Predicting Secondary Structure of All-Helical Proteins Using Hidden Markov Support Vector Machines

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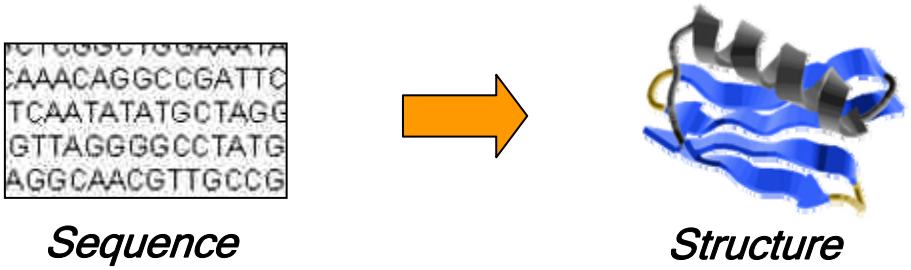
Protein Structure Prediction

- **Classical problem: given sequence, predict structure**



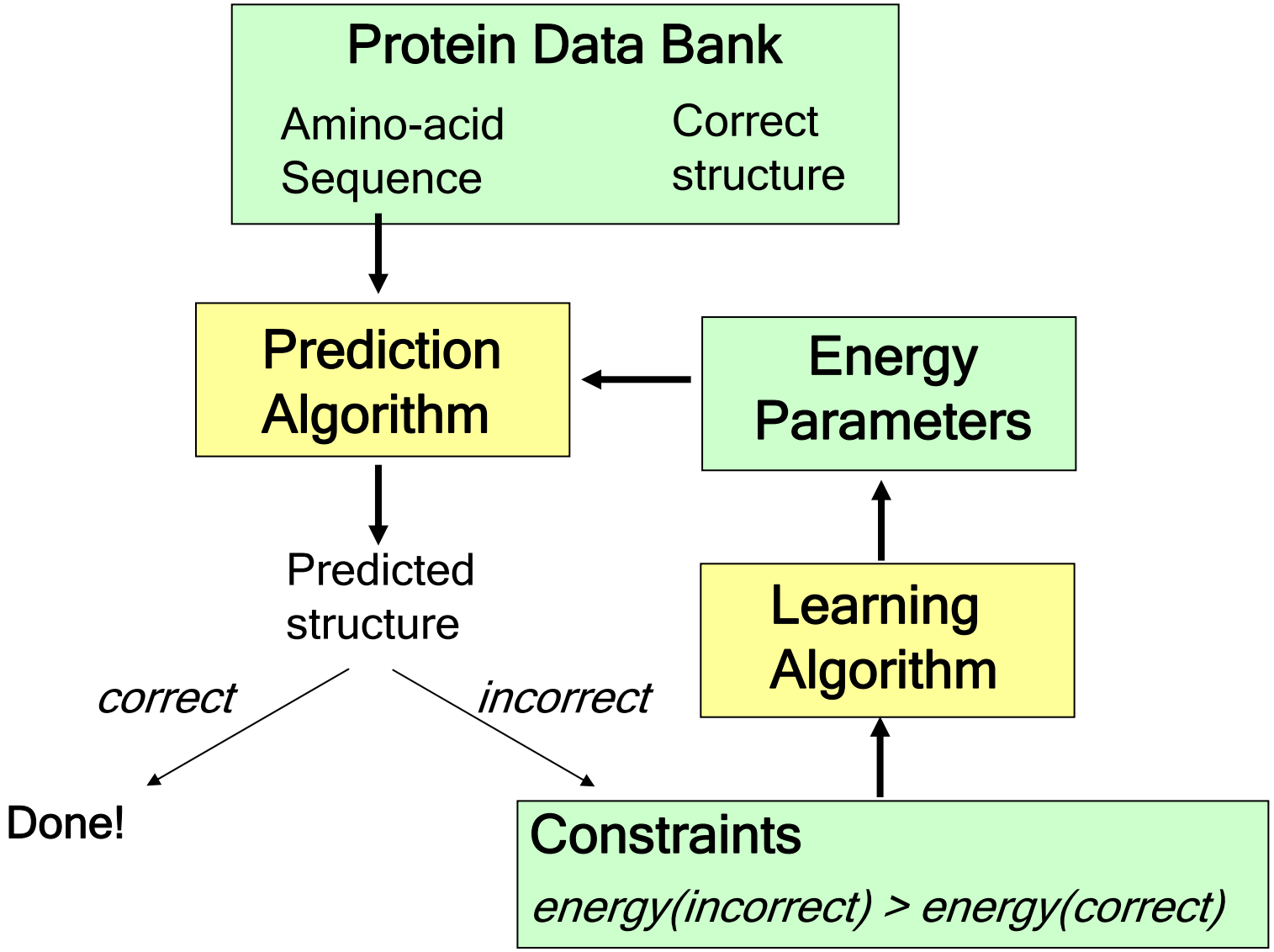
Sequence *Structure*

- **High-level approaches**

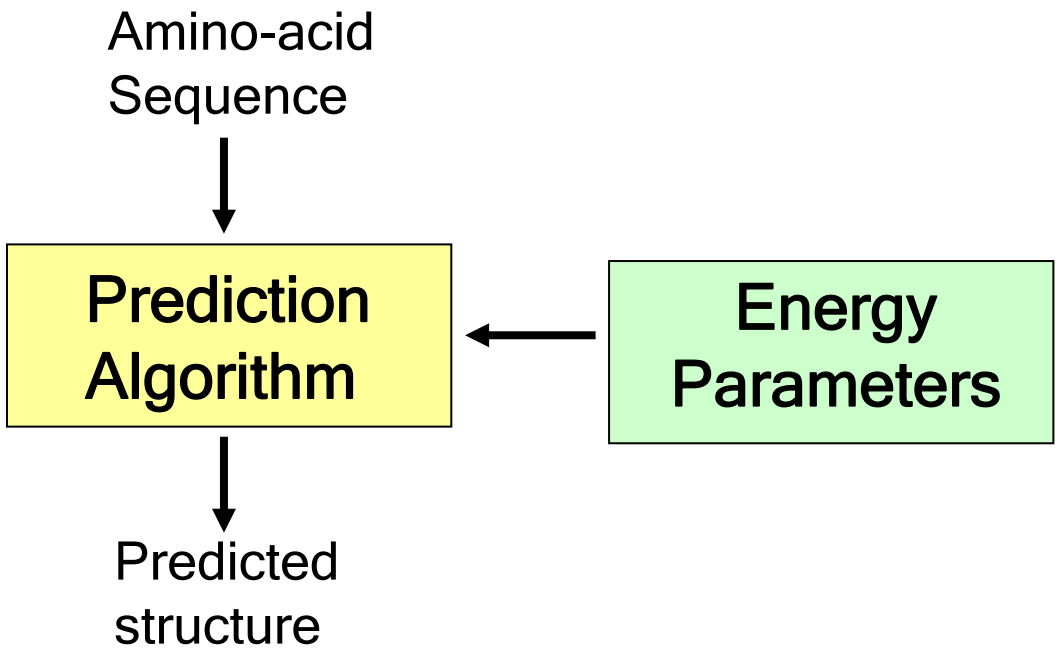
1. Energy-minimization (ab-initio) techniques
   - Elegant, but often lack correct parameters
2. Homology-based techniques
   - Useful, but hard to predict new proteins

Our approach:
Use energy minimization, but
learn parameters from existing proteins

Our Framework (Training)



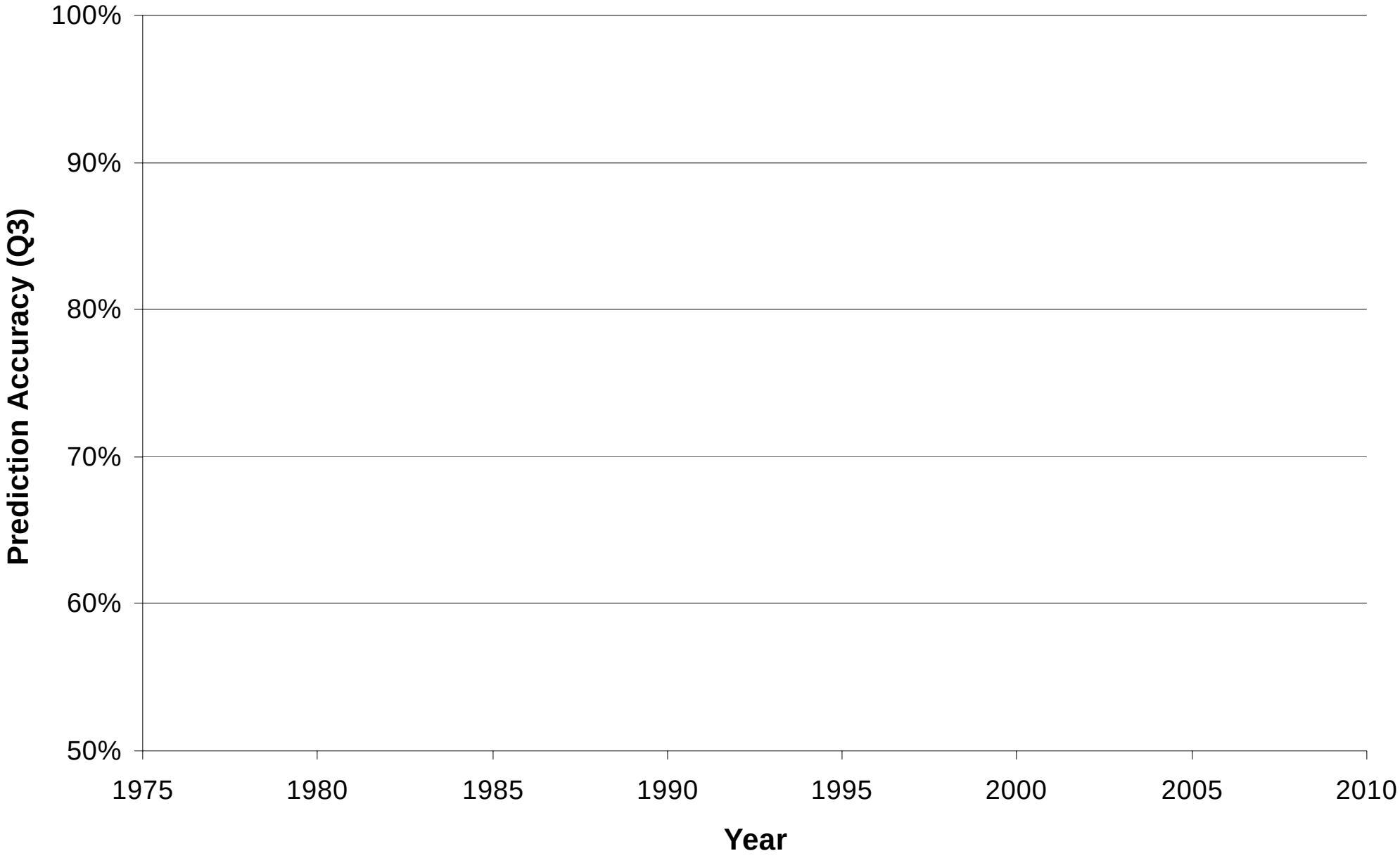
Our Framework (Testing)



Initial Focus: Secondary Structure

- **Classify each residue as alpha helix, beta strand, coil**
  - In this paper, restrict to all-alpha proteins
- **Applications:**
  - Informing tertiary structure predictors
  - Identification of homologous proteins
  - Identification of active sites (coils)

Secondary Structure Predictors



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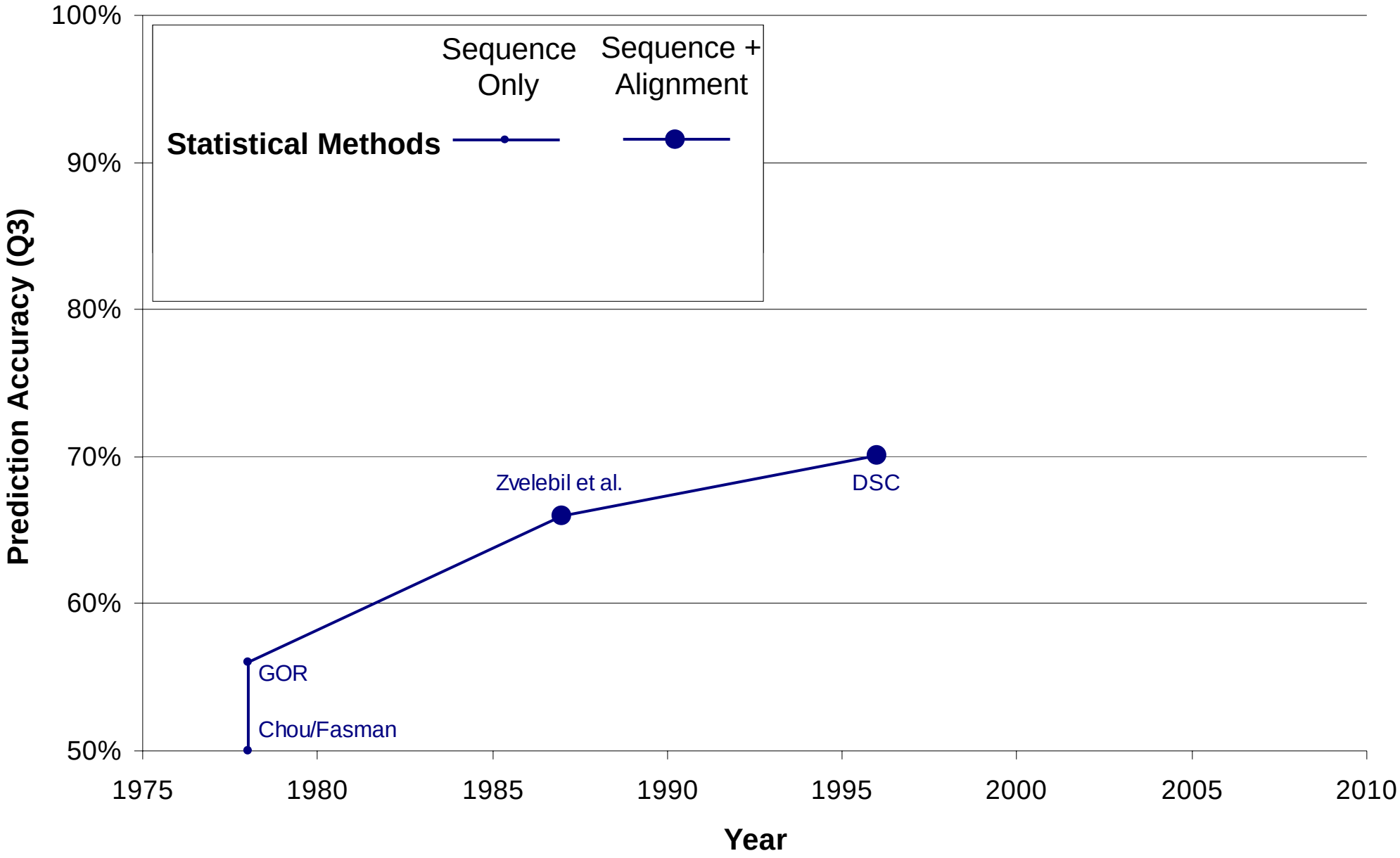

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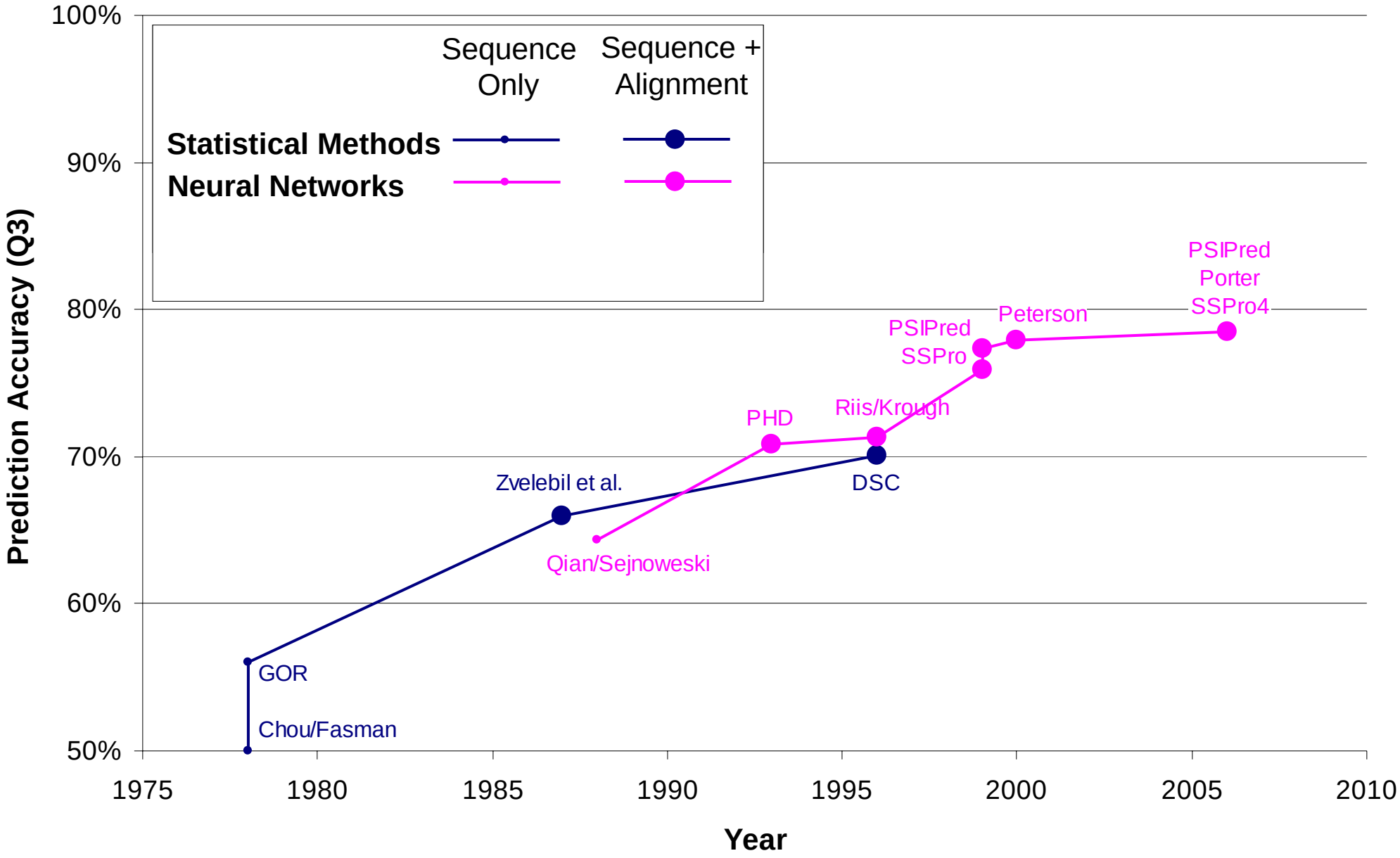
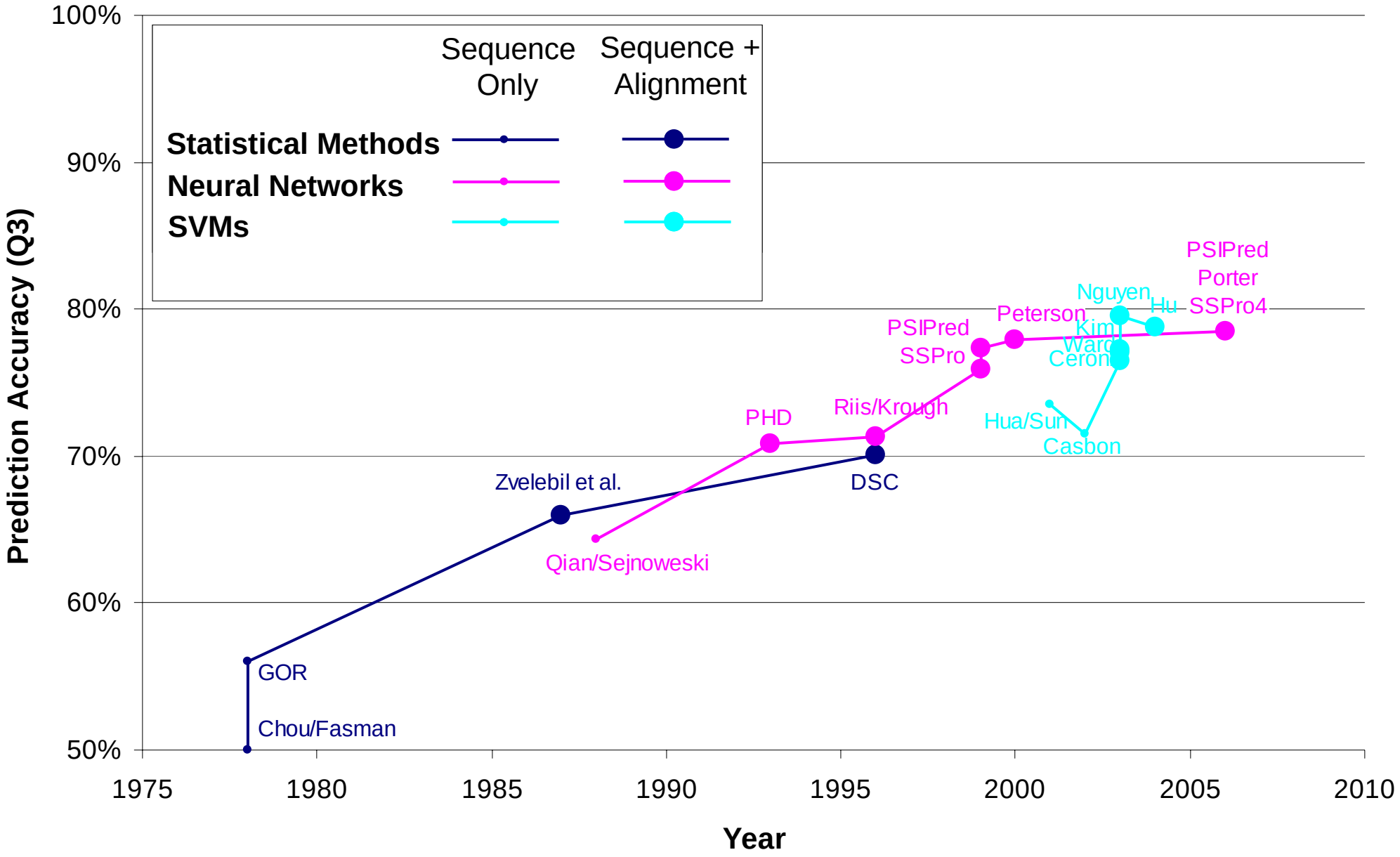


Secondary Structure Predictors



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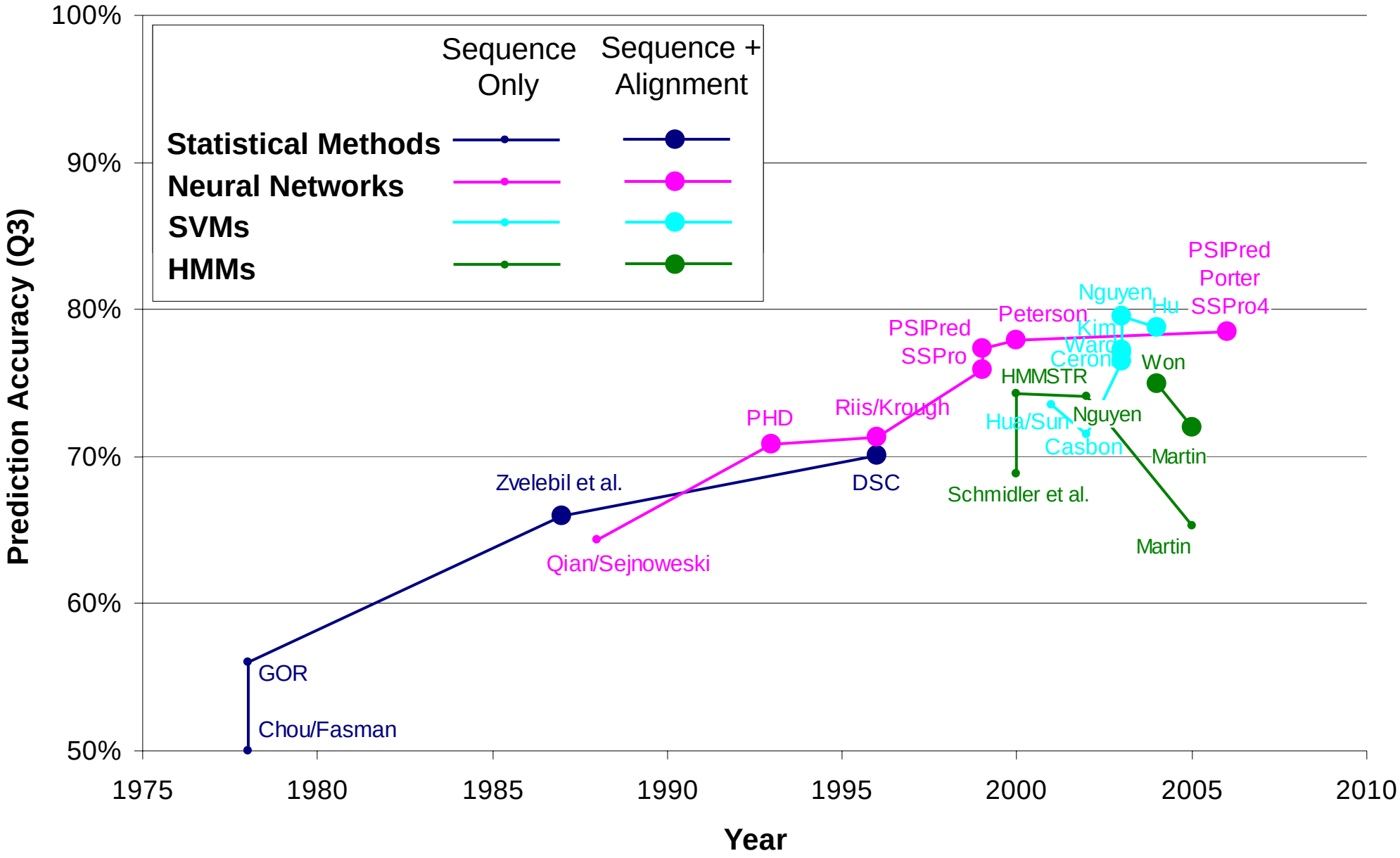

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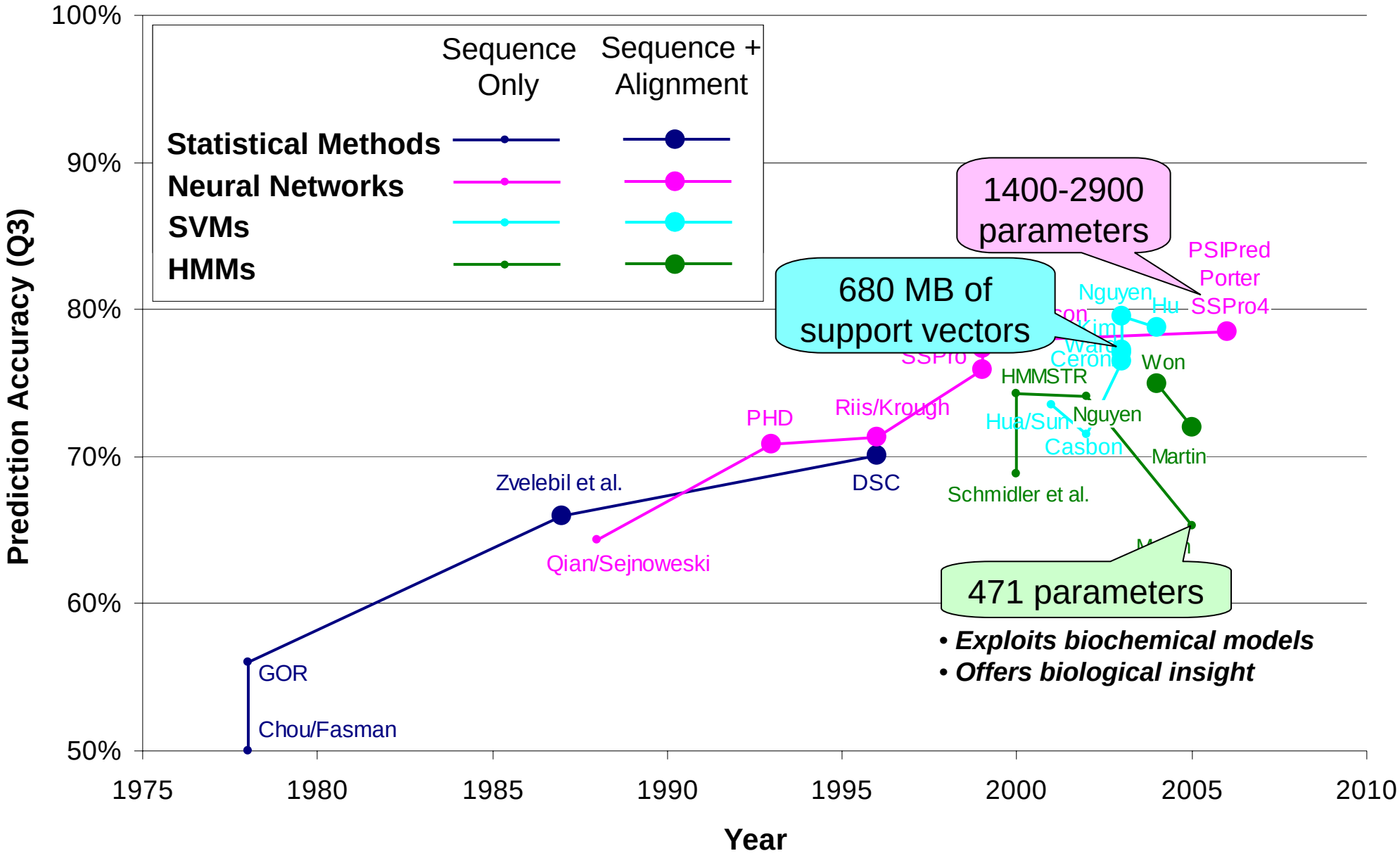

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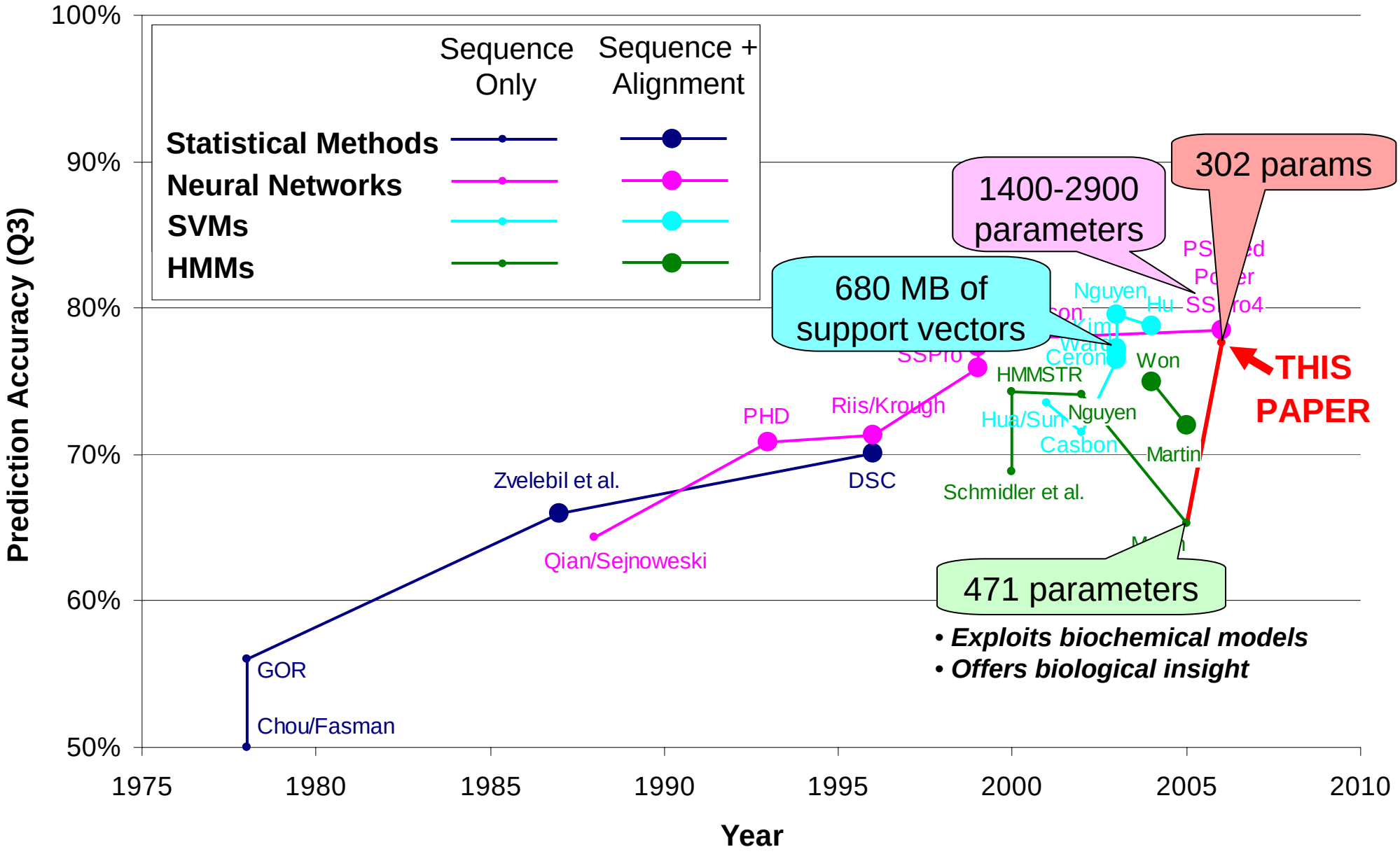
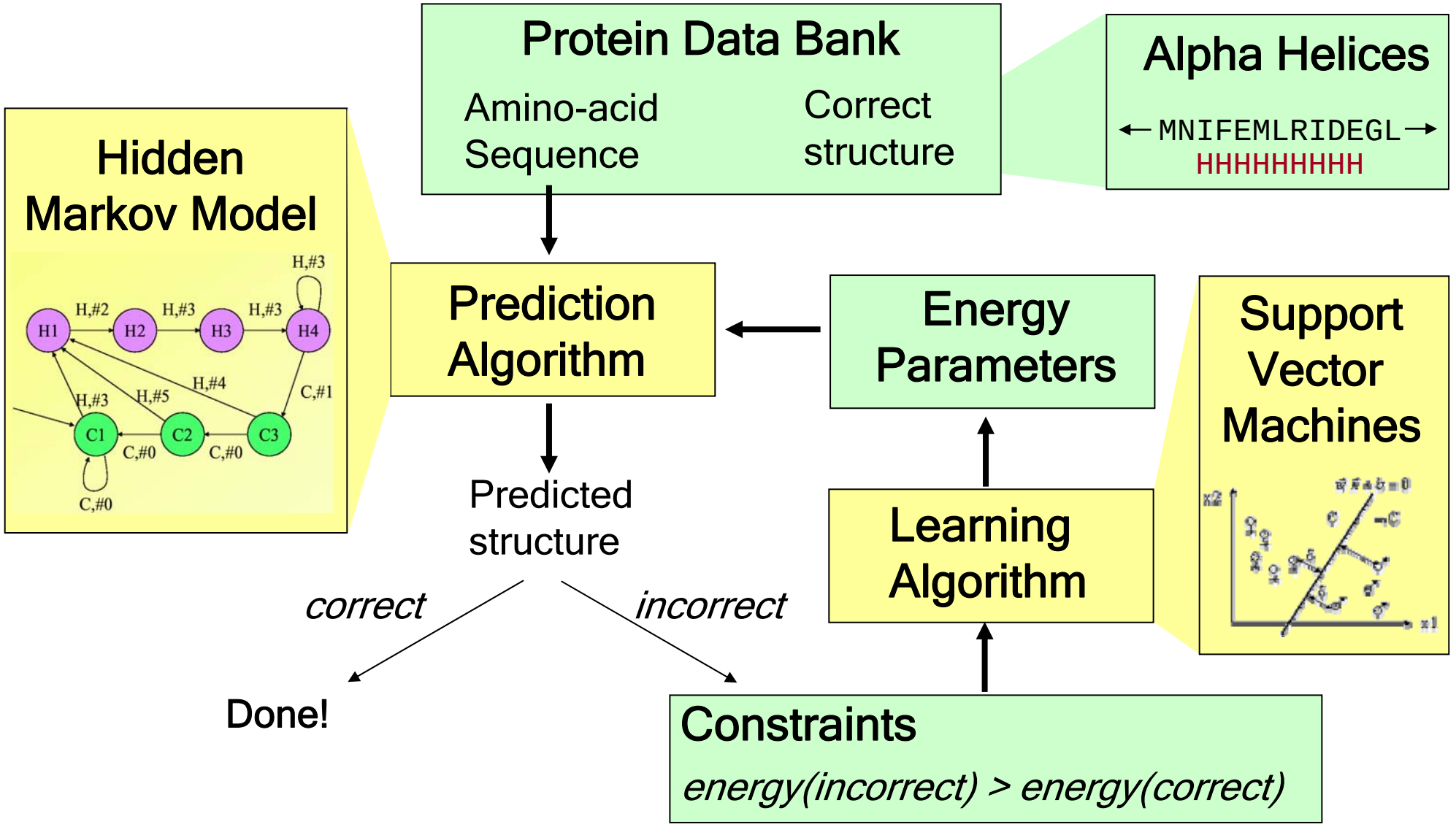


Our Framework Applied to Helix Prediction



Energy Parameters

Description of Energy Parameters	Number of Parameters	Name
Energy of residue R in a helix	20	H_R
Energy of residue R at offset i (-3…3) from N-cap	140	$N_{R,i}$
Energy of residue R at offset i (-3…3) from C-cap	140	$C_{R,i}$
Penalty for coils of length 1 or 2	2	
	302 Total	

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- **Example:**

  Sequence: **MNIFELRIDEGL**

  Structure: **HHHHHH**

  Energy =

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- **Example:**

  Sequence: **MNIFELRIDEGL**

  Structure: **HHHHHH**

  Energy = $H_F + H_E + H_L + H_R + H_I + H_D$ (Helix)

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$$\text{Energy} = H_F + H_E + H_L + H_R + H_I + H_D \quad \text{(Helix)}$$

$$+ N_{M,-3} + N_{N,-2} + N_{I,-1} + N_{F,0} + N_{E,1} + N_{L,2} + N_{R,3} \quad \text{(N-cap)}$$

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$$+ C_{L,-3} + C_{R,-2} + C_{I,-1} + C_{D,0} + C_{E,1} + C_{G,2} + C_{L,3} \quad \text{(C-cap)}$$

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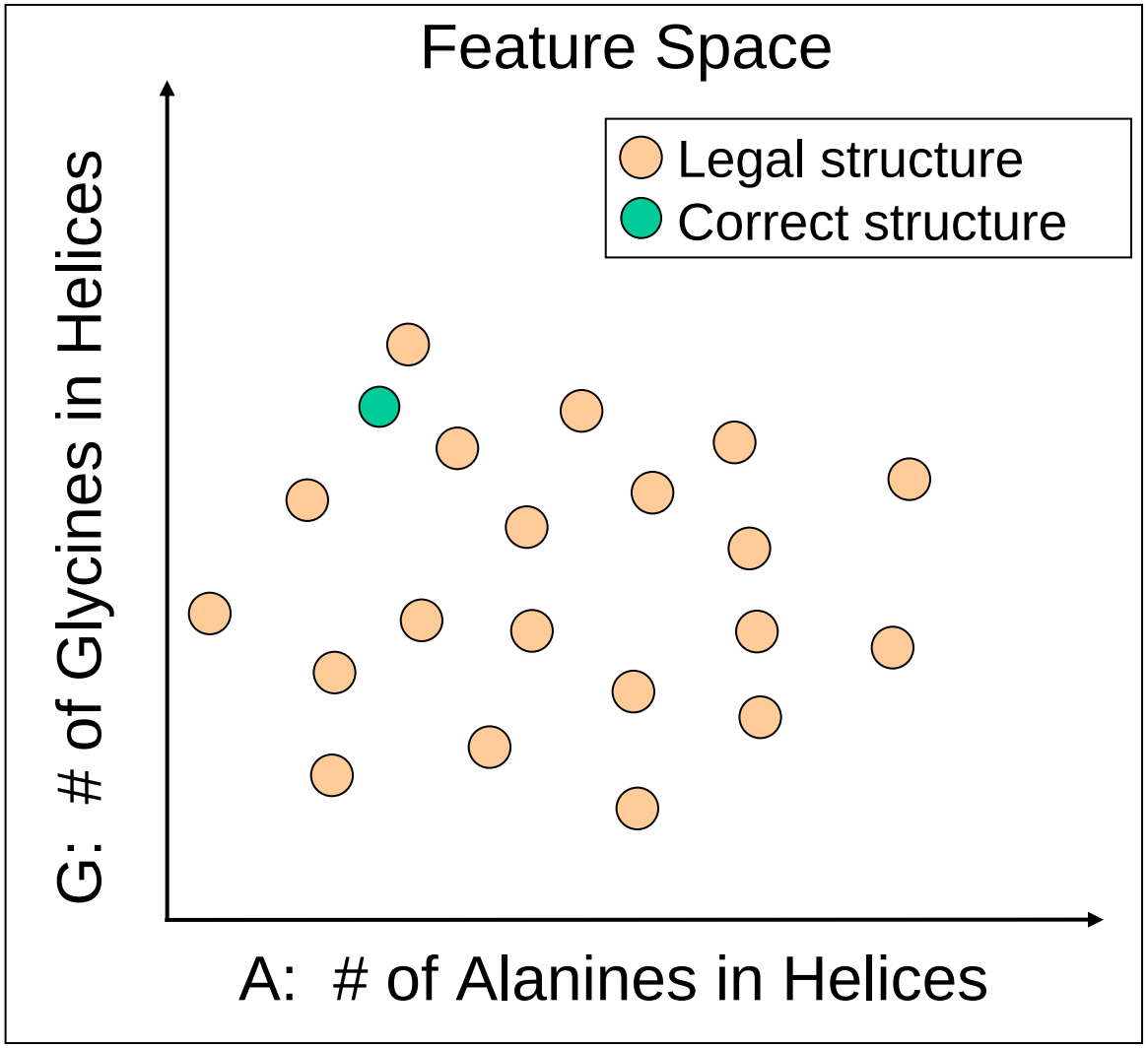
$$+ C_{L,-3} + C_{R,-2} + C_{I,-1} + C_{D,0} + C_{E,1} + C_{G,2} + C_{L,3} \quad \text{(C-cap)}$$

Learning the Parameters



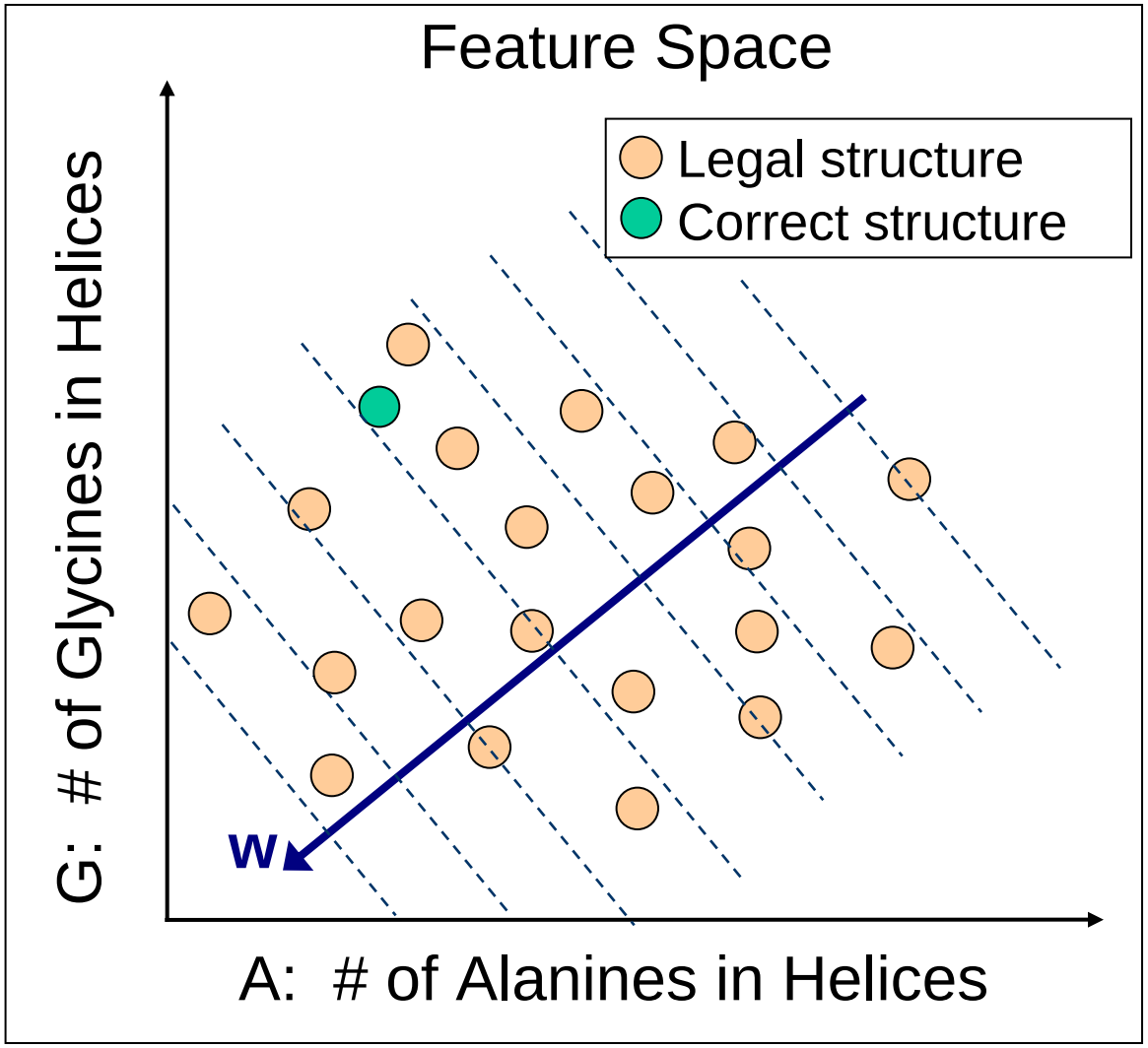
Energy (○) = H_A*A + H_G*G

= **w** · [A G]

where **w** represents the energy parameters [H_A H_G]

Highest energy in direction of energy parameters **w**

Learning the Parameters



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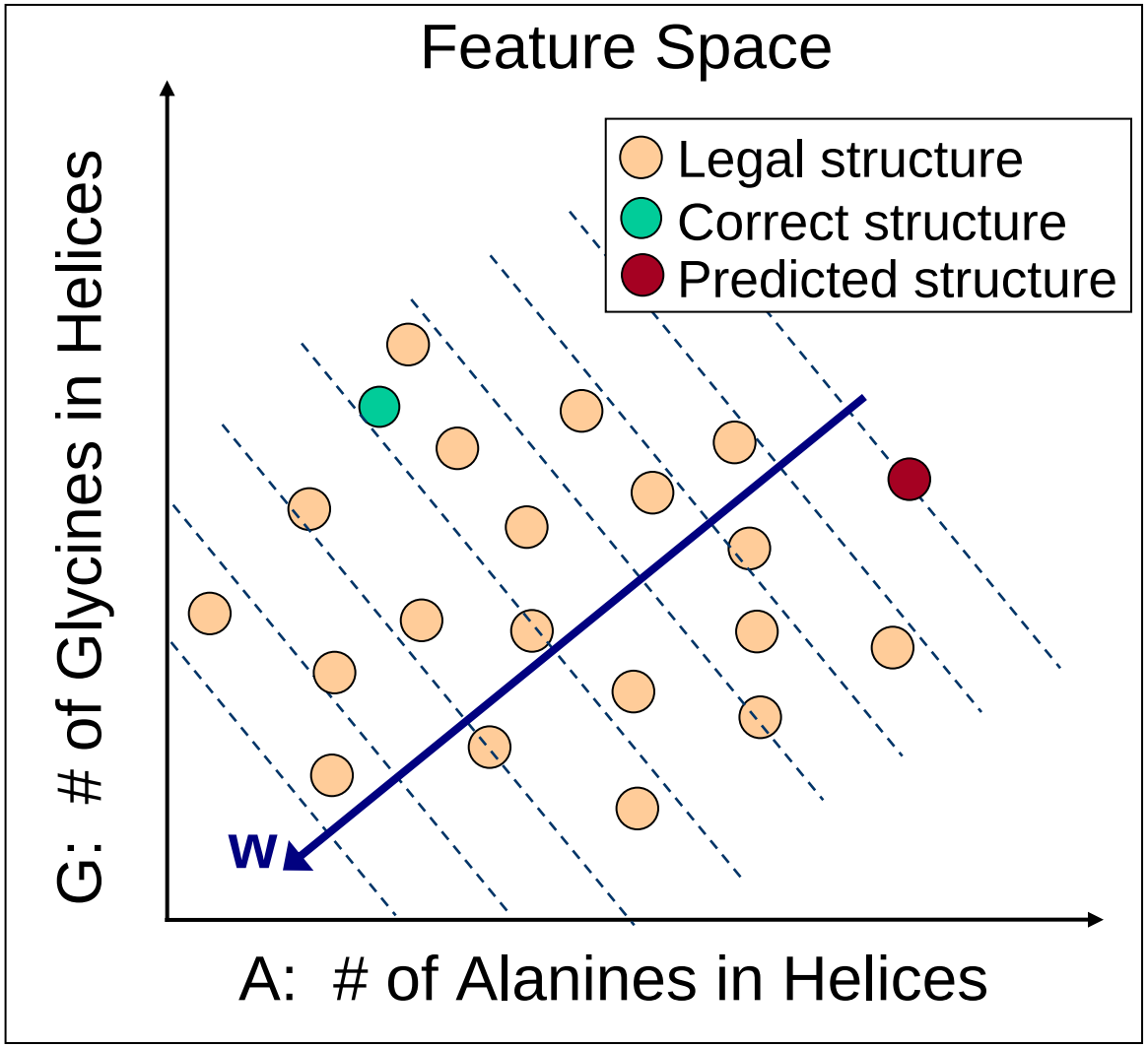
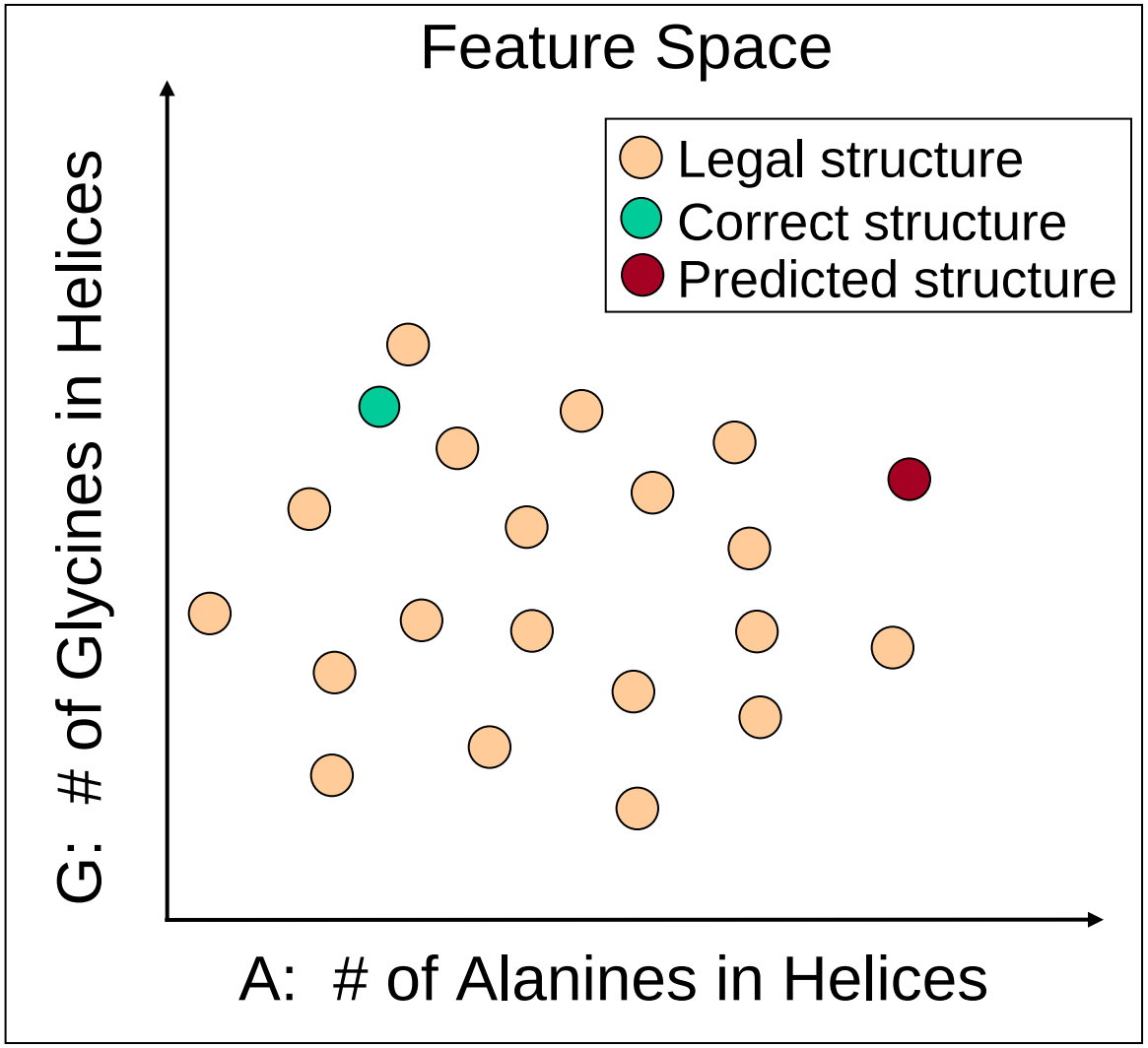
Learning the Parameters



1. Predict stucture

Learning the Parameters



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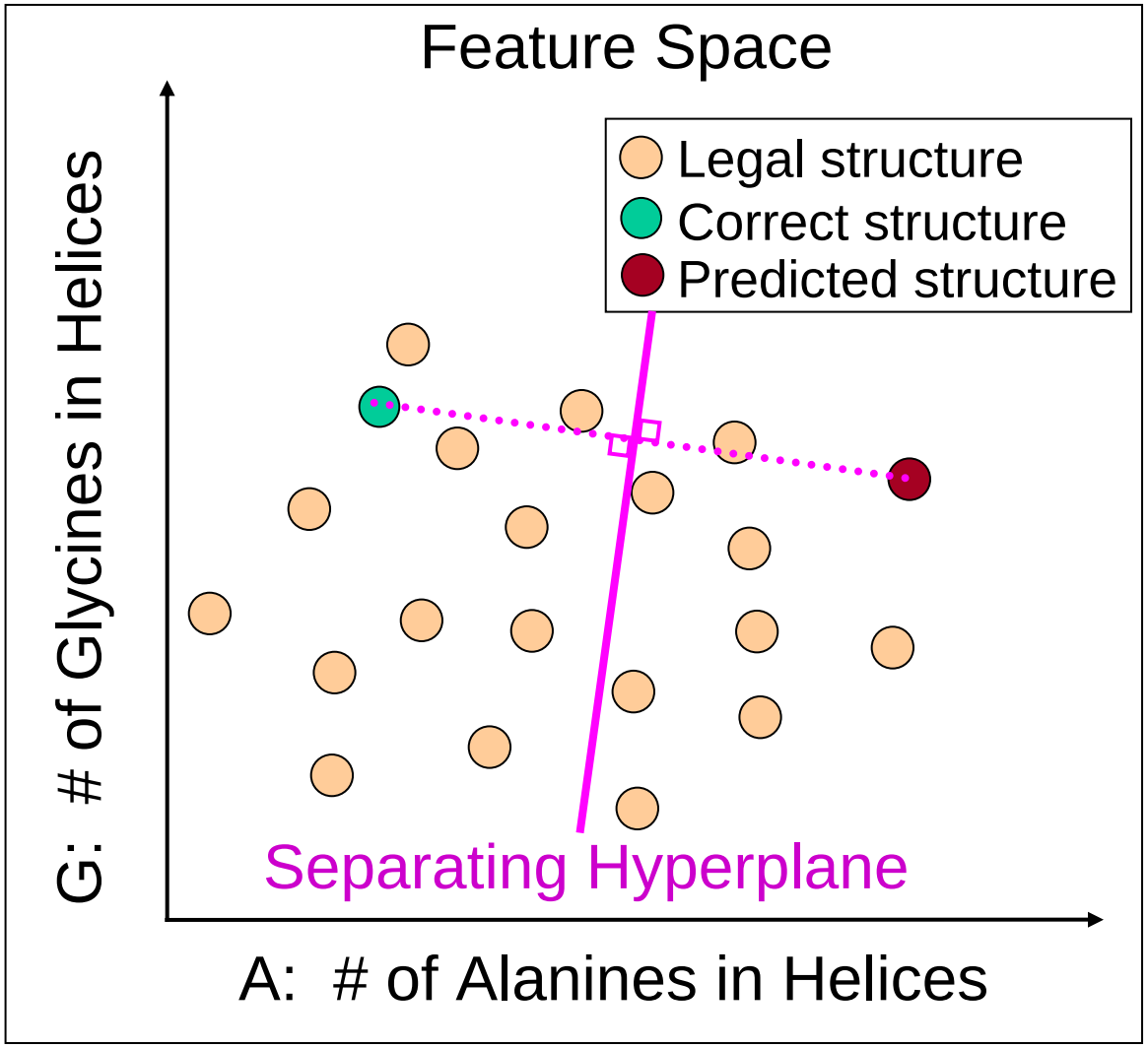
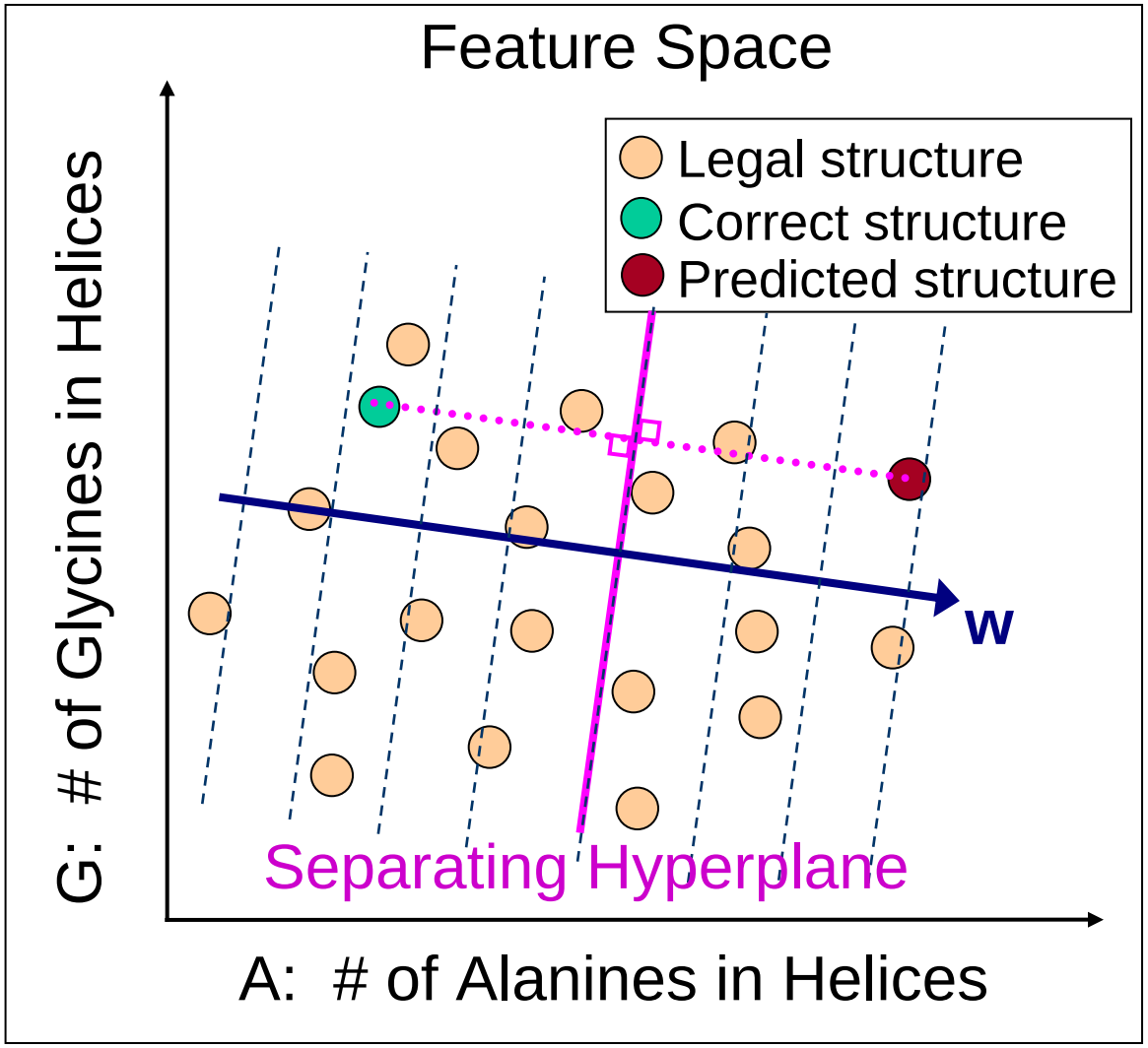


1. Predict stucture
2. Refine parameters

Learning the Parameters



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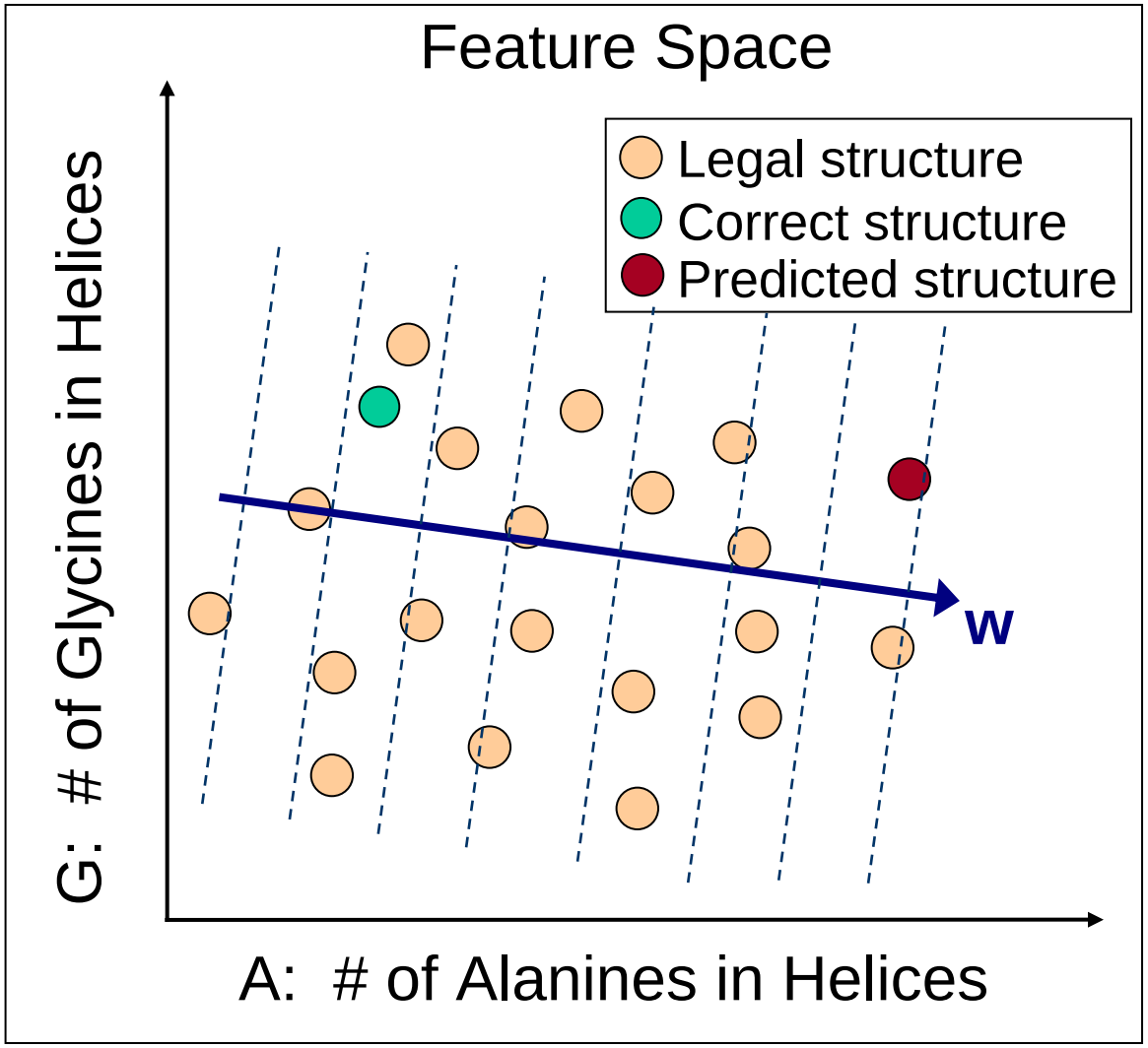

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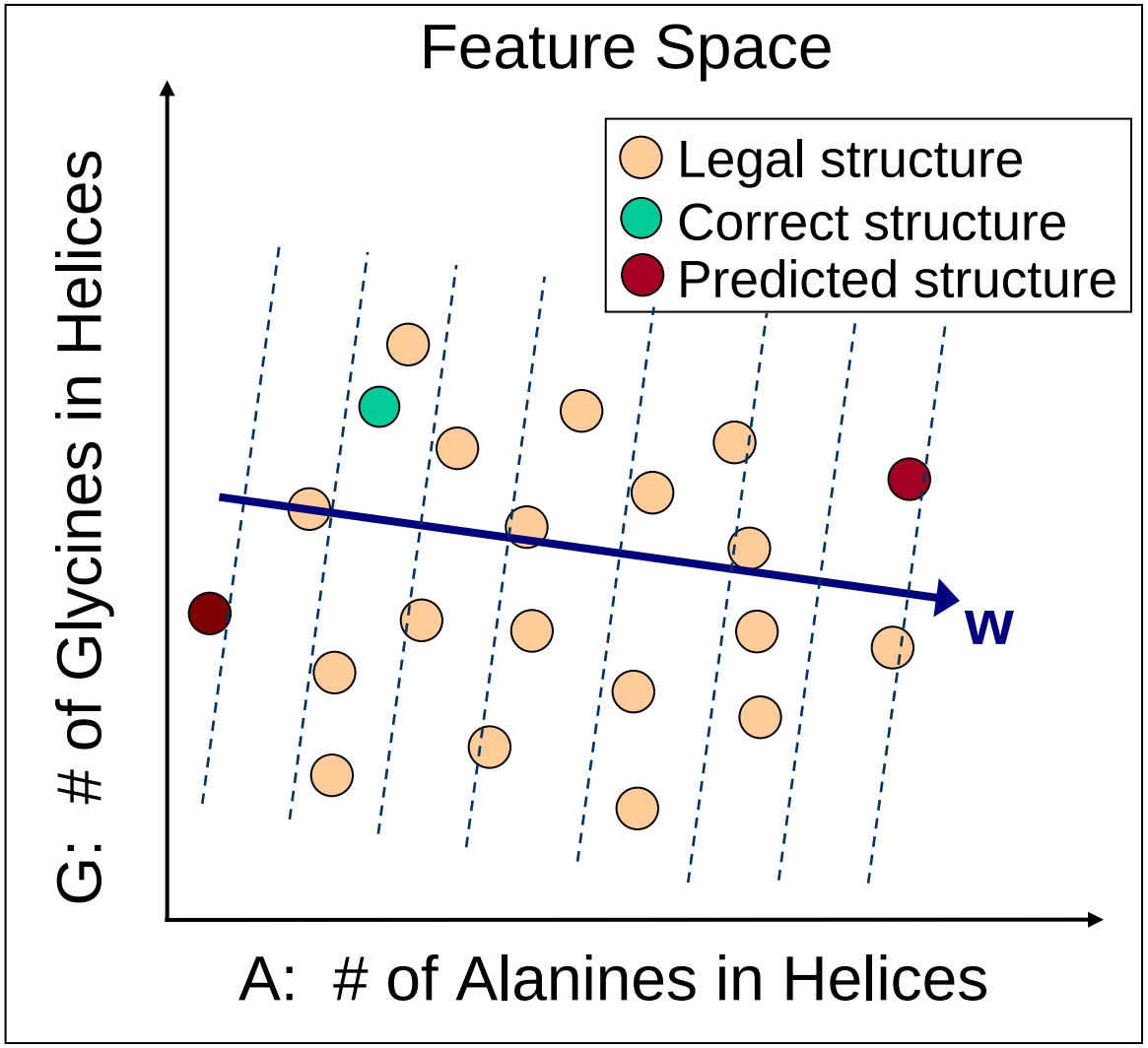

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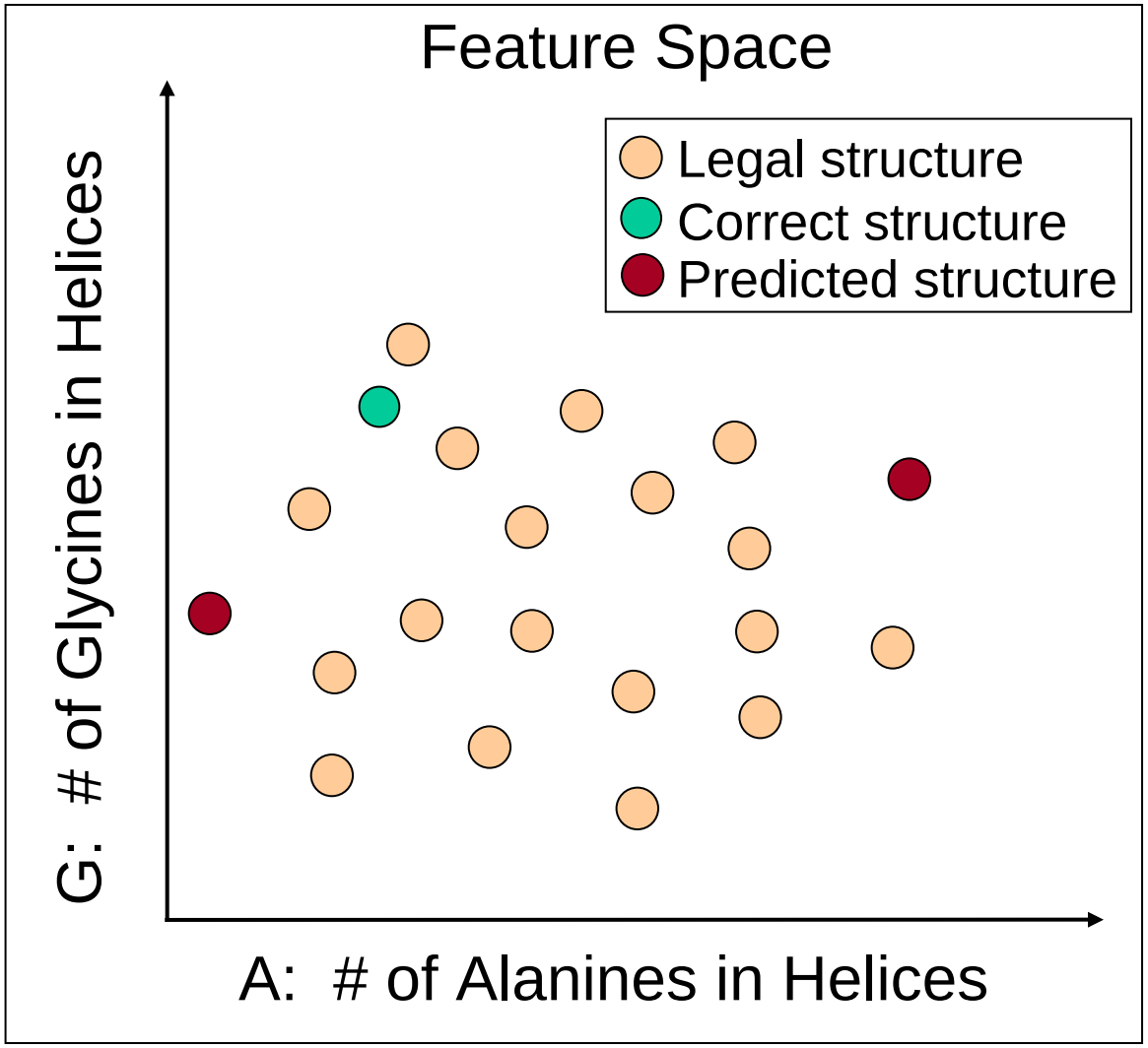

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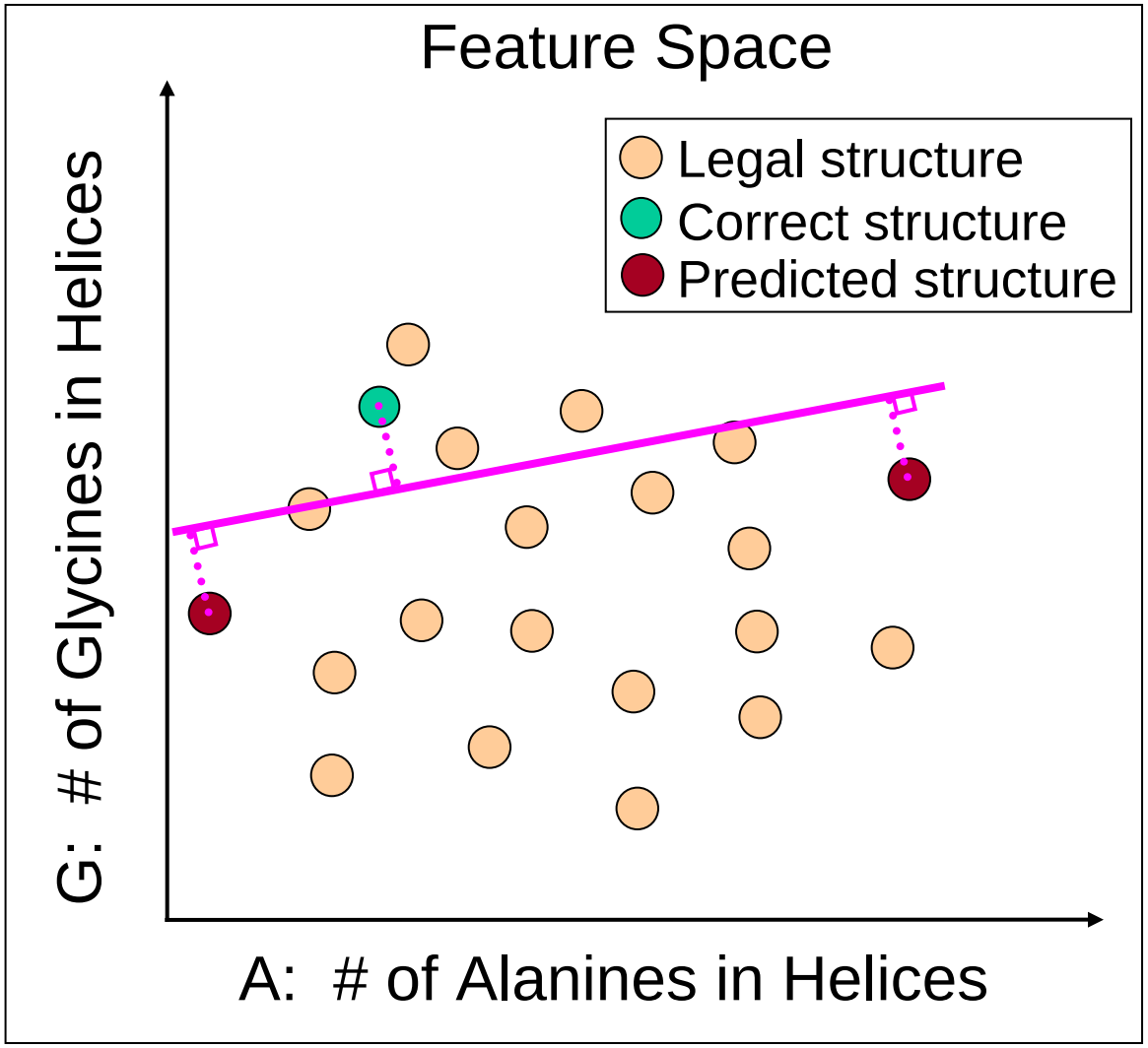

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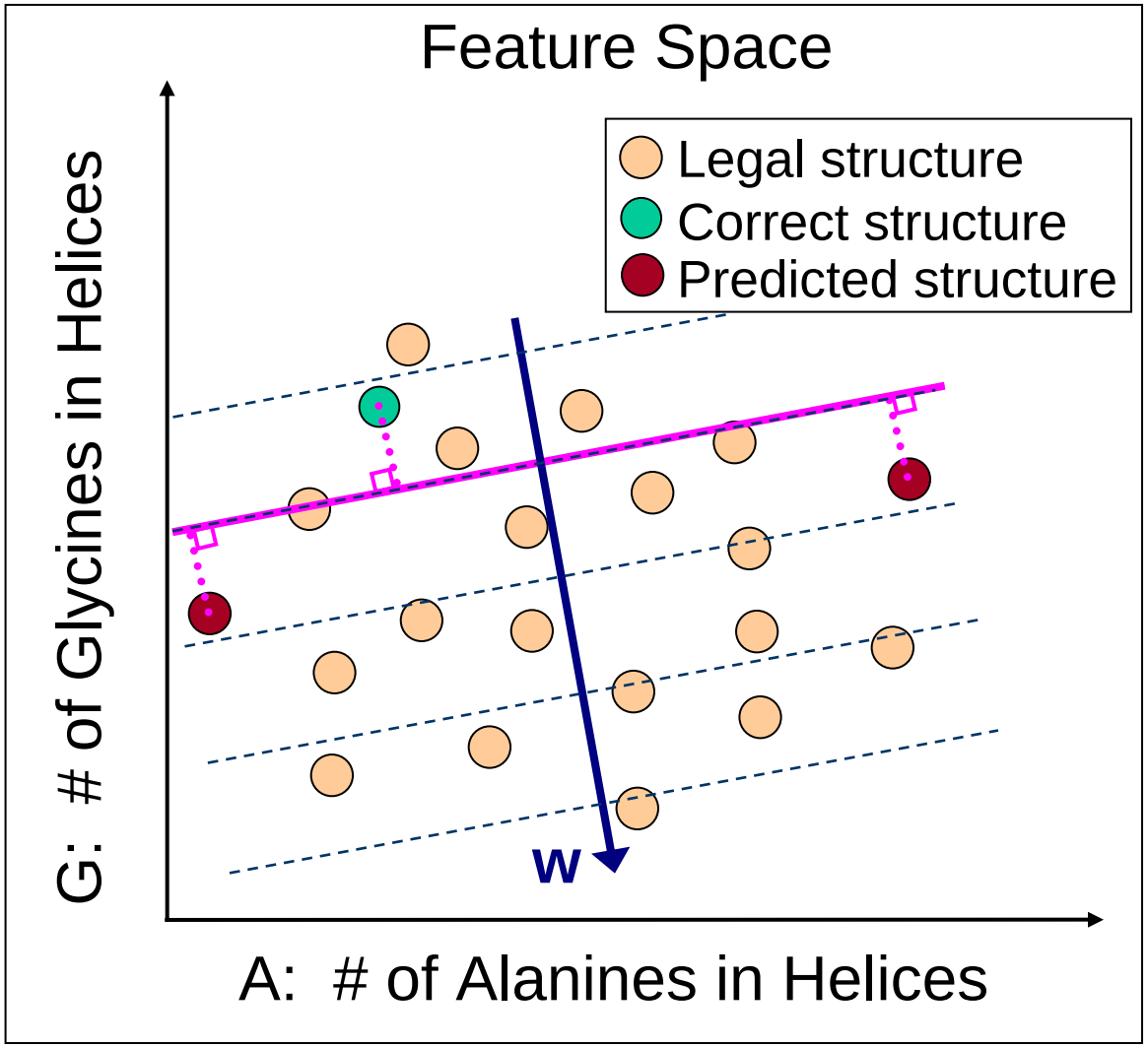

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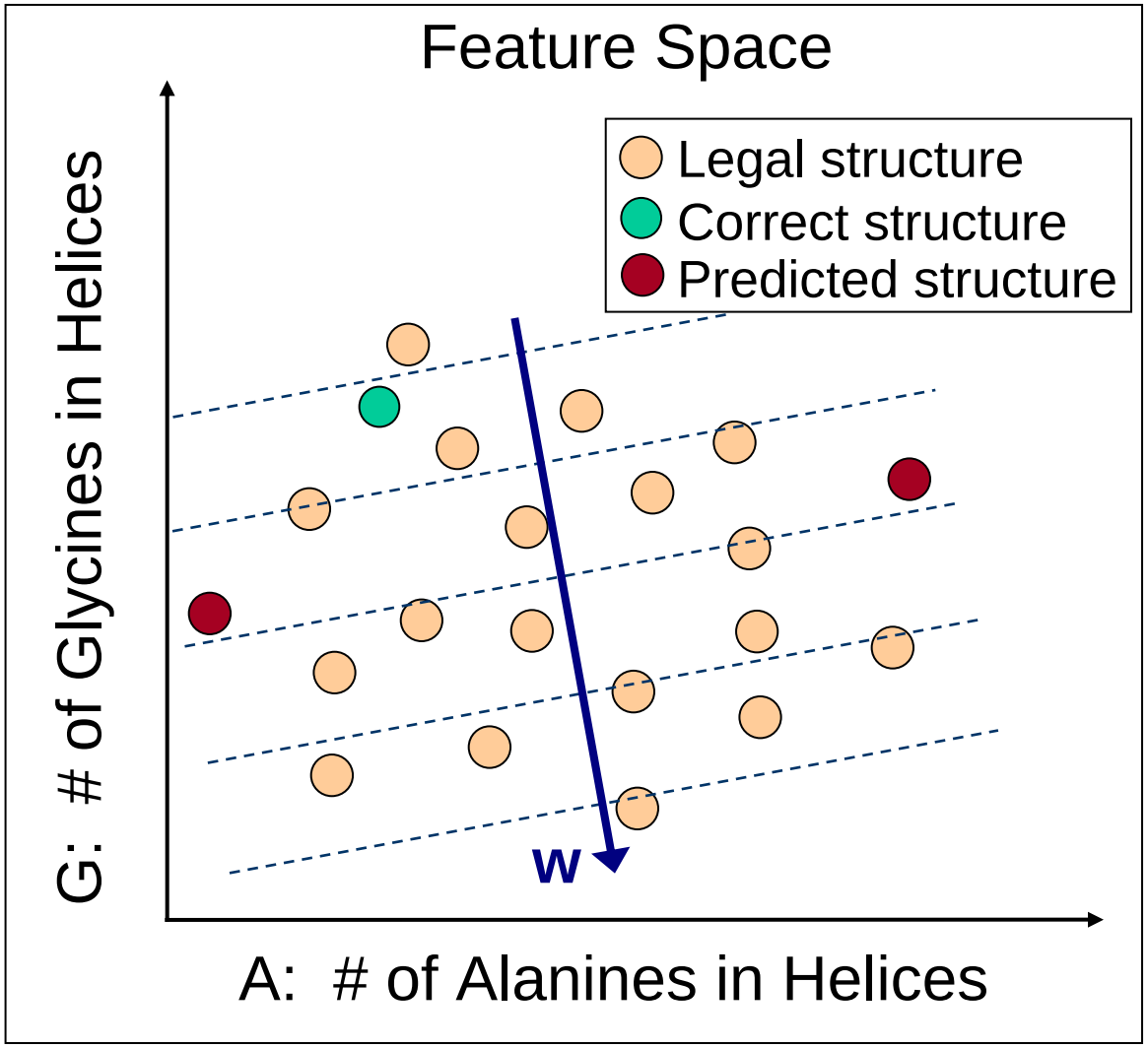

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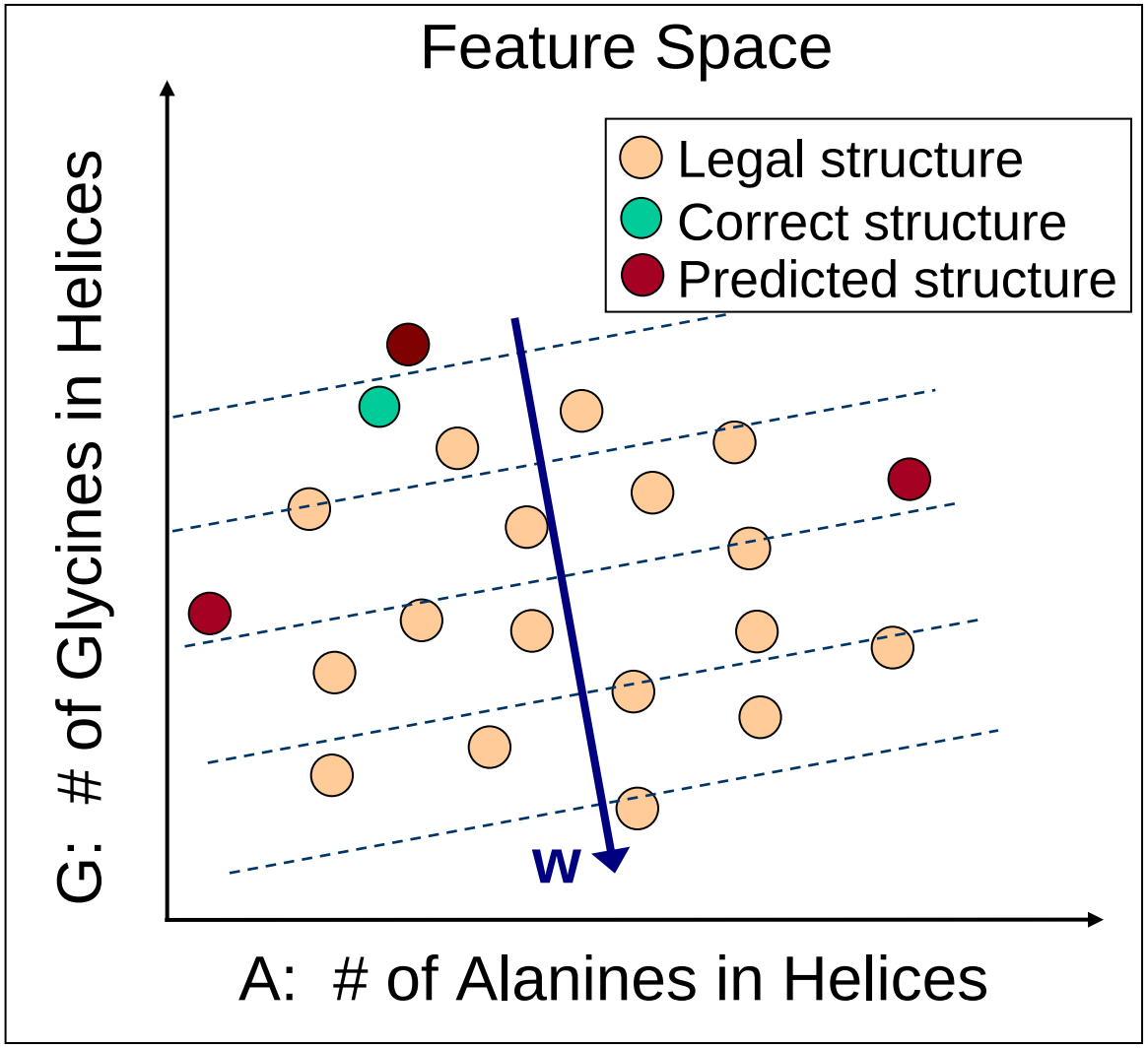

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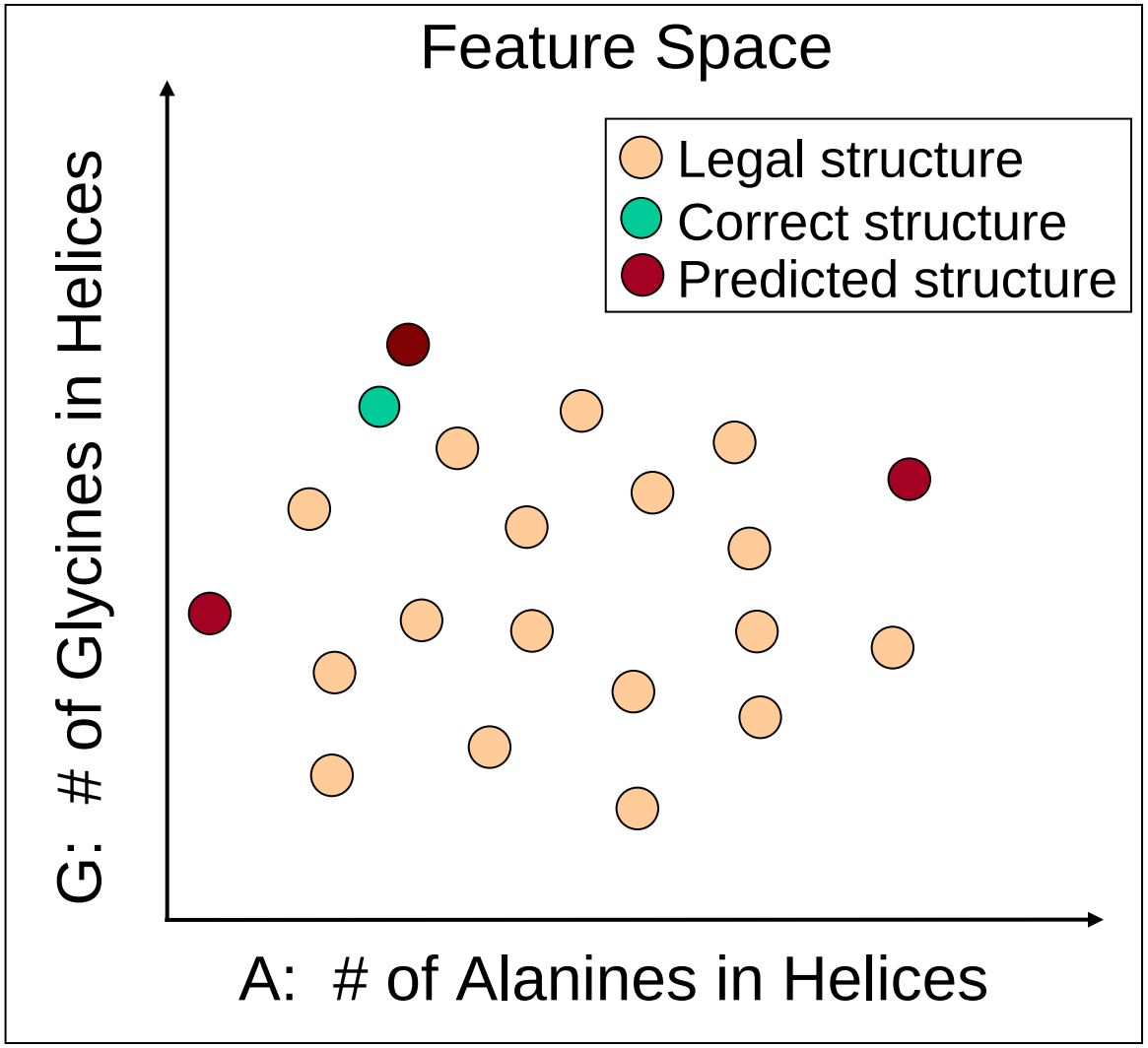
Learning the Parameters



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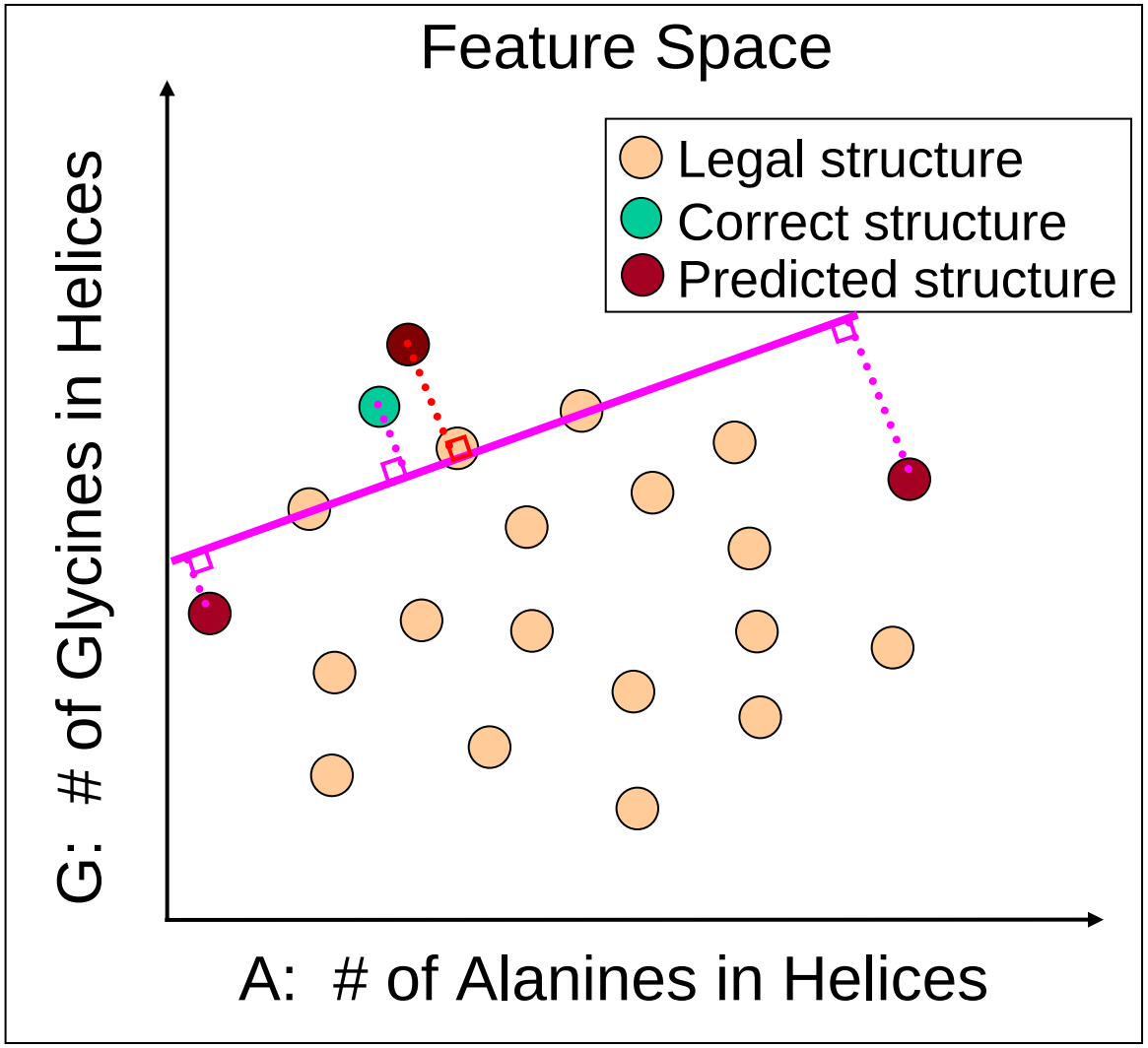

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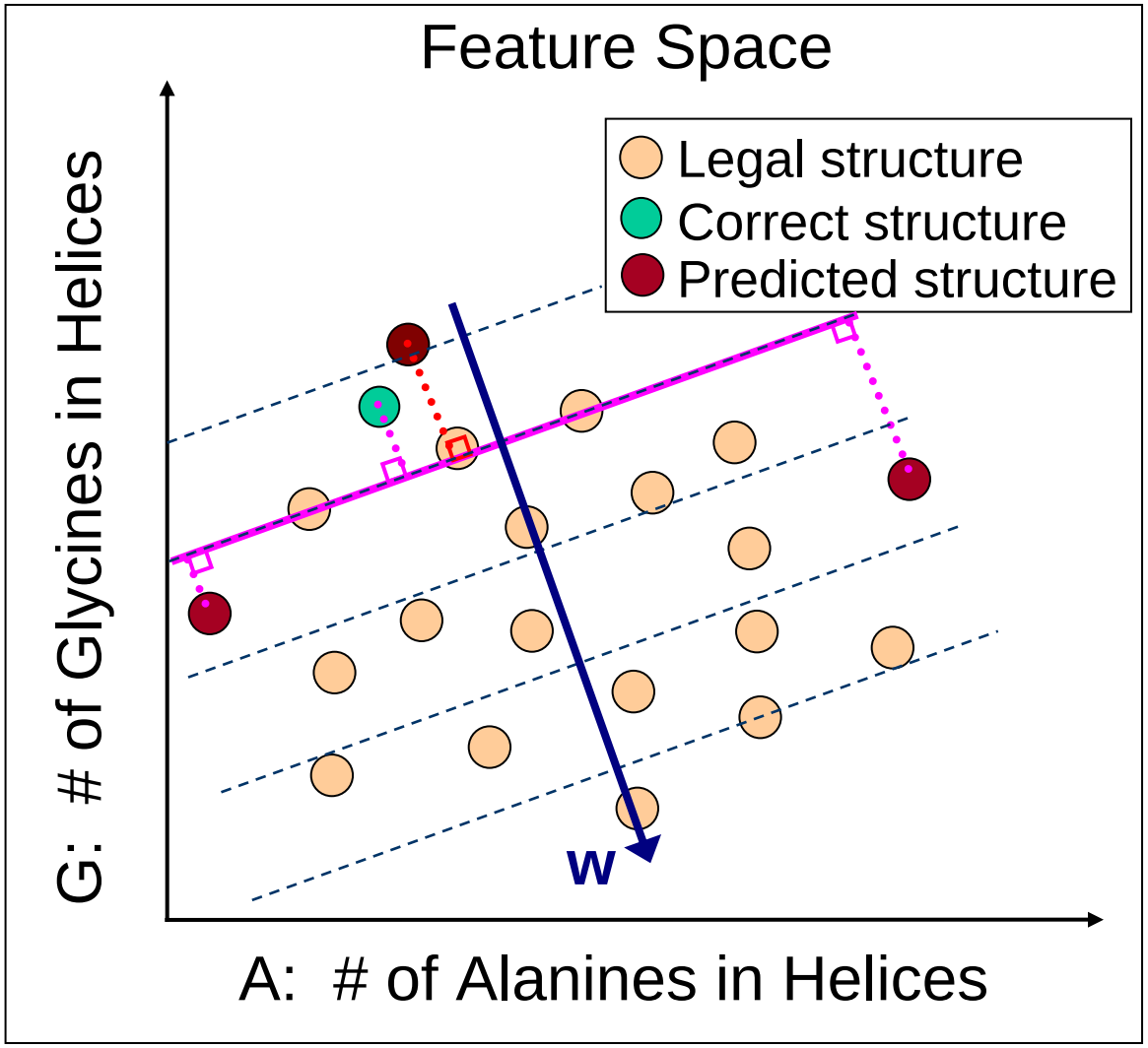
6. Refine parameters

Learning the Parameters



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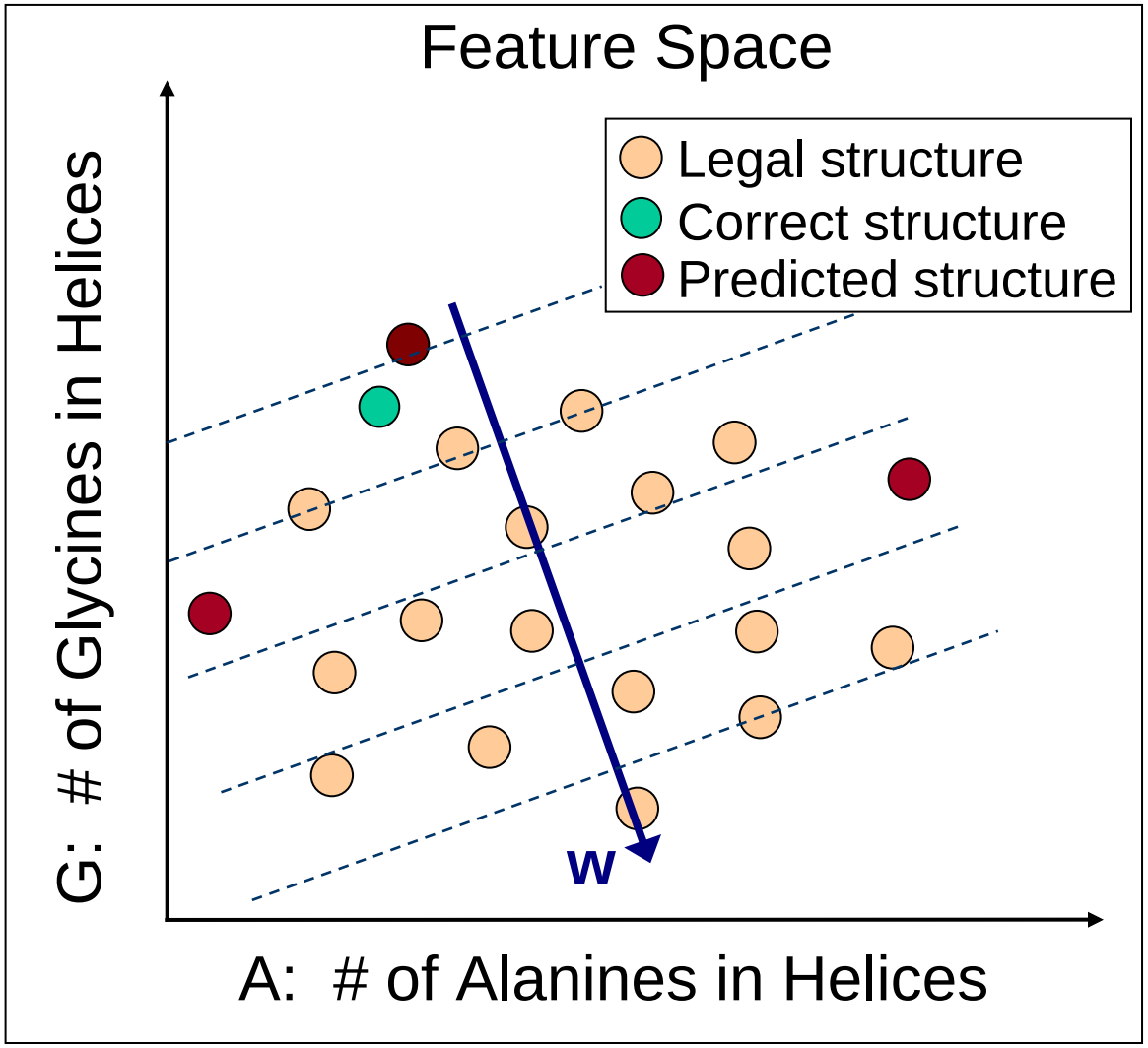

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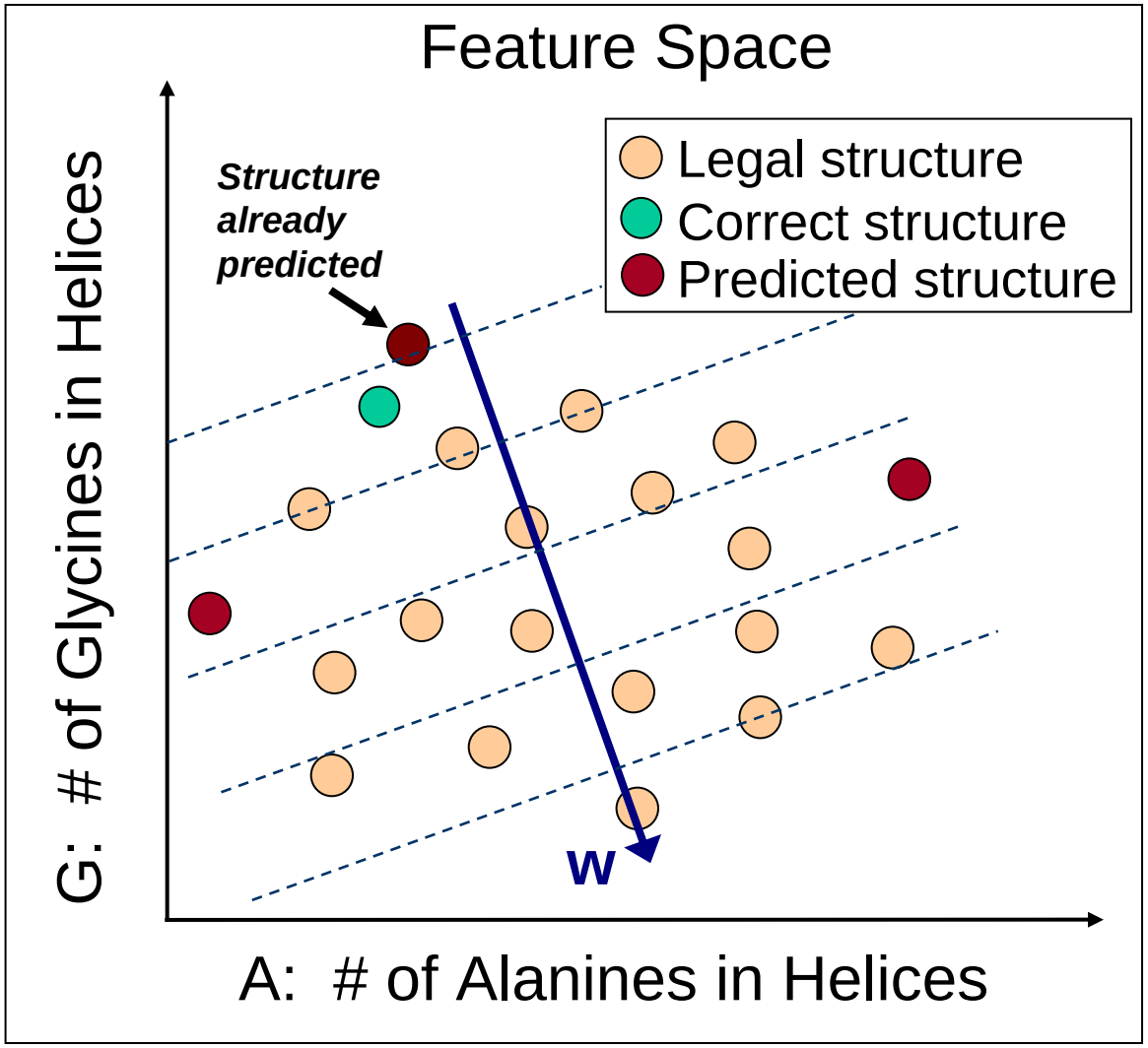

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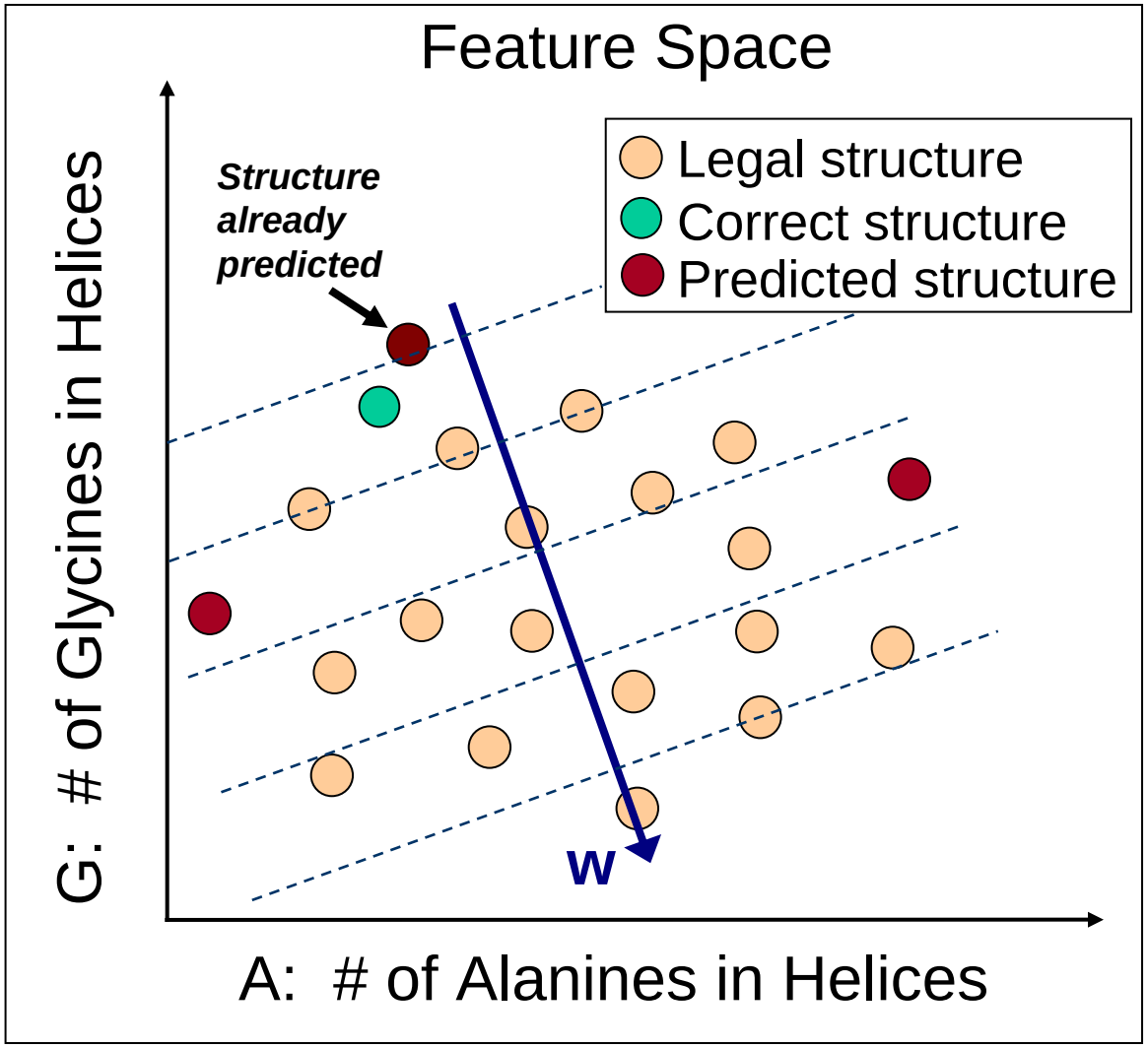
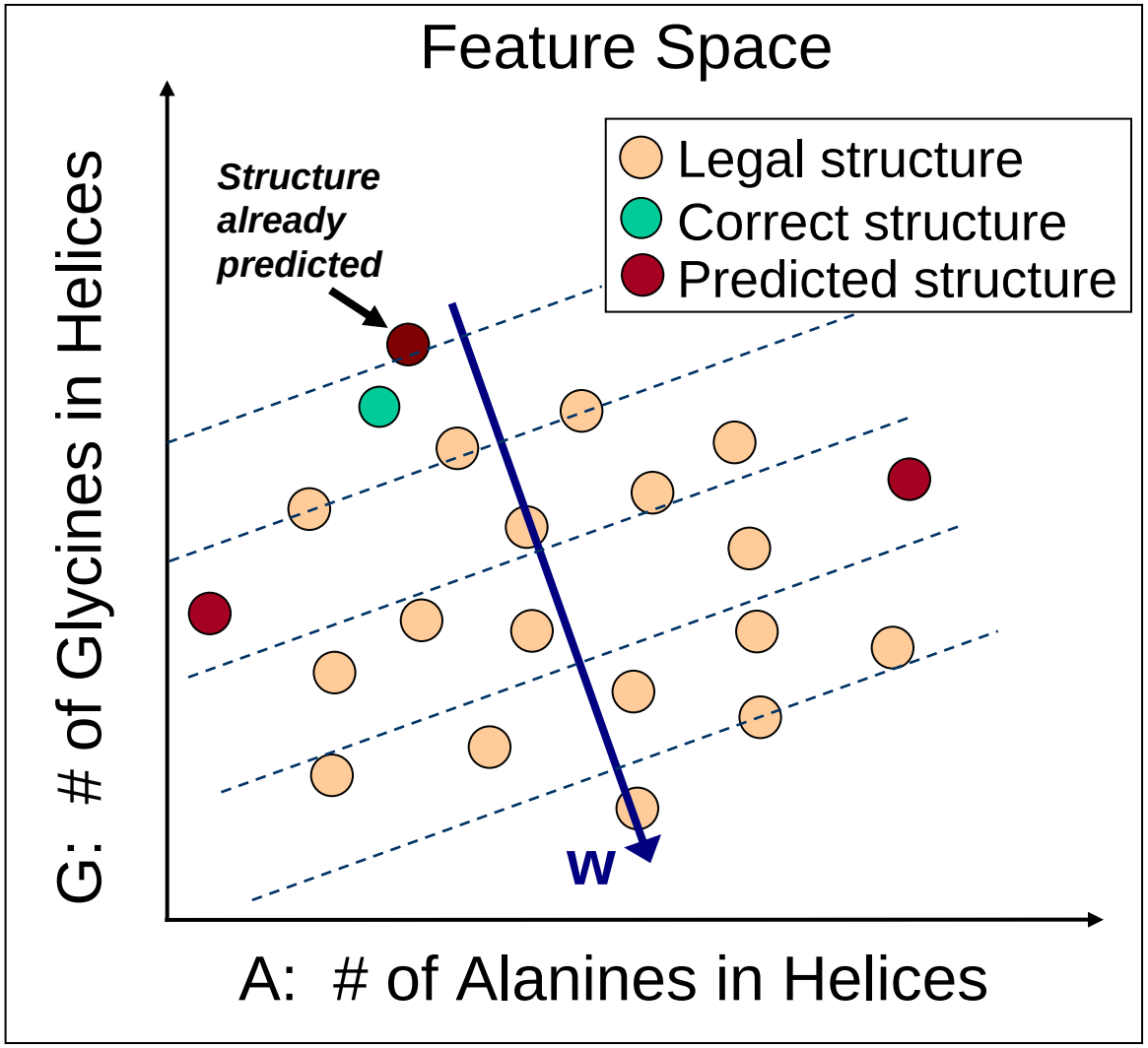
Learning the Parameters



1. Predict stucture
2. Refine parameters
3. Predict structure
4. Refine parameters
5. Predict structure
6. Refine parameters
7. Predict structure
8. Terminate

Learning the Parameters



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Details in paper:

- How to converge faster
- Early termination condition
- [Tsochantaridis et al., ICML'02]

Experimental Methodology

- **Data set: 300 non-homologous all-alpha proteins**
  - From EVA's sequence-unique subset of the PDB, July 2005
  - Only consider alpha helices ("H" symbol in DSSP)
- **Randomly split into 150 training, 150 test proteins**

Results

Metric	Value	Explanation
Q_α	77.6%	percent of residues correctly predicted
SOV_α	73.4%	segment overlap measure [Zemla'99]

- **Comparison to others**
  - **Best HMM method to date** that does not utilize alignment info
    - Offers 3.5% (Q_α), 0.2% (SOV_α) over previous best [Nguyen02]
  - Lags behind neural networks; e.g., Porter overall SOV = 76.6%
  - However, we could likely gain 6-8% from alignment profiles
- **Caveats**
  - Moving beyond all-alpha proteins, we could suffer 3% [Rost93]
  - By considering 3/10 helices, we could decrease 2% [Jones99]

Conclusions

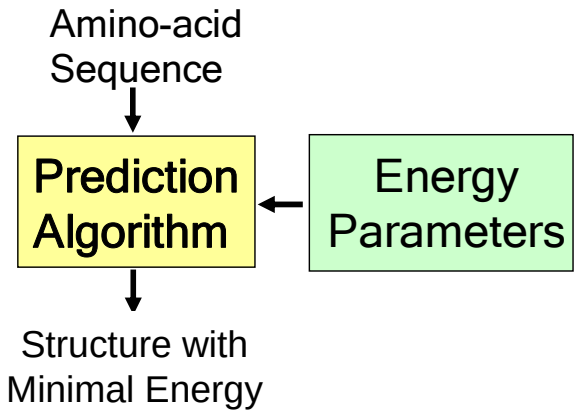
- **Represents first step toward learning biophysical parameters for energy minimization techniques**
  - Iterative, demand-driven learning process using SVMs
- **Promising results on alpha-helix prediction**
  - 77.6% among best Q_α for methods without alignment info
- **Future work: super-secondary structure**
  - Will predict full “contact maps” rather than 3-state labels
  - For beta sheets, replace HMMs by multi-tape grammars

http://protein.csail.mit.edu/

Extra Slides

Prediction Algorithm

- **Parameters represent energetic benefit of a given feature in a protein structure**
  - Features are fixed, chosen by designer
  - Example features:
    - Number of prolines in an alpha helix
    - Number of coils shorter than 2 residues



- **Energy (structure) = $\sum_{\text{features} \in \text{structure}}$ Energy (feature)**
- **Minimal-energy structure found with dynamic prog.**
  - Idea: consider all structures, exploiting overlapping problems
  - Implemented as HMM using Viterbi algorithm

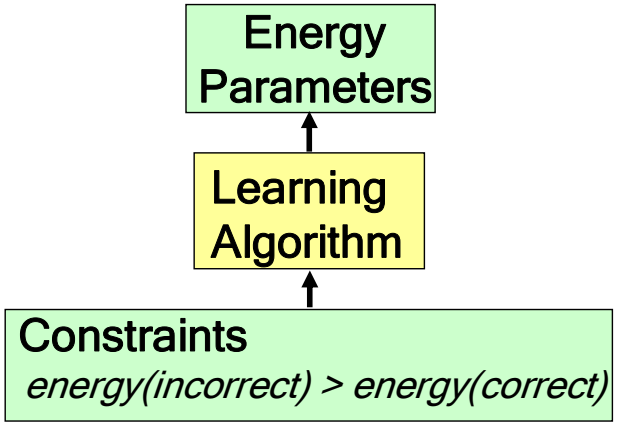
Learning Algorithm

- **Constraints have form:**

  For all incorrectly predicted structures S_i,

  in future selection of the parameters **w**:

  $\text{Energy}_w(S_i) > \text{Energy}_w(\text{correct structure})$



  Constraints are linear in the energy parameters.

- **If feasible, could solve with linear programming**
- **In general, solve with Support Vector Machines (SVMs)**
  - $\text{Energy}(S_i) \geq \text{Energy (correct structure)} + 1 - \xi_i \qquad (\xi_i \geq 0)$
  - Find parameters **w** minimizing $\frac{1}{2} \|\mathbf{w}\|^2 + C/n \sum_{i=1}^{n} \xi_i$

  ➡ Provides general solution using soft-margin criterion