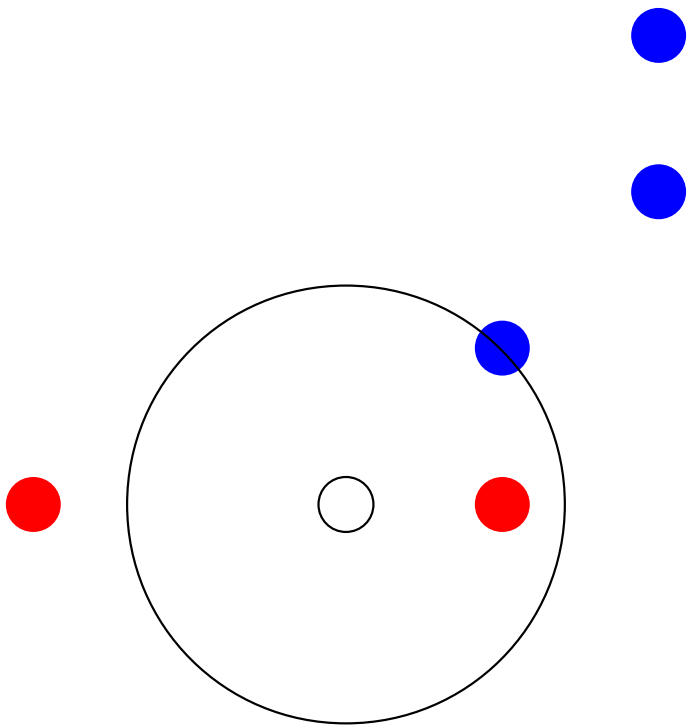

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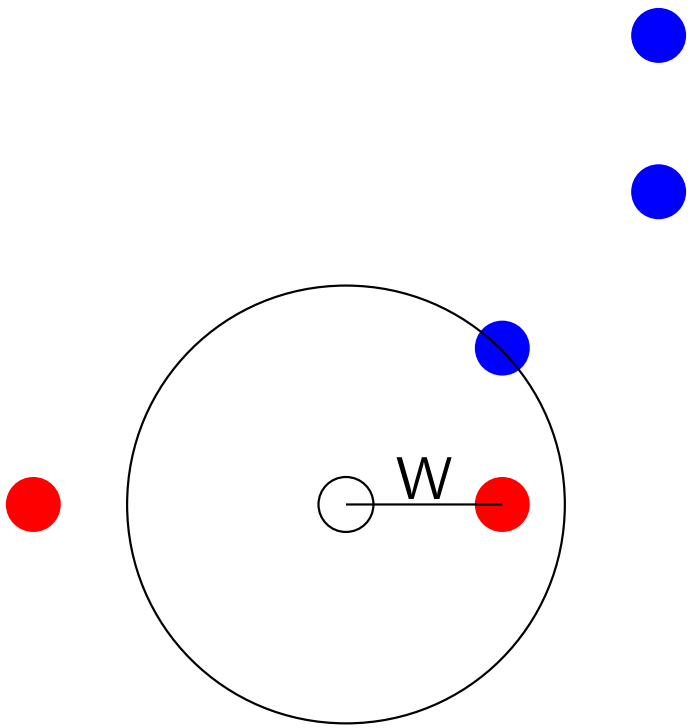

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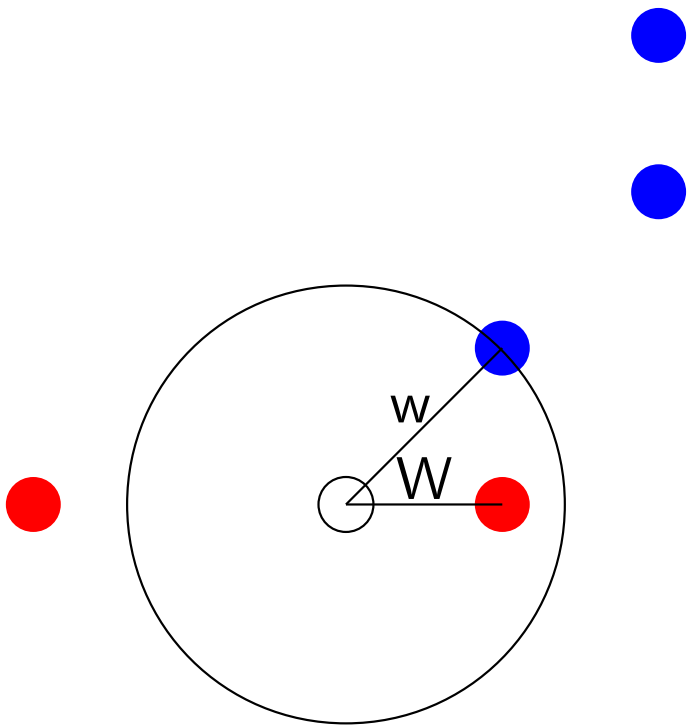

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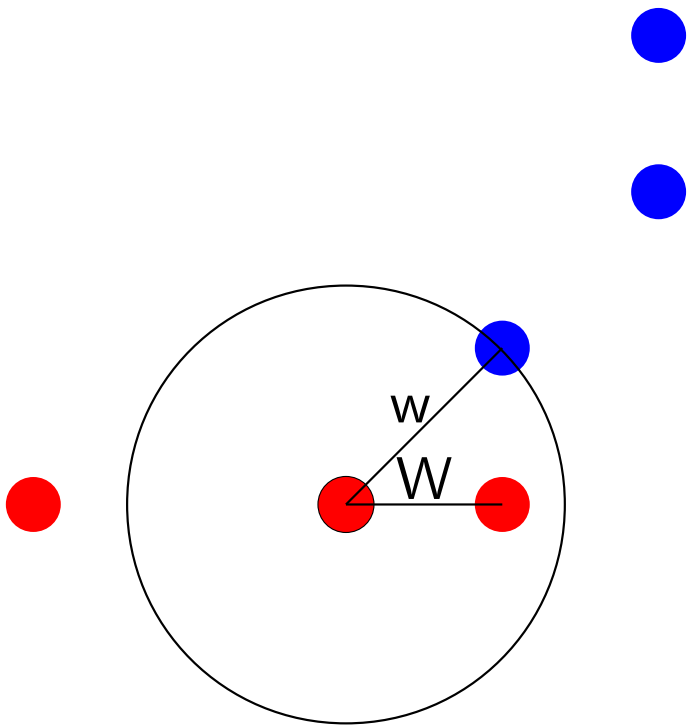

k-Nearest-Neighbors (kNN)

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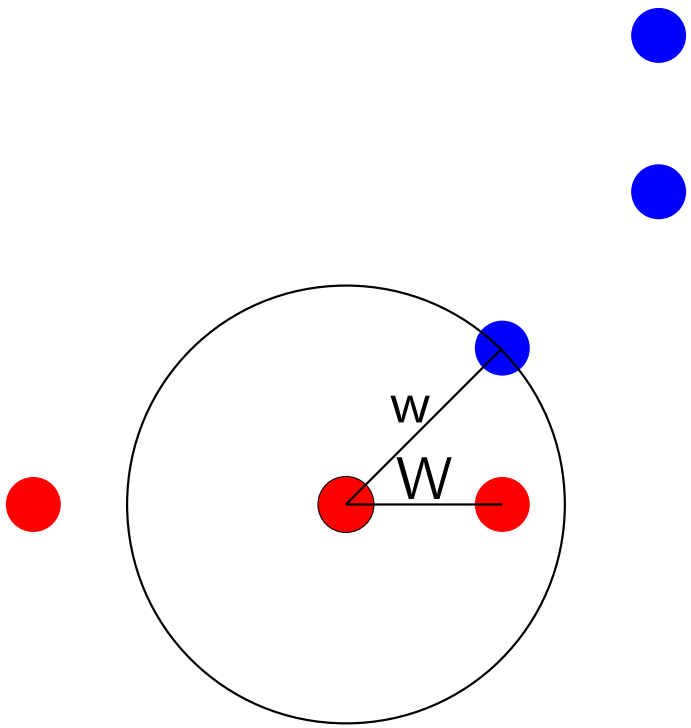
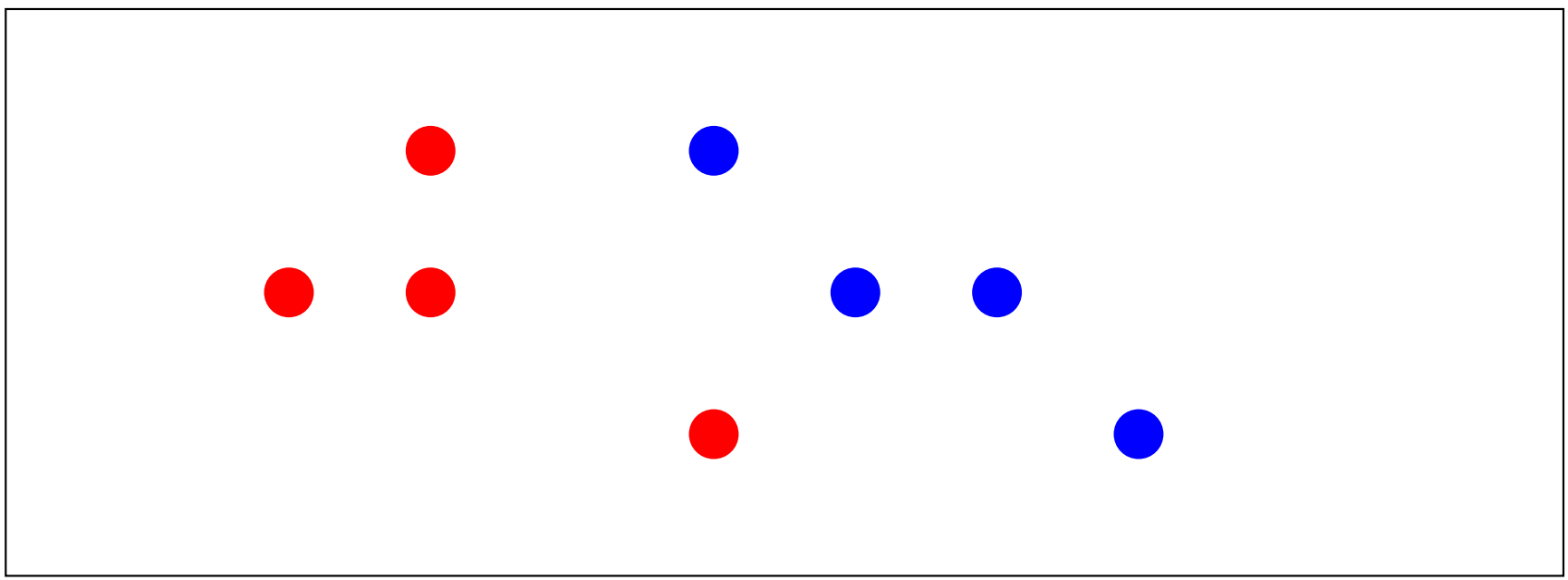


Support Vector Machines (SVM)

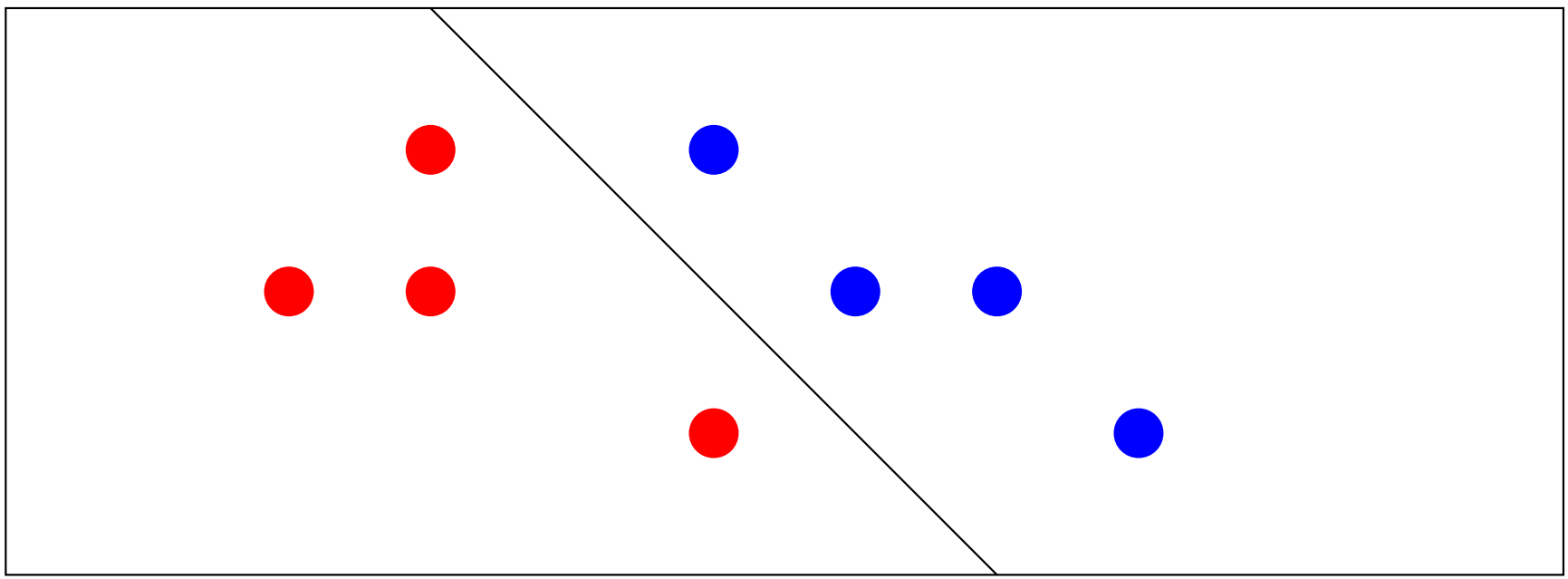
SVM technique



Support Vector Machines (SVM)

SVM technique

- Construct the optimal separating hyperplane.



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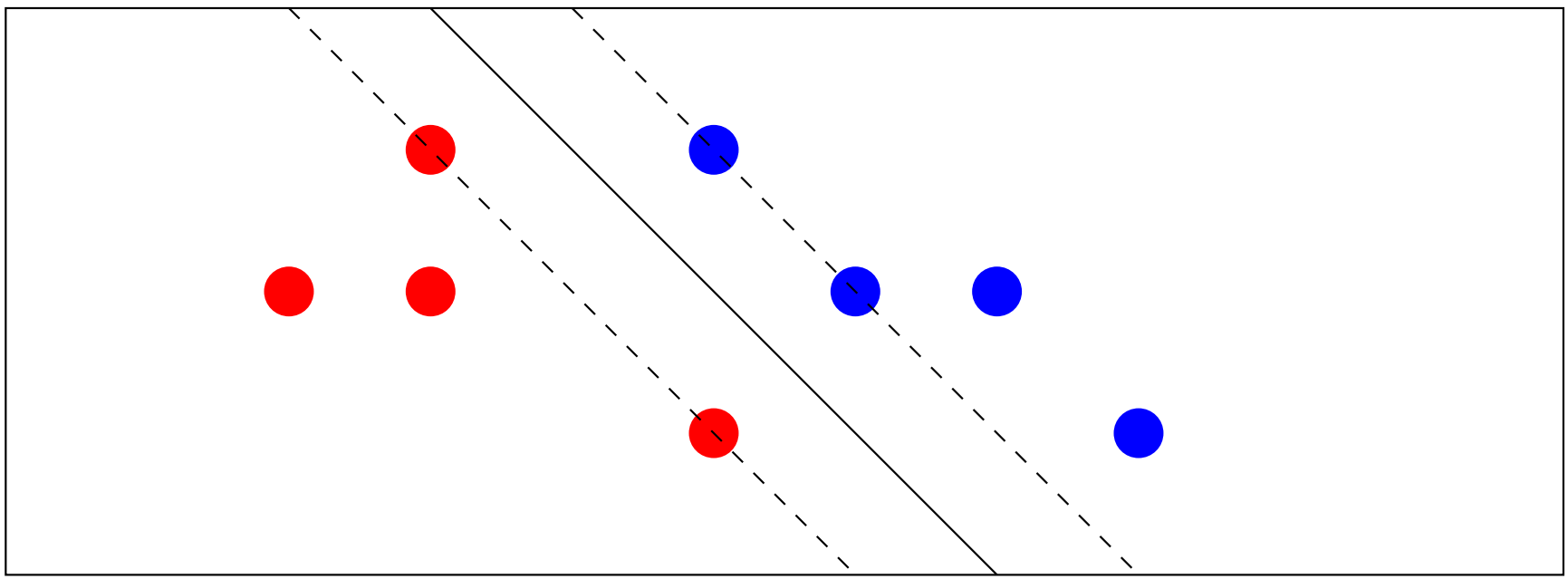
SVM technique

- Construct the optimal separating hyperplane.
- Maximize the margins.

Definition

Margin: Minimal distance away from the hyperplane.



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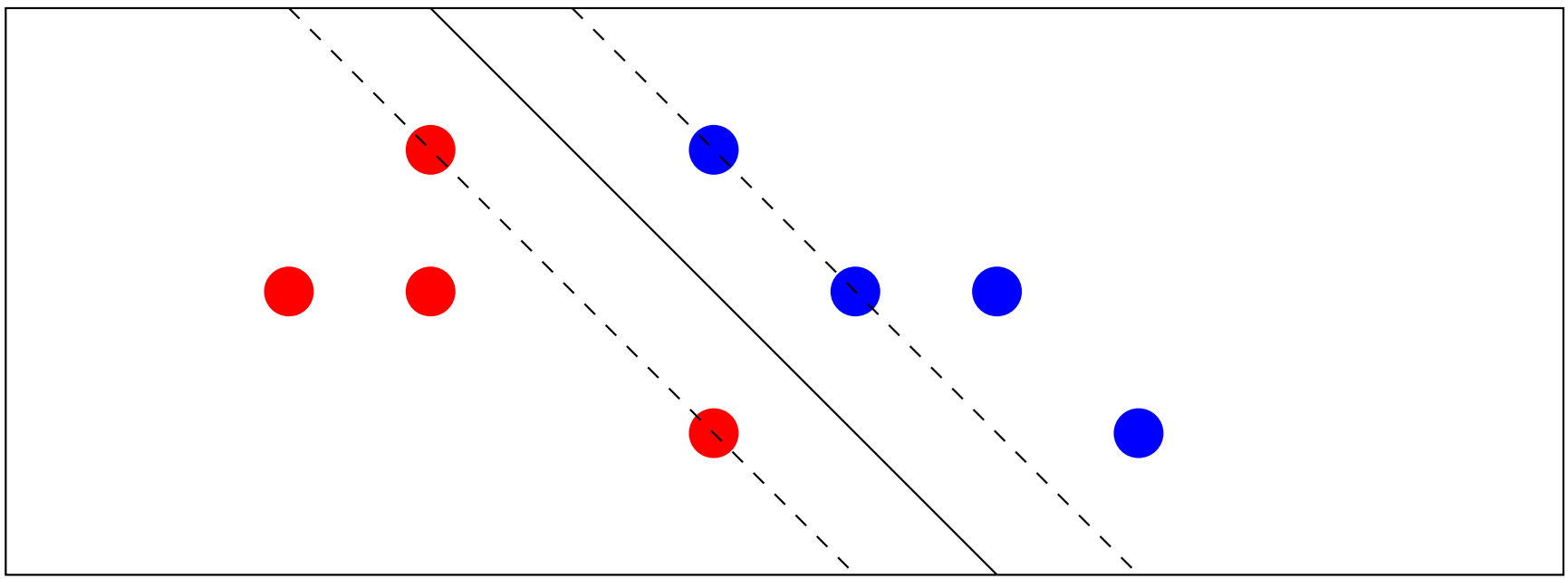

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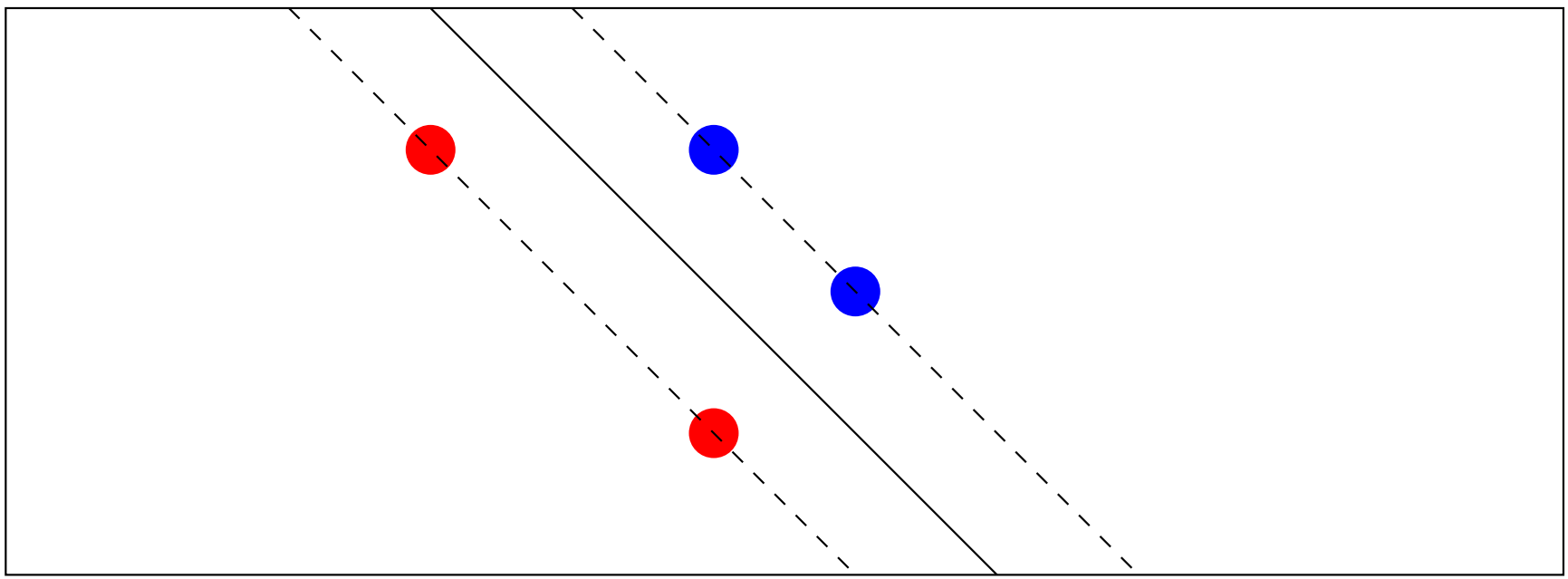

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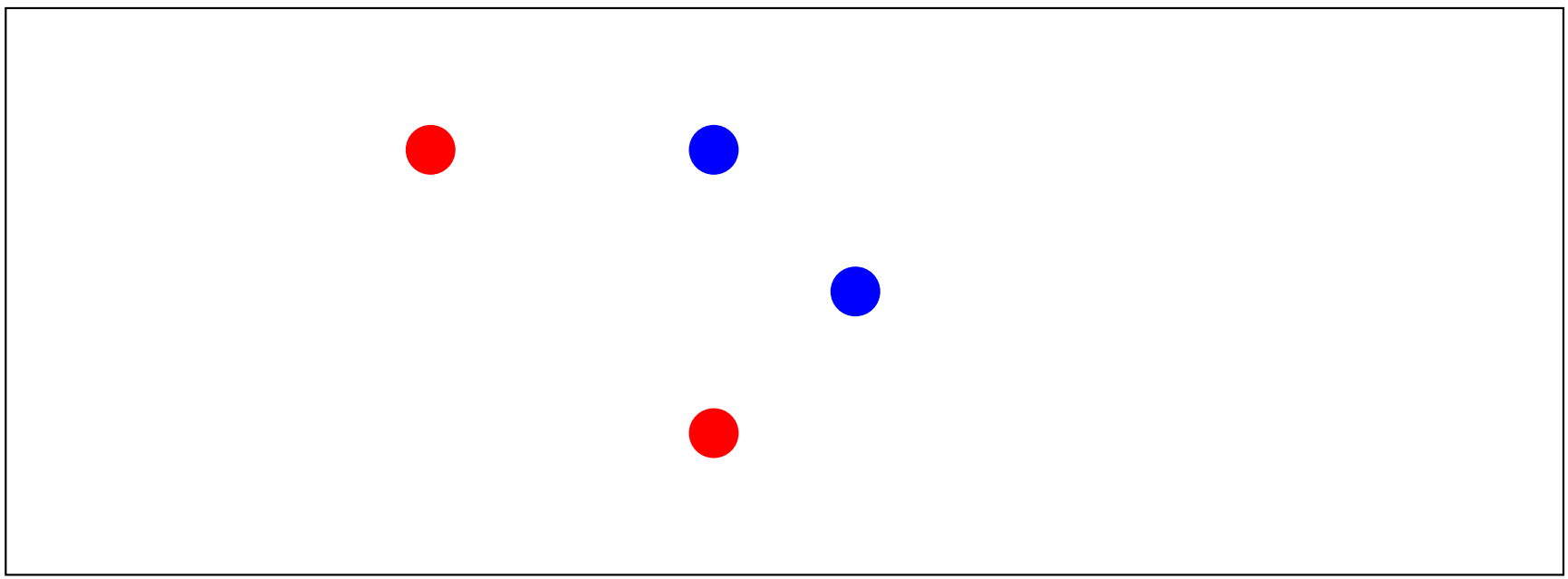
- Called Support Vectors (SV).



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Kernel function: A function that maps input data to a higher dimensional feature space and computes their scalar product.

$$K(\overrightarrow{a}, \overrightarrow{b}) = \phi(\overrightarrow{a})^t \cdot \phi(\overrightarrow{b}) \qquad \text{for} \quad \overrightarrow{a}, \overrightarrow{b} \in X$$

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Generalization: Ability to correctly classify new data.

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- Small number of support vectors $\Leftrightarrow$ good generalization.

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Problem Representation

A good classifier must be trained on:

1. Representative data

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2. How the features are represented

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- Repository of 3-D structures of biological molecules

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Perl:

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- Parse a PDB file, represent it as an object and query its fields.

Data Mining

In a PDB file, glucose can be:

- Covalently bonded to the protein (glycoprotein)
- Floating around in the medium
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Solution Approach

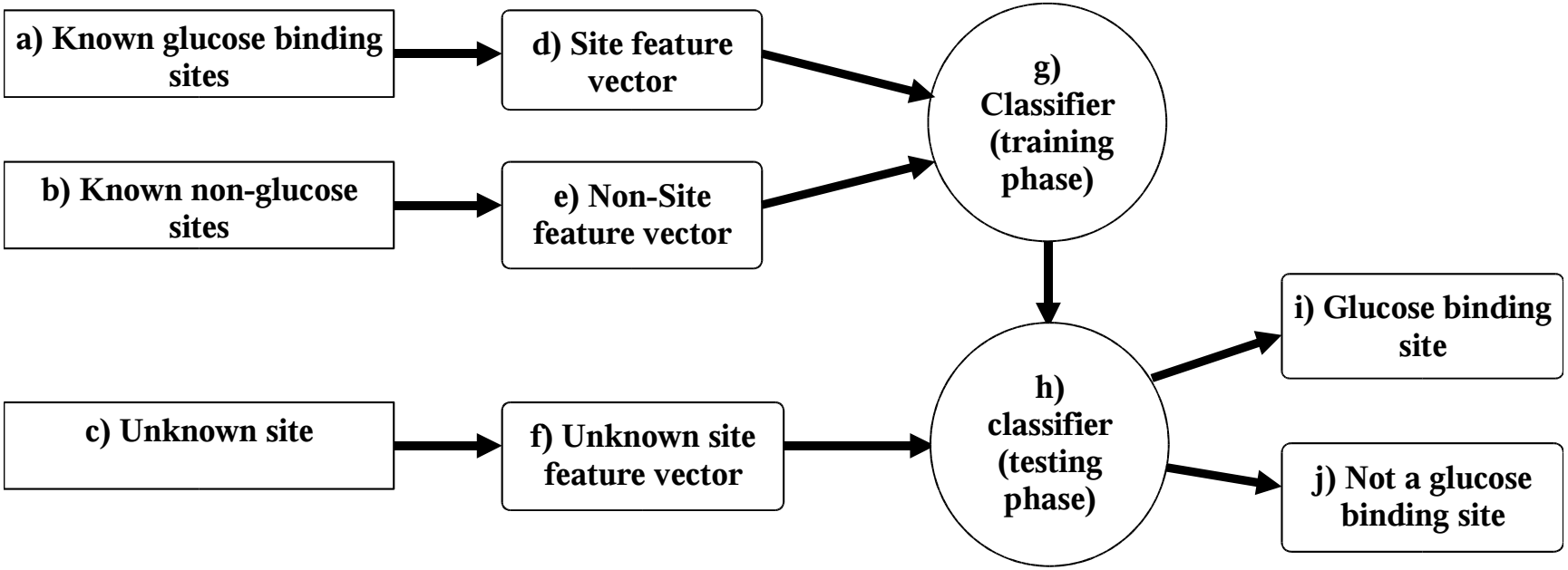
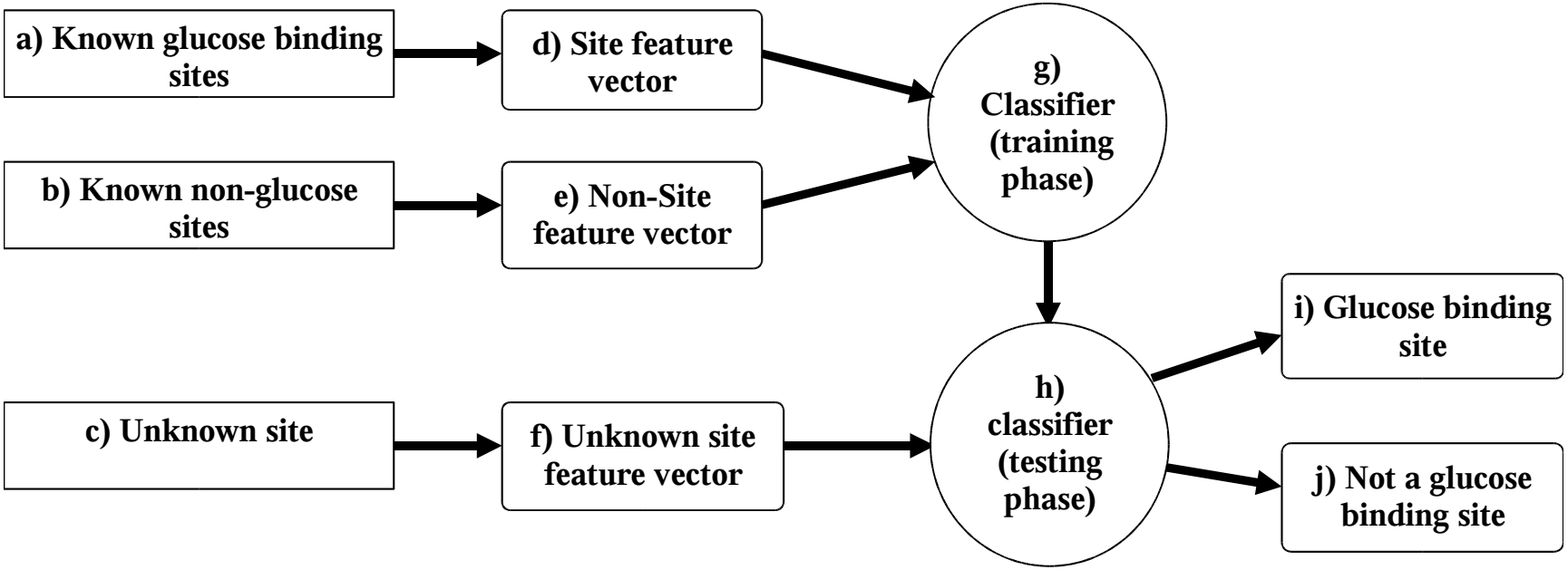


Figure: The classifier algorithm outline.

Solution Approach

Non-glucose sites

1. Binding sites that do not bind glucose



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Solution Approach

Non-glucose sites

1. Binding sites that do not bind glucose
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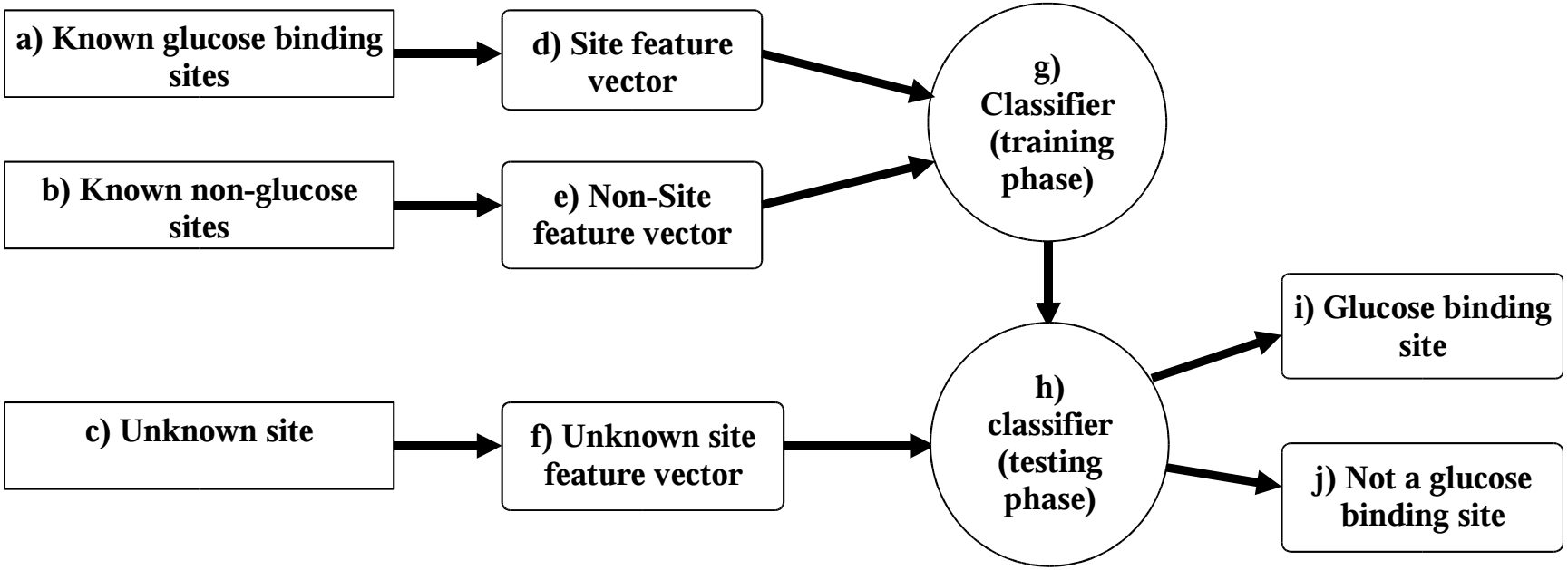

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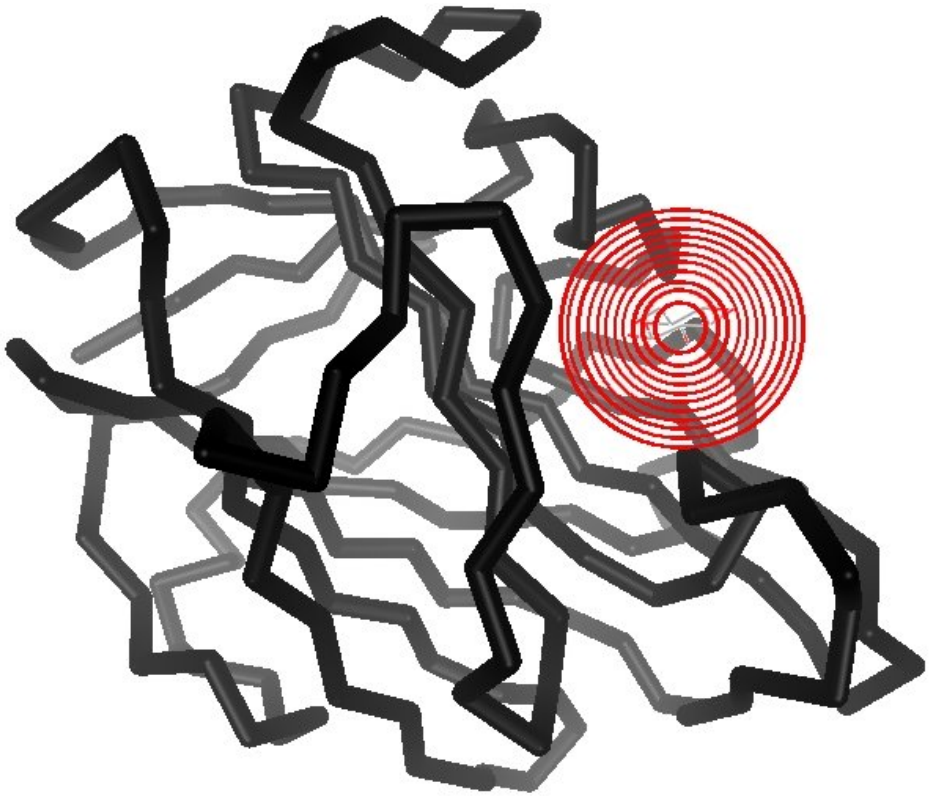

Figure: Glucose bound to a hydrolase, PDB entry 1I8A.

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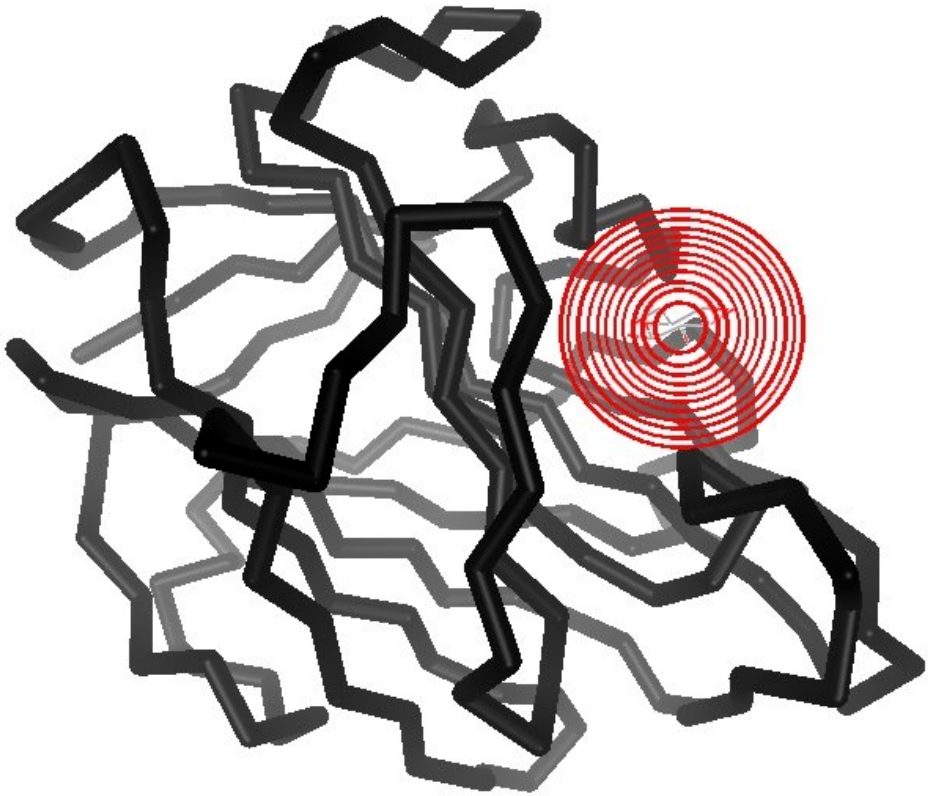

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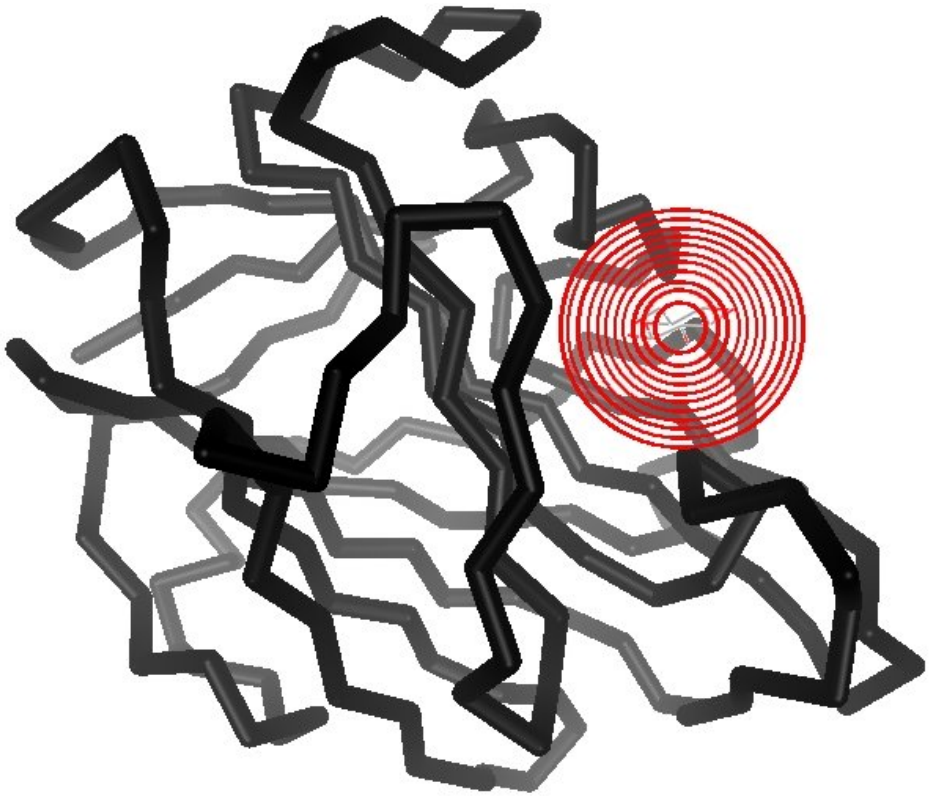

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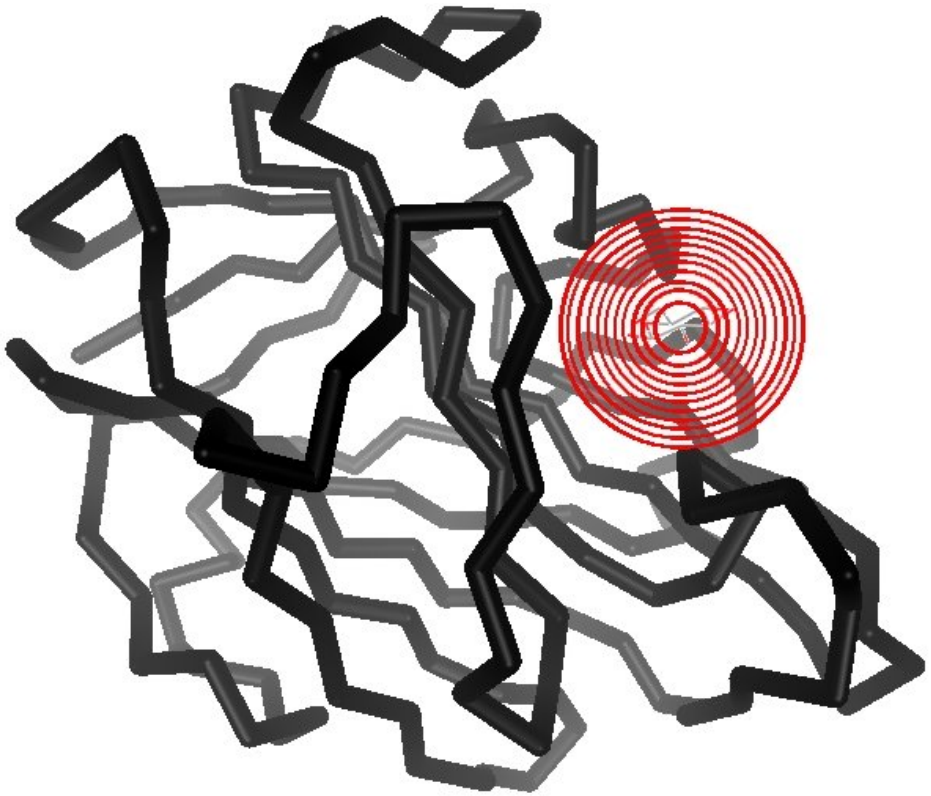

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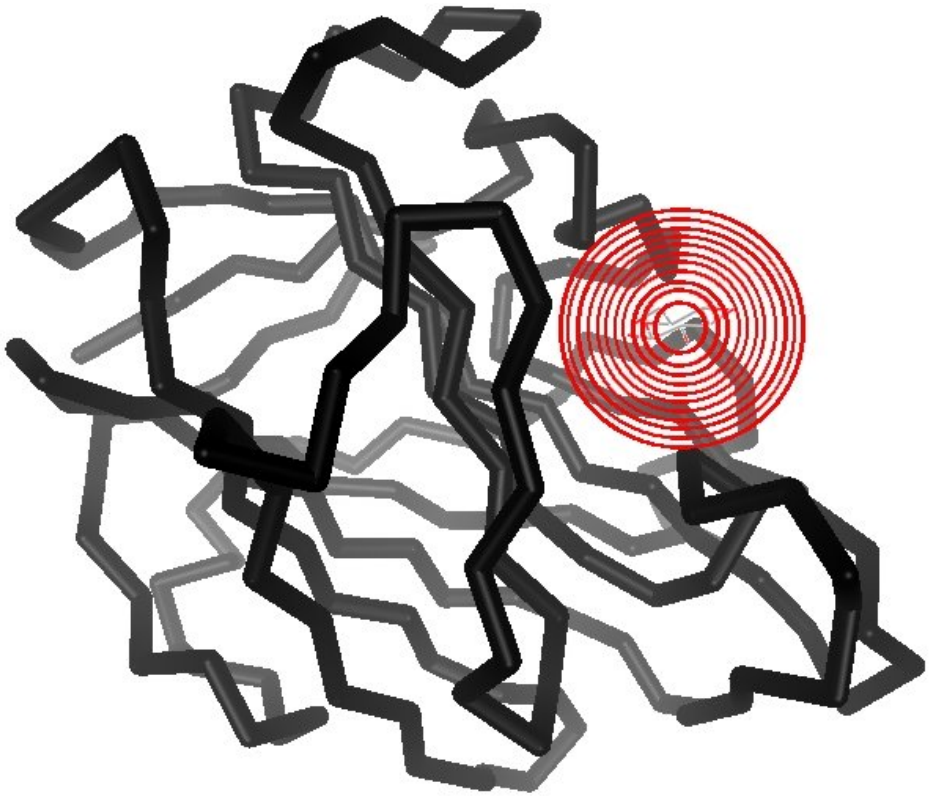

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- Sphere of 10 Å centered at the ligand
- Pyranose ring centroid
- Divided into 8 concentric layers
- Gather features for each layer

Atomic Features

1. Charge

Atomic Features

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2. Hydrogen Bond

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2. Hydrogen Bond
3. Hydrophobicity

Atomic Features

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   1. Hydrogen-bonding
   2. Non hydrogen-bonding
3. Hydrophobicity
   1. Hydrophobic
   2. Neutral

Atomic Features

1. Charge
   1. Positive
   2. Neutral
   3. Negative
2. Hydrogen Bond
   1. Hydrogen-bonding
   2. Non hydrogen-bonding
3. Hydrophobicity
   1. Hydrophobic
   2. Neutral
   3. Hydrophilic

Residue Schemes

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified1

- Planar polar residues
- Form an extensive hydrogen-bond network with glucose

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified1

- Planar polar residues
- Form an extensive hydrogen-bond network with glucose
- Remaining residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified2

- Planar polar residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified2

- Planar polar residues
- Aromatic residues
- Ring containing residues
- Stack against pyranose ring thru hydrophobic and van der Waals forces.

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified2

- Planar polar residues
- Aromatic residues
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- Stack against pyranose ring thru hydrophobic and van der Waals forces.
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Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified3

- Planar polar residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified3

- Planar polar residues
- Aromatic residues
- Histidine is reported to interact with glucose in a similar way to aromatic residues.

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Simplified3

- Planar polar residues
- Aromatic residues
- Histidine is reported to interact with glucose in a similar way to aromatic residues.
- Remaining residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed1

- Aromatic residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed1

- Aromatic residues
- Neutral residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed1

- Aromatic residues
- Neutral residues
- Carboxylate residues (negatively charged)

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed1

- Aromatic residues
- Neutral residues
- Carboxylate residues (negatively charged)
- Positively charged residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed1

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- Neutral residues
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Residue Schemes

Detailed1

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- Positively charged residues
- Aliphatic residues
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Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Residue Schemes

Detailed2

- Aromatic residues
- Neutral residues
- Carboxylate residues (negatively charged)
- Positively charged residues
- Aliphatic residues

Asparagine	Glutamine	Arginine	Glutamate
Aspartate	Tyrosine	Tryptophan	Phenylalanine
Histidine	Serine	Threonine	Glycine
Proline	Cysteine	Lysine	Alanine
Valine	Leucine	Isoleucine	Methionine

Experimental Results

What determines a binding-site:

Experimental Results

What determines a binding-site:

1. Amino acids biochemical properties

Experimental Results

What determines a binding-site:

1. Amino acids biochemical properties
2. Amino acids spatial arrangement

Experimental Results

What determines a binding-site:

1. Amino acids biochemical properties
2. Amino acids spatial arrangement

The approach consists of:

Experimental Results

What determines a binding-site:

1. Amino acids biochemical properties
2. Amino acids spatial arrangement

The approach consists of:

1. Learning phase

Experimental Results

What determines a binding-site:

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2. Amino acids spatial arrangement

The approach consists of:

1. Learning phase
2. Feature selection

Experimental Results

What determines a binding-site:

1. Amino acids biochemical properties
2. Amino acids spatial arrangement

The approach consists of:

1. Learning phase
2. Feature selection
3. Testing phase

Atomic Combinations Results

Table: Atomic properties classification error rates.

Properties	kNN	SVM	SV
Charge	14.55%	14.55%	78.18%
H-Bond	21.82%	16.36%	92.73%
Hydrophobicity	21.82%	20.00%	92.73%
Charge + H-Bond	14.55%	14.55%	89.09%
Charge + Hydro	12.73%	14.55%	47.27%
H-Bond + Hydro	21.82%	18.18%	100%
Charge + H-Bond + Hydro	16.36%	16.36%	60.00%

Atomic Combinations Results

- Charge outperforms hydrophobicity and hydrogen bond

Table: Atomic properties classification error rates.

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Charge + H-Bond	14.55%	14.55%	89.09%
Charge + Hydro	12.73%	14.55%	47.27%
H-Bond + Hydro	21.82%	18.18%	100%
Charge + H-Bond + Hydro	16.36%	16.36%	60.00%

Atomic Combinations Results

- Charge outperforms hydrophobicity and hydrogen bond
- Charge, linked with another property, yields similar or slightly better results

Table: Atomic properties classification error rates.

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Charge	14.55%	14.55%	78.18%
H-Bond	21.82%	16.36%	92.73%
Hydrophobicity	21.82%	20.00%	92.73%
Charge + H-Bond	14.55%	14.55%	89.09%
Charge + Hydro	12.73%	14.55%	47.27%
H-Bond + Hydro	21.82%	18.18%	100%
Charge + H-Bond + Hydro	16.36%	16.36%	60.00%

Atomic Combinations Results

- "Charge + Hydro" is the best atomic combination

Table: Atomic properties classification error rates.

Properties	*k*NN	SVM	SV
Charge	14.55%	14.55%	78.18%
H-Bond	21.82%	16.36%	92.73%
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Charge + H-Bond	14.55%	14.55%	89.09%
Charge + Hydro	12.73%	14.55%	47.27%
H-Bond + Hydro	21.82%	18.18%	100%
Charge + H-Bond + Hydro	16.36%	16.36%	60.00%

Atomic Combinations Results

- kNN and SVM give similar results

Table: Atomic properties classification error rates.

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H-Bond	21.82%	16.36%	92.73%
Hydrophobicity	21.82%	20.00%	92.73%
Charge + H-Bond	14.55%	14.55%	89.09%
Charge + Hydro	12.73%	14.55%	47.27%
H-Bond + Hydro	21.82%	18.18%	100%
Charge + H-Bond + Hydro	16.36%	16.36%	60.00%

Hydrogen Bond Property

- Hydrogen bond is a primary factor in glucose binding

Hydrogen Bond Property

- Hydrogen bond is a primary factor in glucose binding
- Hydrogen bond preforms poorly

Hydrogen Bond Property

- Hydrogen bond is a primary factor in glucose binding
- Hydrogen bond preforms poorly

Hypothesis

1. Negative set composed mainly of non-glucose binding sites

Hydrogen Bond Property

- Hydrogen bond is a primary factor in glucose binding
- Hydrogen bond preforms poorly

Hypothesis

1. Negative set composed mainly of non-glucose binding sites
2. Most binding sites rely on hydrogen bonds

Hydrogen Bond Property

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- Hydrogen bond preforms poorly

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1. Negative set composed mainly of non-glucose binding sites
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3. Therefore hydrogen bond is a bad discriminating factor

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To validate this hypothesis:

Hydrogen Bond Property

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To validate this hypothesis:

1. Negative set composed of random protein surface regions

Hydrogen Bond Property

Hypothesis

1. Negative set composed mainly of non-glucose binding sites
2. Most binding sites rely on hydrogen bonds
3. Therefore hydrogen bond is a bad discriminating factor

To validate this hypothesis:

1. Negative set composed of random protein surface regions
2. Hydrogen bond should outperform charge and hydrophobicity

Hydrogen Bond Property

To validate this hypothesis:

1. Negative set composed of random protein surface regions
2. Hydrogen bond should outperform charge and hydrophobicity

Hydrogen Bond Property

To validate this hypothesis:

1. Negative set composed of random protein surface regions
2. Hydrogen bond should outperform charge and hydrophobicity

The results confirm the hypothesis:

Table: Classifier training using an exclusively non-binding sites negative set.

Properties	kNN	SVM	SV
Charge	05.26%	05.26%	73.68%
H-Bond	03.51%	03.51%	61.40%
Hydrophobicity	05.26%	05.26%	68.42%

Residue Schemes Comparison

Table: Comparison of the different residue schemes.

Residue scheme	kNN	SVM	SV
Simplified1	16.36%	18.18%	76.36%
Simplified2	18.18%	18.18%	70.91%
Simplified3	16.36%	16.36%	70.91%
Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- Detailed schemes outperform simplified schemes

Table: Comparison of the different residue schemes.

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Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- Detailed schemes outperform simplified schemes
- Simplified schemes have better generalization

Table: Comparison of the different residue schemes.

Residue scheme	kNN	SVM	SV
Simplified1	16.36%	18.18%	76.36%
Simplified2	18.18%	18.18%	70.91%
Simplified3	16.36%	16.36%	70.91%
Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- Detailed schemes yield similar results to the atomic properties

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Simplified2	18.18%	18.18%	70.91%
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Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- Detailed schemes yield similar results to the atomic properties
- Incorporate in themselves some of the atomic knowledge?

Table: Comparison of the different residue schemes.

Residue scheme	kNN	SVM	SV
Simplified1	16.36%	18.18%	76.36%
Simplified2	18.18%	18.18%	70.91%
Simplified3	16.36%	16.36%	70.91%
Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- "Simplified2" scheme gives similar results to "simplified1" while adding the aromatic subgroup

Table: Comparison of the different residue schemes.

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Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- "Simplified2" scheme gives similar results to "simplified1" while adding the aromatic subgroup
- Aromatic residues play an important role in glucose binding

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Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- "Simplified2" scheme gives similar results to "simplified1" while adding the aromatic subgroup
- Aromatic residues play an important role in glucose binding
- Aromatic residues do not seem to contribute to the classification accuracy

Table: Comparison of the different residue schemes.

Residue scheme	kNN	SVM	SV
Simplified1	16.36%	18.18%	76.36%
Simplified2	18.18%	18.18%	70.91%
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Residue Schemes Comparison

- "Simplified3" improves the "simplified2" classification rate by one hit

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Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Residue Schemes Comparison

- "Simplified3" improves the "simplified2" classification rate by one hit
- Adding histidine to the aromatic subgroup gives slightly better results

Table: Comparison of the different residue schemes.

Residue scheme	kNN	SVM	SV
Simplified1	16.36%	18.18%	76.36%
Simplified2	18.18%	18.18%	70.91%
Simplified3	16.36%	16.36%	70.91%
Detailed1	16.36%	14.55%	81.82%
Detailed2	21.82%	14.55%	81.82%

Water and Ion inclusion

- Ordered water molecules and ions play a role in glucose binding

Table: Testing the importance of water and ions to glucose specificity

Mode	Properties	kNN	SVM	SV
Water + ions	Charge + Hydro	12.73%	14.55%	47.27%
	Residue + Charge + Hydro	20.00%	09.09%	100%
Ions	Charge + Hydro	14.55%	16.36%	83.64%
	Residue + Charge + Hydro	20.00%	10.91%	100%
Water	Charge + Hydro	16.36%	18.18%	83.64%
	Residue + Charge + Hydro	20.00%	10.91%	100%
	Charge + Hydro	14.55%	16.36%	52.73%
	Residue + Charge + Hydro	20.00%	12.73%	100%

Water and Ion inclusion

- Ordered water molecules and ions play a role in glucose binding
- We test and validate this hypothesis

Table: Testing the importance of water and ions to glucose specificity

Mode	Properties	*k*NN	SVM	SV
Water + ions	Charge + Hydro	12.73%	14.55%	47.27%
	Residue + Charge + Hydro	20.00%	09.09%	100%
Ions	Charge + Hydro	14.55%	16.36%	83.64%
	Residue + Charge + Hydro	20.00%	10.91%	100%
Water	Charge + Hydro	16.36%	18.18%	83.64%
	Residue + Charge + Hydro	20.00%	10.91%	100%
	Charge + Hydro	14.55%	16.36%	52.73%
	Residue + Charge + Hydro	20.00%	12.73%	100%

Atomic Properties Feature Selection

Table: Classifiers performance on atomic data using feature selection.

Property	RF	Feat. Nb.	kNN Error	SVM Error	Sensitivity	Specificity	SV
Charge	false	24	14.55%	14.55%	96.55%	73.08%	78.18%
	true	6	09.09%	05.45%	93.10%	96.15%	41.82%
H-Bond	false	16	21.82%	16.36%	86.21%	80.77%	92.73%
	true	5	09.09%	07.27%	96.55%	88.46%	16.36%
Hydro	false	24	21.82%	20.00%	79.31%	80.77%	92.73%
	true	5	09.09%	10.91%	96.55%	84.62%	34.55%

Atomic Properties Feature Selection

Definition

Sensitivity: Ability to detect true positives (TP/P)
Specificity: Ability to reject true negatives (TN/N)

Table: Classifiers performance on atomic data using feature selection.

Property	RF	Feat. Nb.	kNN Error	SVM Error	Sensitivity	Specificity	SV
Charge	false	24	14.55%	14.55%	96.55%	73.08%	78.18%
	true	6	09.09%	05.45%	93.10%	96.15%	41.82%
H-Bond	false	16	21.82%	16.36%	86.21%	80.77%	92.73%
	true	5	09.09%	07.27%	96.55%	88.46%	16.36%
Hydro	false	24	21.82%	20.00%	79.31%	80.77%	92.73%
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Atomic Properties Feature Selection

- Classification error decreases

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	true	6	09.09%	05.45%	93.10%	96.15%	41.82%
H-Bond	false	16	21.82%	16.36%	86.21%	80.77%	92.73%
	true	5	09.09%	07.27%	96.55%	88.46%	16.36%
Hydro	false	24	21.82%	20.00%	79.31%	80.77%	92.73%
	true	5	09.09%	10.91%	96.55%	84.62%	34.55%

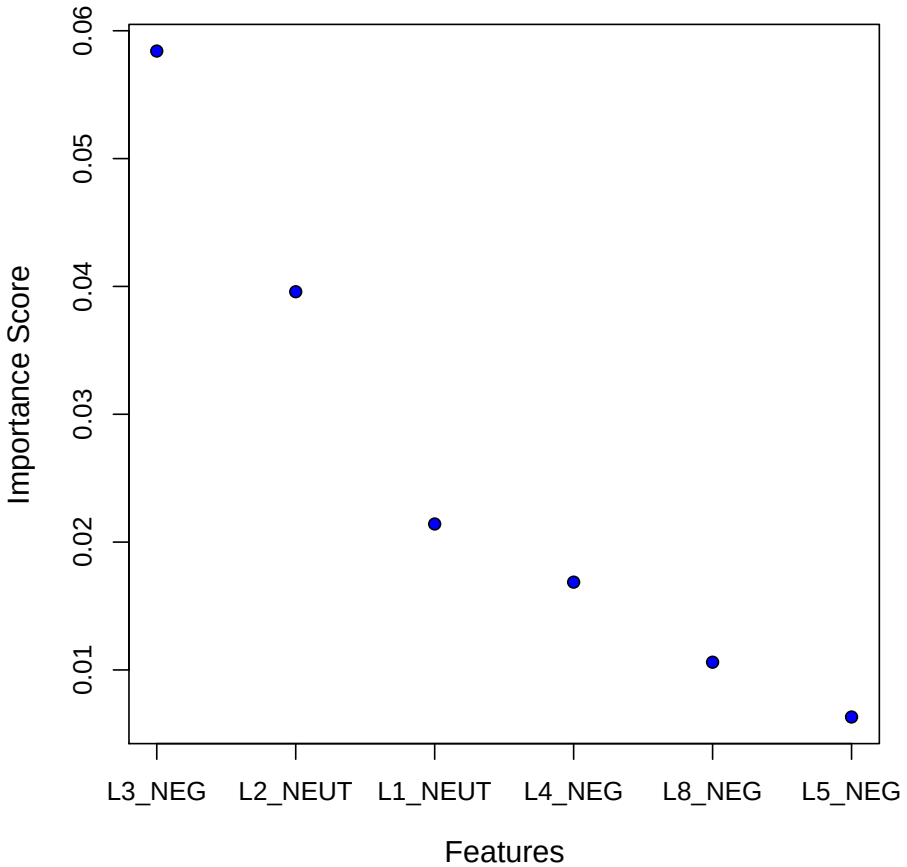
Atomic Properties Feature Selection

- Classification error decreases
- SV percentage decreases (generalization capacity increases)

Table: Classifiers performance on atomic data using feature selection.

Property	RF	Feat. Nb.	kNN Error	SVM Error	Sensitivity	Specificity	SV
Charge	false	24	14.55%	14.55%	96.55%	73.08%	78.18%
	true	6	09.09%	05.45%	93.10%	96.15%	41.82%
H-Bond	false	16	21.82%	16.36%	86.21%	80.77%	92.73%
	true	5	09.09%	07.27%	96.55%	88.46%	16.36%
Hydro	false	24	21.82%	20.00%	79.31%	80.77%	92.73%
	true	5	09.09%	10.91%	96.55%	84.62%	34.55%

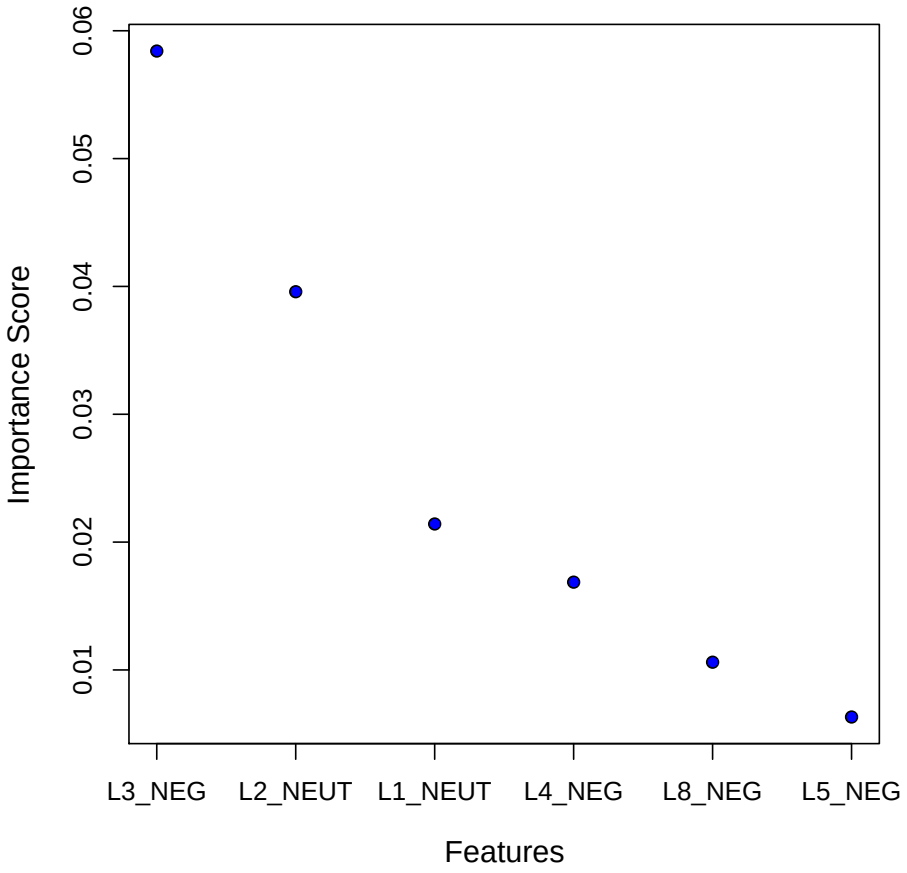
Charge Feature Selection



- Remains the best discriminating factor

Figure: Importance of charge features

Charge Feature Selection



- Remains the best discriminating factor
- Negatively charged glucose binding site

Figure: Importance of charge features

Charge Feature Selection

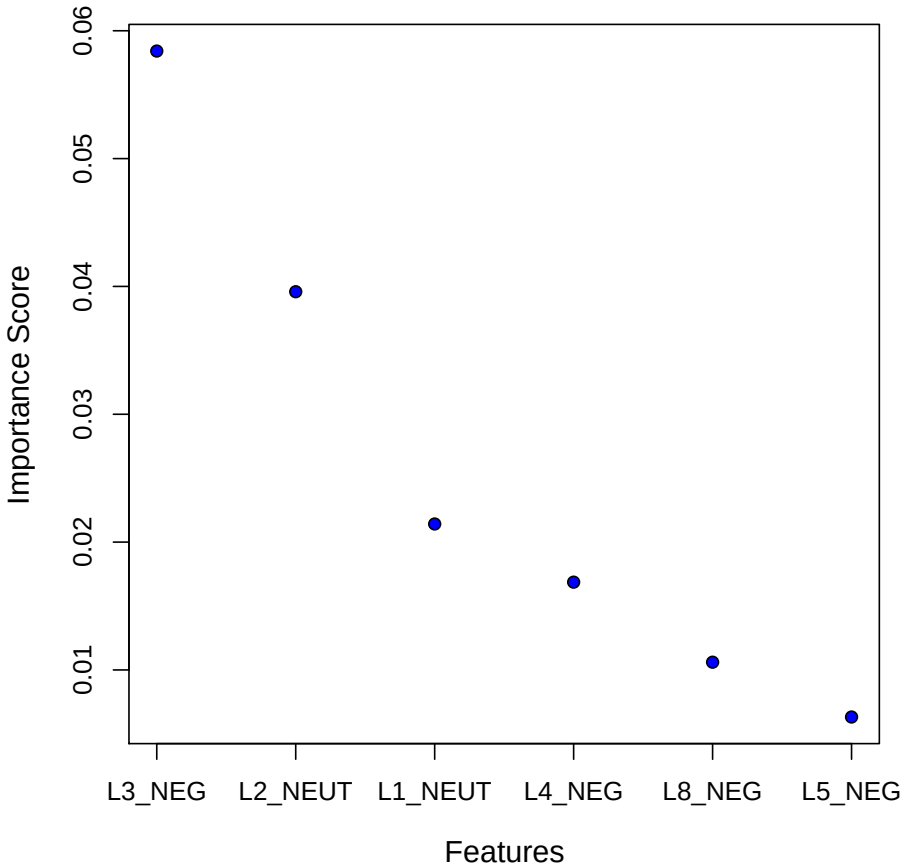
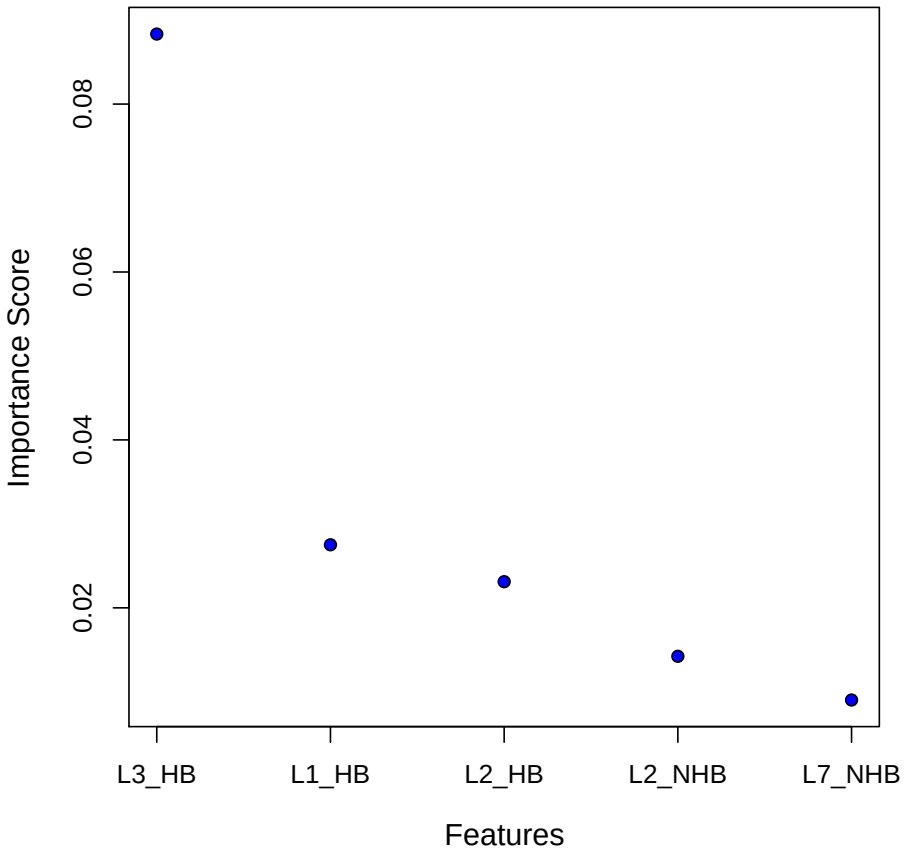


Figure: Importance of charge features

- Remains the best discriminating factor
- Negatively charged glucose binding site
- Layers 1 and 2: overlap with glucose

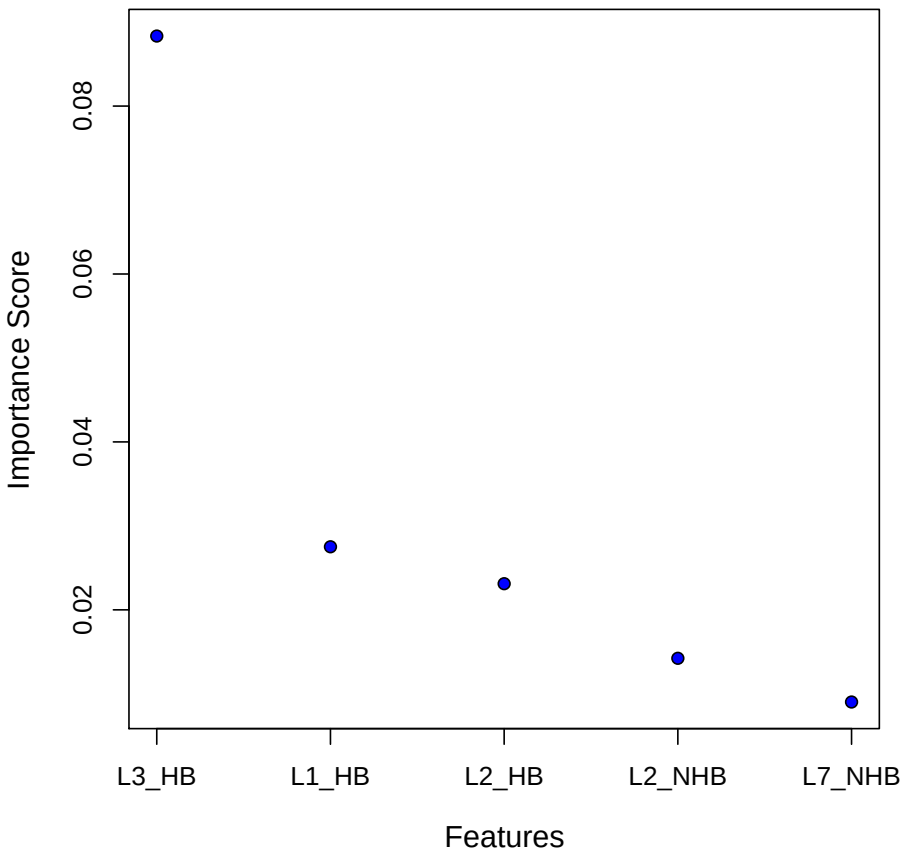
Hydrogen Bond Feature Selection



- A record low SV percentage

Figure: Importance of hbond features

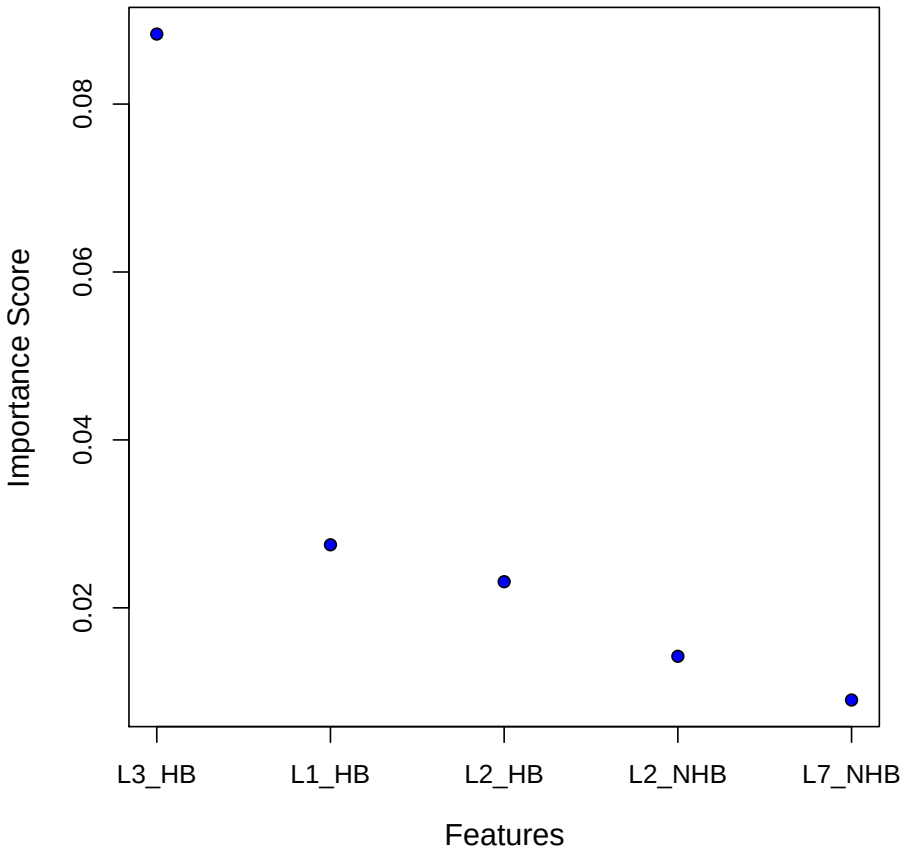
Hydrogen Bond Feature Selection



- A record low SV percentage
- Both positive and negative sets rely on H-Bond

Figure: Importance of hbond features

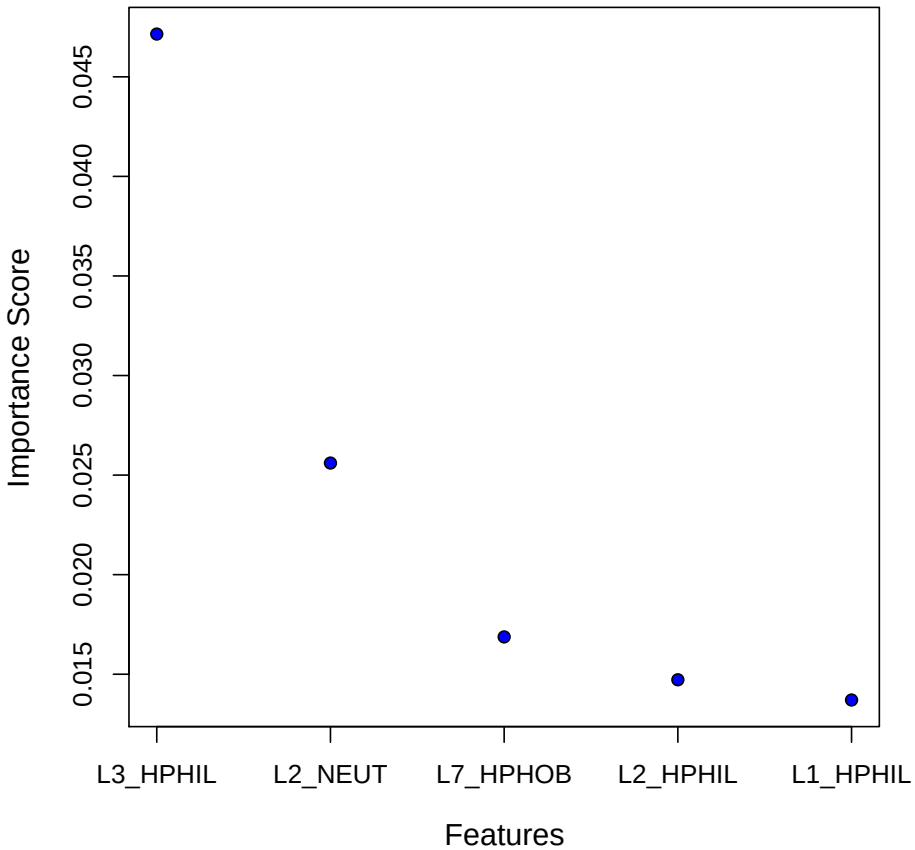
Hydrogen Bond Feature Selection



- A record low SV percentage
- Both positive and negative sets rely on H-Bond
- Differ by their distribution

Figure: Importance of hbond features

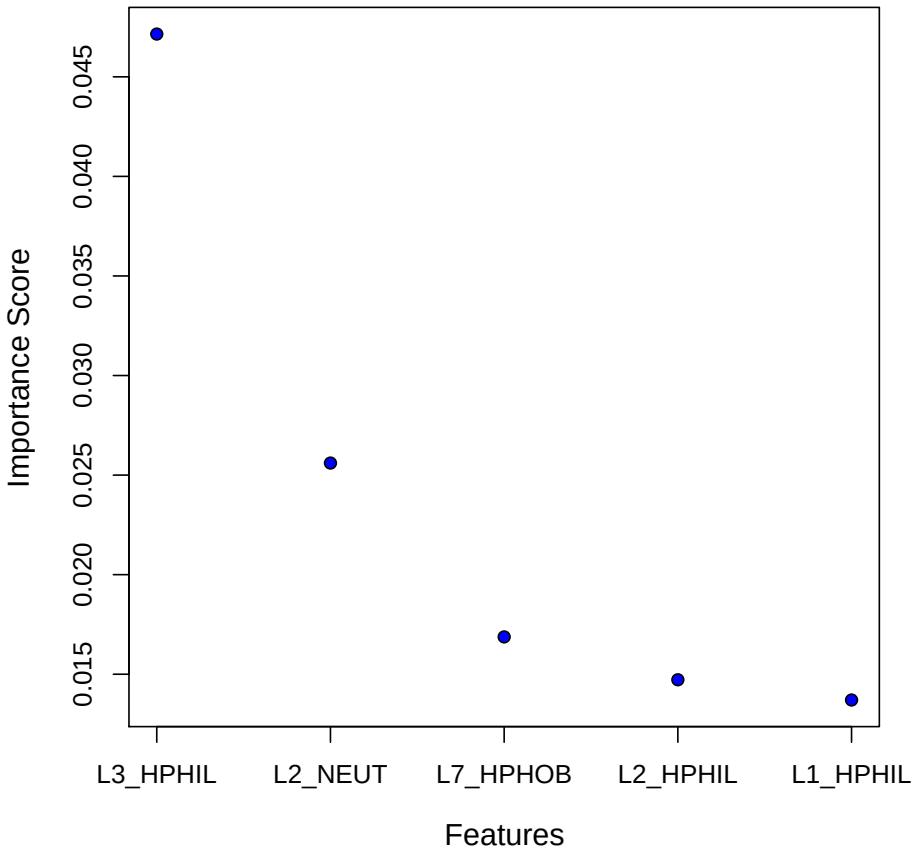
Hydrophobicity Feature Selection



- Remains the worst discriminating factor

Figure: Importance of hydro features

Hydrophobicity Feature Selection



- Remains the worst discriminating factor
- Positive set: high concentration of hydrophilic atoms in layer 3

Figure: Importance of hydro features

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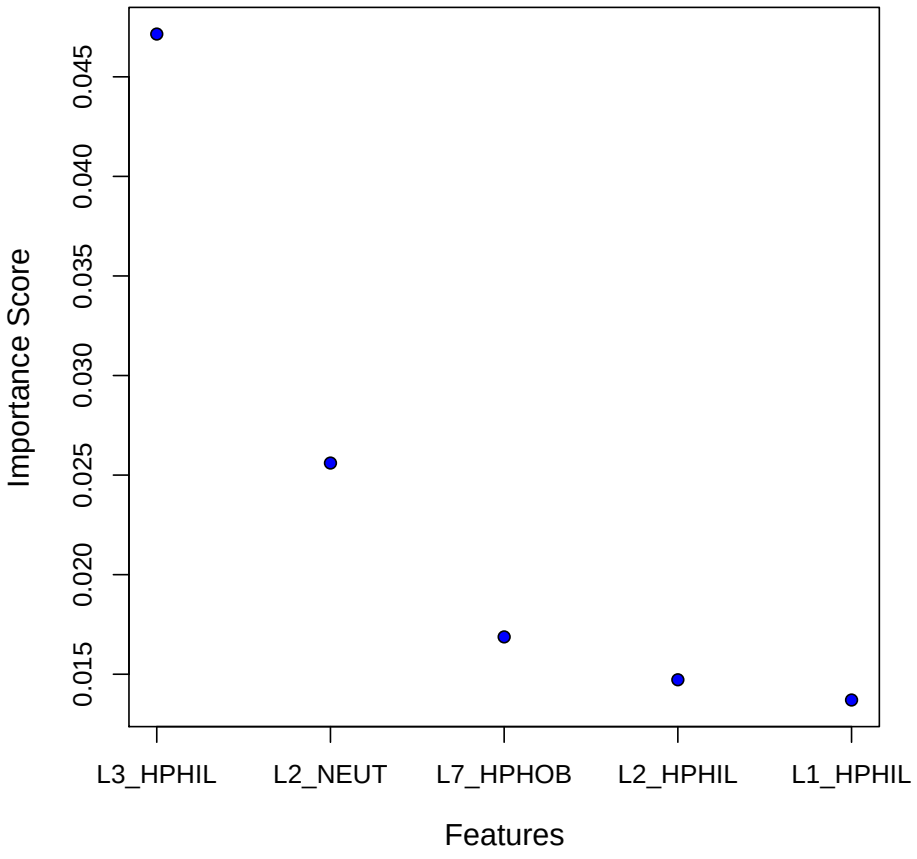
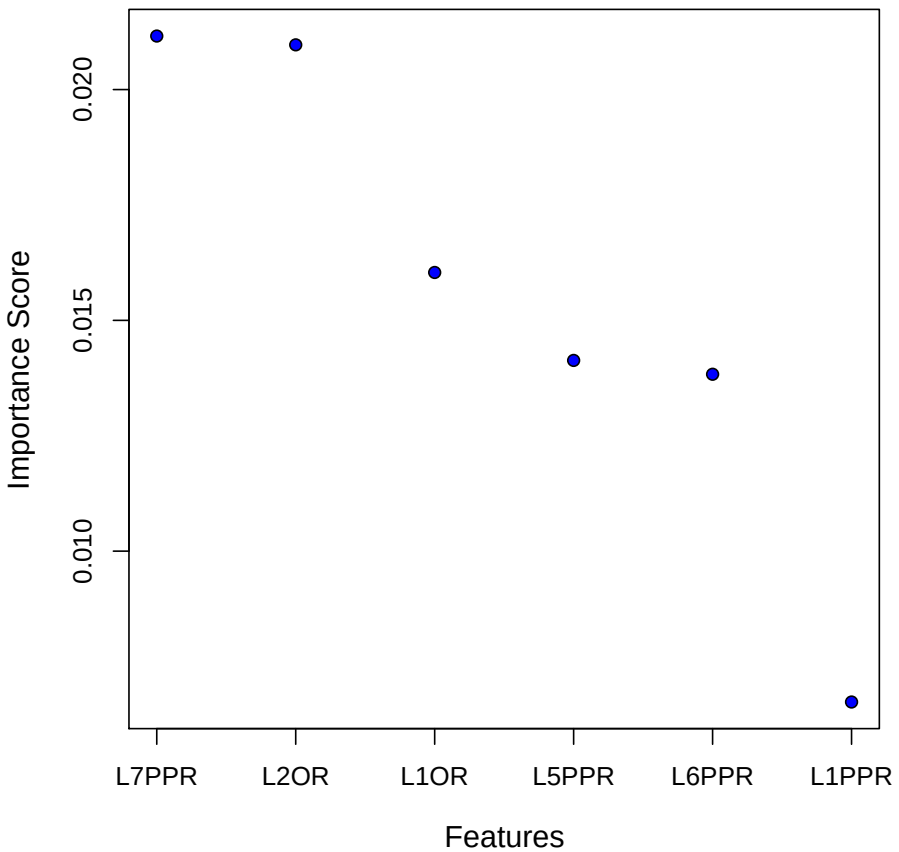


- Remains the worst discriminating factor
- Positive set: high concentration of hydrophilic atoms in layer 3
- Low importance score of hydrophobic features

Figure: Importance of hydro features

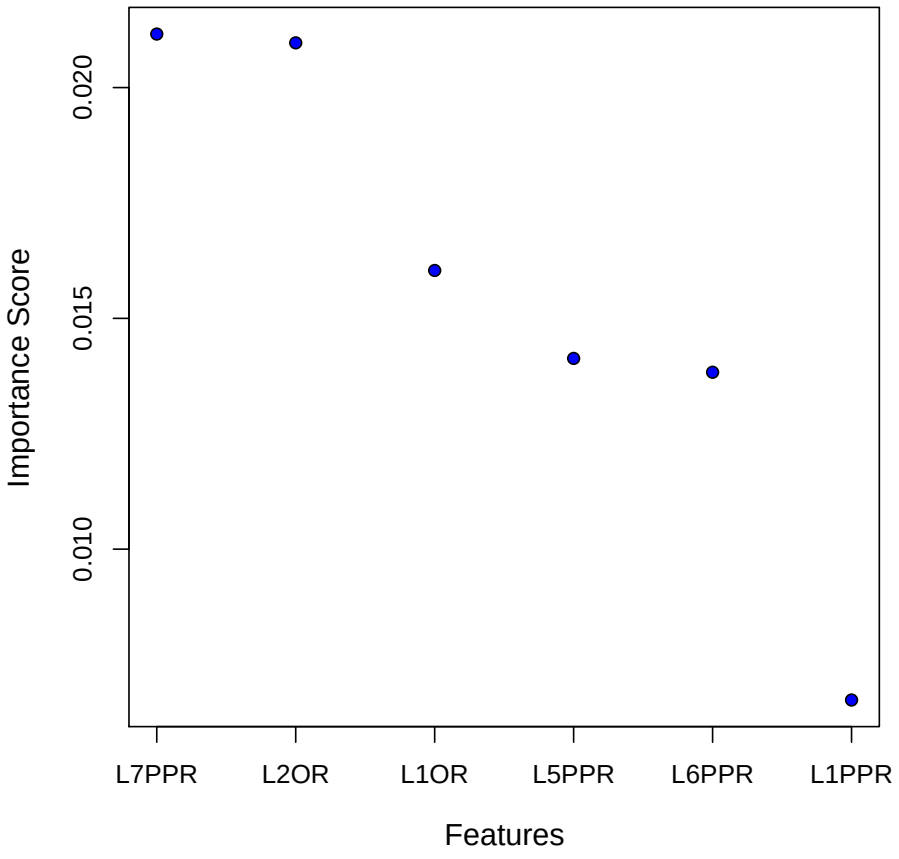
Simplified Residue Schemes Feature Selection



- Similar results for the 3 simplified schemes

Figure: Importance of simplified features

Simplified Residue Schemes Feature Selection



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- Importance of planar polar residues

Figure: Importance of simplified features

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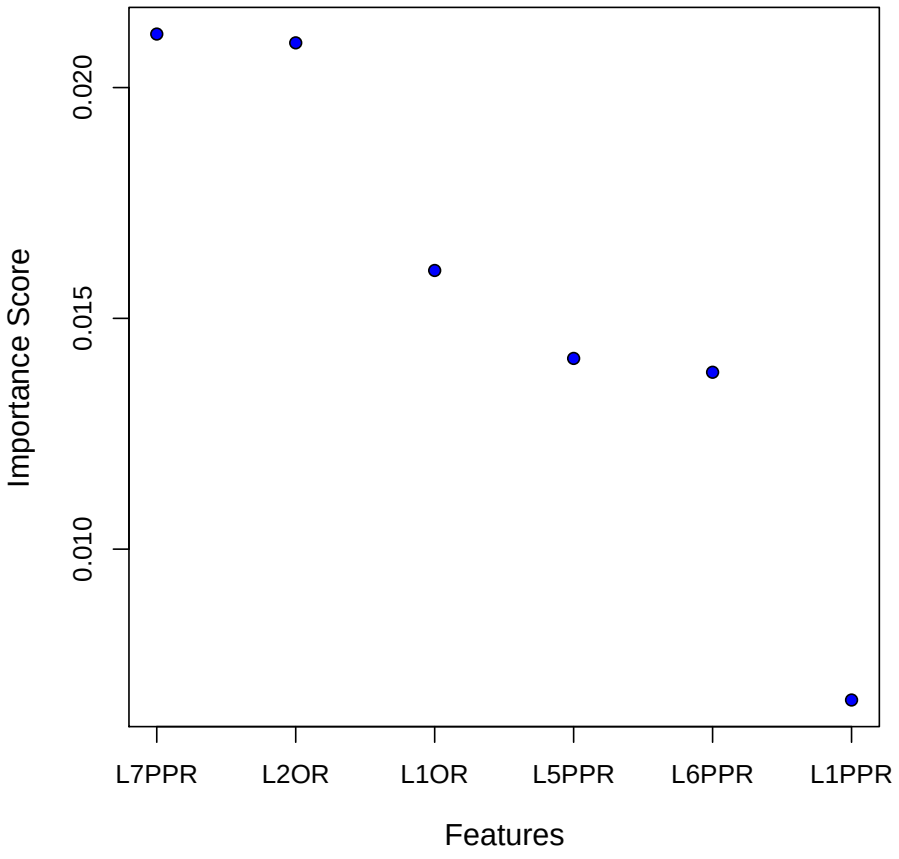
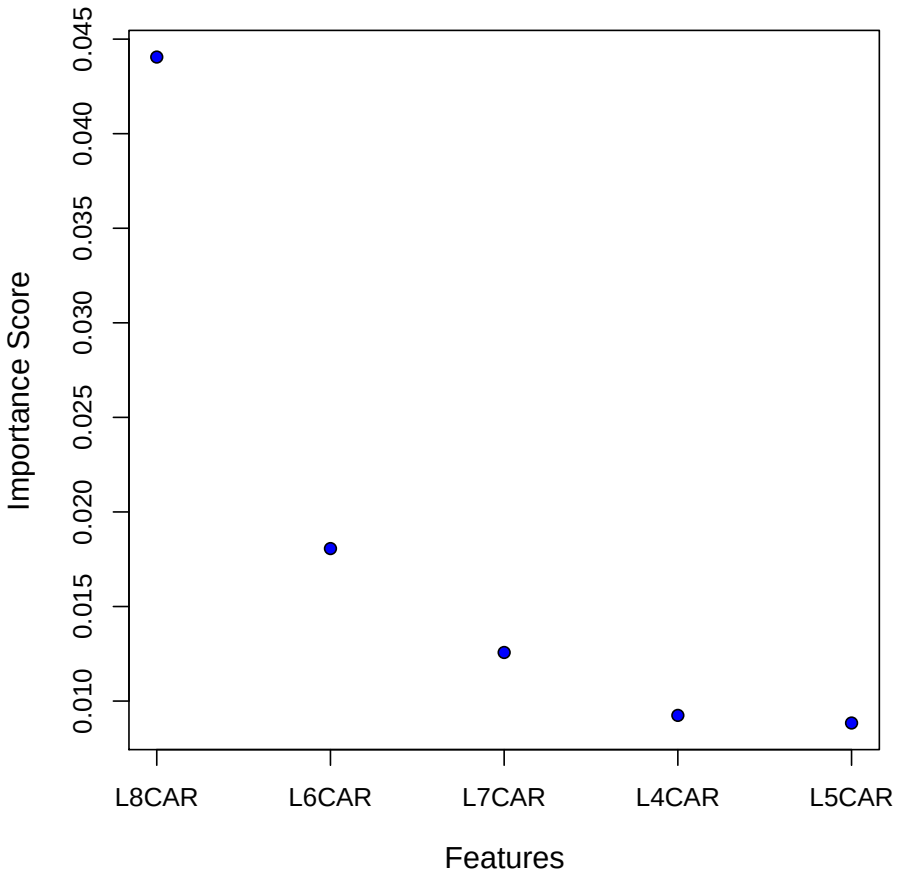


- Similar results for the 3 simplified schemes
- Importance of planar polar residues
- Low importance score of aromatic residues

Figure: Importance of simplified features

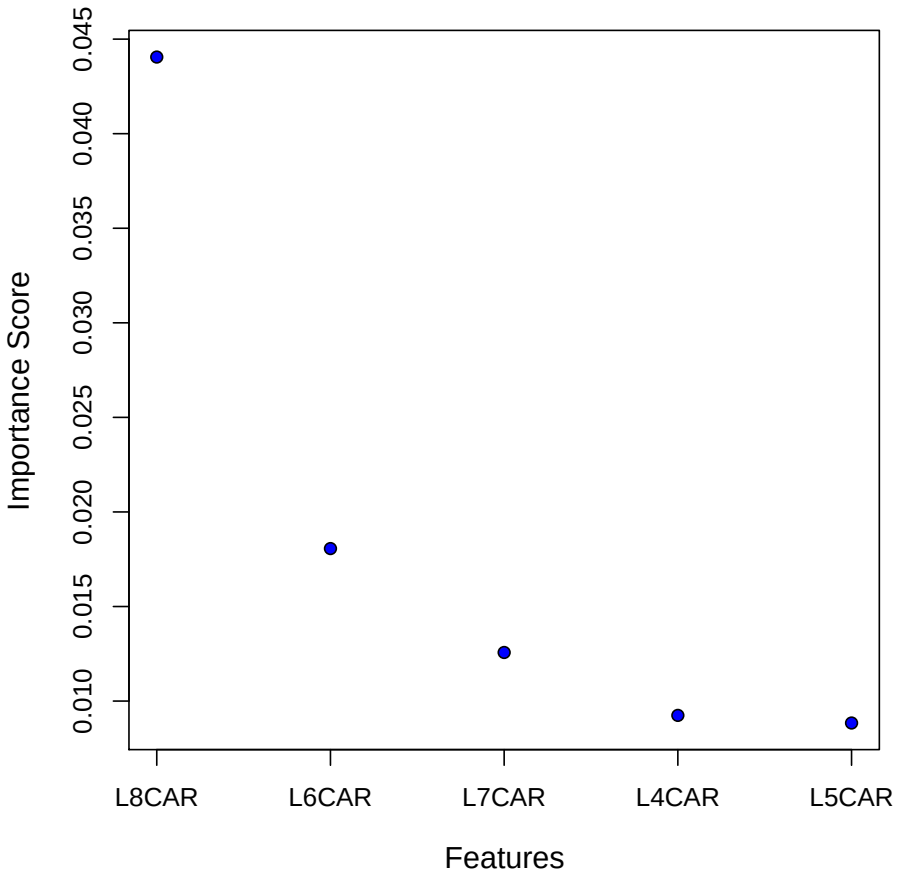
Detailed Residue Schemes Feature Selection



- Similar results for both detailed schemes

Figure: Importance of detailed features

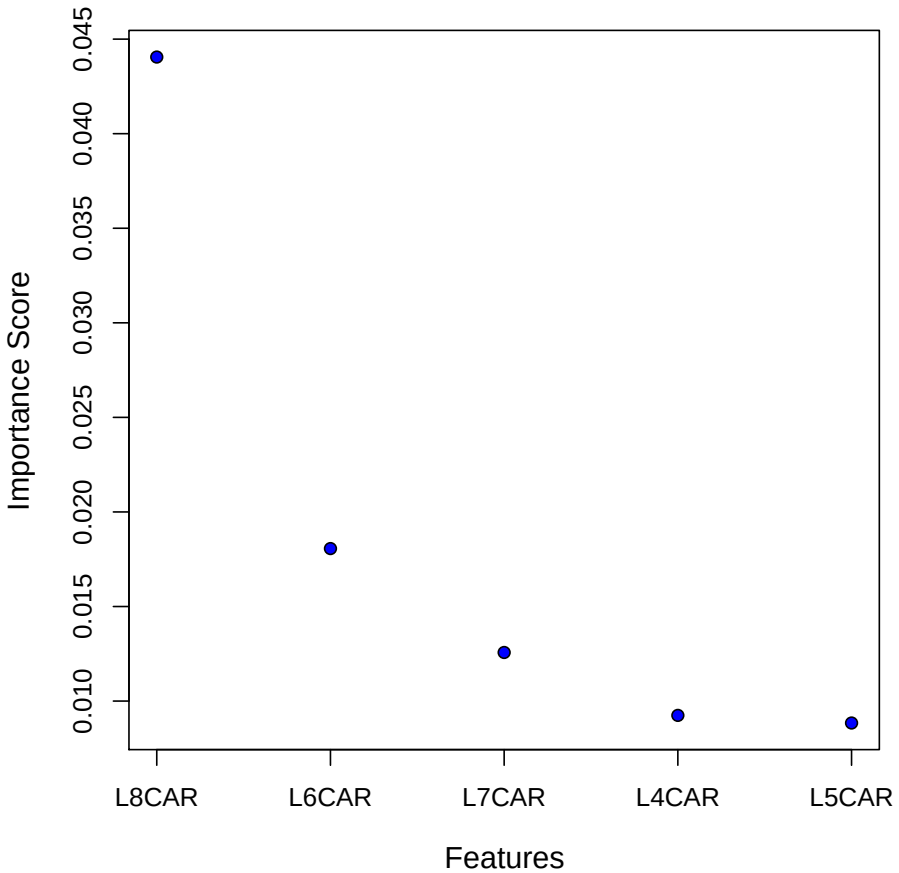
Detailed Residue Schemes Feature Selection



- Similar results for both detailed schemes
- Still outperform simplified schemes.

Figure: Importance of detailed features

Detailed Residue Schemes Feature Selection



- Similar results for both detailed schemes
- Still outperform simplified schemes.
- High density of the negatively charged carboxylate residues

Figure: Importance of detailed features

Combined Atomic and Residue Feature Selection

- 3.64% error for both classifiers.

Table: Classifiers performance using feature selection.

Property	RF	Feat. Nb.	kNN Error	SVM Error	Sensi-tivity	Speci-ficity	SV
Detailed2	false	104	14.06%	07.81%	93.10%	91.43%	53.13%
+ Charge							
+ H-Bond	true	15	03.64%	03.64%	96.55%	96.15%	69.09%
+ Hydro							

Selected Feature Subset

Table: The selected feature subset.

Property	Features	L1	L2	L3	L4	L5	L6	L7	L8
Charge	Negative			X					
	Neutral	X	X						
H-Bond	H-Bonding			X					
Hydro	Hydrophilic	X	X	X					
	Neutral		X						
	Hydrophobic							X	X
Residues	Neutral						X		
	Carboxylate					X	X		X
	Aliphatic			X					

Feature Selection Findings

- The difference in spatial configuration

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- Charge is the best discriminant property
- Discriminating atomic properties on layer 3
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- The relevance of planar polar residues
- Low discrimination capacity of hydrophobic interactions and aromatic residues
- Possibly due to their one-correctly-placed relationship

Testing Phase

- Parse PDB for entries newer than October 2004

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- 7 distinct glucose binding sites

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Table: Testing phase results.

Classifier	TP	FP	TN	FN	Error	Sensitivity	Specificity	Precision
SVM	6	0	15	1	04.55%	85.71%	100%	100%
*k*NN	6	2	13	1	13.64%	85.71%	86.67%	75.00%
COTRAN	94	27	633	12	05.09%	88.68%	95.91%	77.69%

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- *Precision:* ability to reject false positives.

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- Extend this study to other sugars

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- The committee members
- The audience

Amino Acids Table

Table: Standard amino acids names, three- and one-letter abbreviations. They are sorted according to biological convention based on the size and properties of the side chain.

Name	3-L	1-L	Name	3-L	1-L
Glycine	Gly	G	Cysteine	Cys	C
Alanine	Ala	A	Serine	Ser	S
Valine	Val	V	Threonine	Thr	T
Leucine	Leu	L	Aspartate	Asp	D
Isoleucine	Ile	I	Glutamate	Glu	E
Proline	Pro	P	Histidine	His	H
Phenylalanine	Phe	F	Lysine	Lys	K
Tyrosine	Tyr	Y	Arginine	Arg	R
Tryptophan	Trp	W	Asparagine	Asn	N
Methionine	Met	M	Glutamine	Gln	Q

Atomic Features

Atom Type	Functional Group	Location	Residue	PDB Atom Symbol	Chrg	Hydrophob	H Bond
Oxygen	Amide peptide linkage	Backbone	All	O	0	-1	H Bond
Oxygen	Carboxyl – C terminus	Backbone	All	OXT	-ve	-1	H Bond
Oxygen	Carboxyl	Side Chain	GLU	OE1	-ve	-1	H Bond
Oxygen	Carboxyl	Side Chain	GLU	OE2	-ve	-1	H Bond
Oxygen	Carboxyl	Side Chain	ASP	OD1	-ve	-1	H Bond
Oxygen	Carboxyl	Side Chain	ASP	OD2	-ve	-1	H Bond
Oxygen	Amide	Side Chain	GLN	OE1	0	-1	H Bond
Oxygen	Amide	Side Chain	ASN	OD1	0	-1	H Bond
Oxygen	Hydroxyl	Side Chain	SER	OG	0	-1	H Bond
Oxygen	Hydroxyl	Side Chain	THR	OG1	0	-1	H Bond
Oxygen	Hydroxyl - Phenolic	Side Chain	TYR	OH	0	-1	H Bond
Nitrogen	Amide peptide linkage	Backbone	All except PRO	N	0	-1	H Bond
Nitrogen	Amide peptide linkage	Backbone	PRO	N	0	-1	--
Nitrogen	Amide	Side Chain	GLN	NE2	0	-1	H Bond
Nitrogen	Amide	Side Chain	ASN	ND2	0	-1	H Bond
Nitrogen	Amine	Side Chain	LYS	NZ	+ve	-1	H Bond
Nitrogen	Guanidino	Side Chain	ARG	NE	+ve	-1	--
Nitrogen	Guanidino	Side Chain	ARG	NH1	+ve	-1	H Bond
Nitrogen	Guanidino	Side Chain	ARG	NH2	+ve	-1	H Bond
Nitrogen	Imidazole	Side Chain	HIS	ND1	0	-1	--
Nitrogen	Imidazole	Side Chain	HIS	NE2	0	-1	H Bond
Nitrogen	Indole	Side Chain	TRP	NE1	0	0	--
Carbon	Amide peptide linkage	Backbone	All	C	0	0	--
Carbon	C-alpha	Backbone	All	CA	0	0	--
Carbon	Aliphatic – neutral	Side Chain	Set A (See below)	CB, CG, CD, CE	0	0	--
Carbon	Aliphatic – hydrophobic	Side Chain	LEU, VAL, ILE, MET	CB, CG, CD, CE	0	1	--
Carbon	Aliphatic – Branch	Side Chain	LEU, VAL, ILE	CG1, CG2, CD1, CD2, CD1	0	1	--
Carbon	Phenyl - aromatic	Side Chain	PHE, TYR	CG,CD1, CD2, CE1, CE2, CZ	0	1	--
Carbon	Imidazole	Side Chain	HIS	CG, CD2, CE1	0	1	--
Carbon	Aromatic	Side Chain	TRP	CG,CD1, CD2,	0	1	--
Carbon	Aromatic	Side Chain	TRP	CE2, CE3, CZ2, CZ3, CH2	0	1	--
Sulfur	Sulfhydril	Side Chain	CYS	SG	0	-1	H Bond
Sulfur	Thioether	Side Chain	MET	SD	0	0	--
Oxygen	Sulfate	HET Group	SO4	O1, O2, O3, O4	-ve	-1	H Bond
Oxygen	Phosphate	HET Group	2HP	O1, O2, O3, O4	-ve	-1	H Bond
Oxygen	Water	HET Group	HOH	O	0	-1	H Bond
Calcium	Ion	HET Group	CA	CA	+ve	-1	H Bond
Magnesium	Ion	HET Group	MG	MG	+ve	-1	H Bond
Zinc	Ion	HET Group	ZN	ZN	+ve	-1	H Bond

Set A = ALA, SER, THR, CYS, ASP, ASN, GLU, GLN, ARG, LYS, PRO

Atomic and Residue Combinations Results

Table: Atomic and residue properties classification error rates.

Properties	kNN	SVM	SV
Residue (detailed1 scheme)	16.36%	14.55%	81.82%
Residue + Charge	18.18%	10.91%	100%
Residue + H-Bond	16.36%	10.91%	94.55%
Residue + Hydro	16.36%	10.91%	90.91%
Residue + Charge + H-Bond	16.36%	10.91%	100%
Residue + Charge + Hydro	20.00%	09.09%	100%
Residue + H-Bond + Hydro	18.18%	10.91%	98.18%
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- Residue property constrains the differences between the various combinations of atomic features

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Atomic and Residue Combinations Results

- "Charge + Hydro + Residue " is the best combination

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Hydrophobicity and Charge Properties

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- May explain why hydrophobicity is the worst discriminant

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  1. Hydrophobic: Aromatic residues stack against pyranose ring
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- May explain why hydrophobicity is the worst discriminant
- Hydrophobicity: secondary discriminating factor

Detailed Schemes Comparison

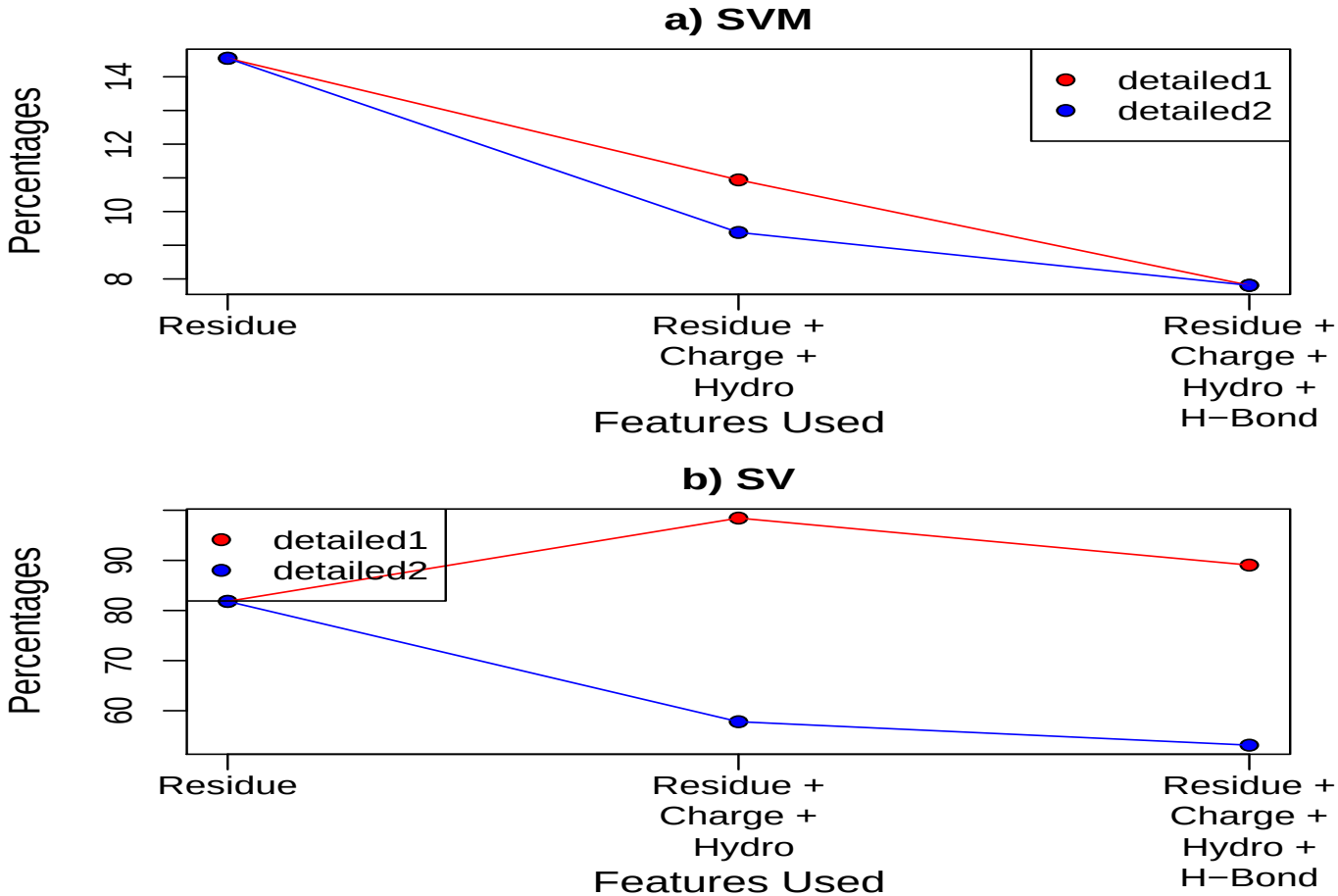

Figure: Comparison of detailed1 and detailed2 schemes

Residue Schemes Feature Selection

Table: Classifiers performance on residue data using feature selection.

Property	RF	Feat. Nb.	kNN Error	SVM Error	Sensitivity	Specificity	SV
Detailed1	false	48	16.36%	14.55%	89.66%	80.77%	81.82%
	true	19	09.09%	12.73%	93.10%	88.46%	56.36%
Detailed2	false	40	21.82%	14.55%	96.55%	73.08%	81.82%
	true	3	10.91%	12.73%	89.66%	88.46%	56.36%
Simplified1	false	16	16.36%	18.18%	96.55%	69.23%	76.36%
	true	6	12.73%	12.73%	93.10%	80.77%	67.27%
Simplified2	false	24	18.18%	18.18%	86.21%	76.92%	70.91%
	true	4	10.91%	10.91%	96.55%	80.77%	54.55%
Simplified3	false	24	16.36%	16.36%	96.55%	69.23%	70.91%
	true	6	12.73%	12.73%	96.55%	76.92%	74.55%

The Selected Features Importance

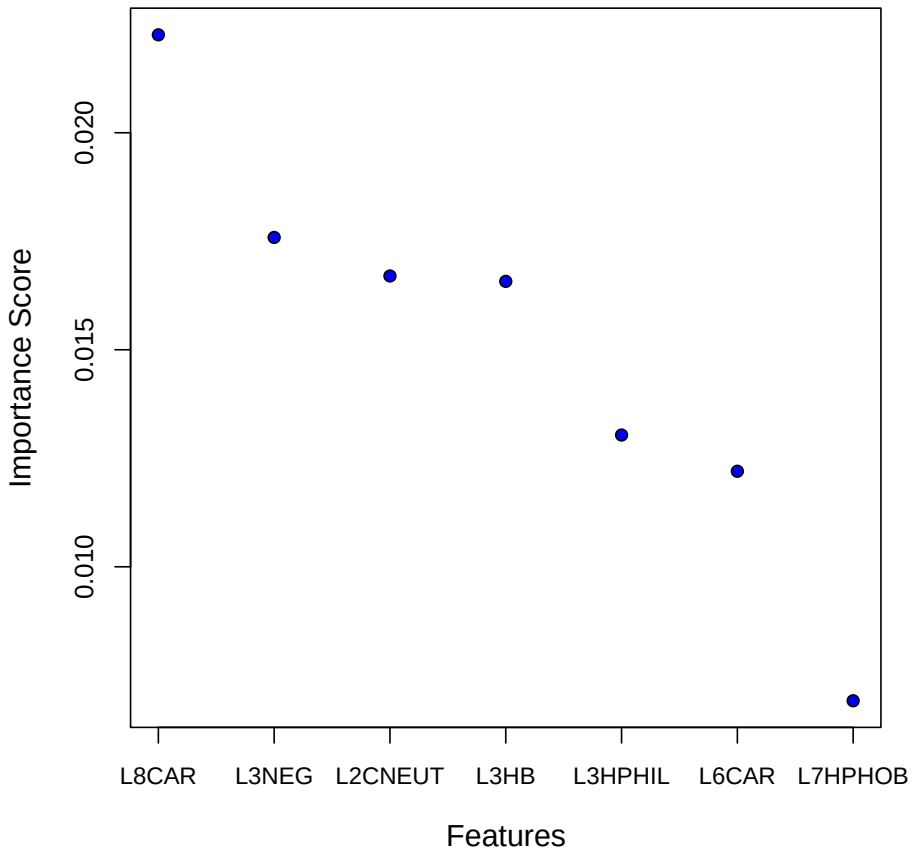

Figure: Importance of the selected features subset