Supervised Ensembles of Prediction Methods for Subcellular Localization

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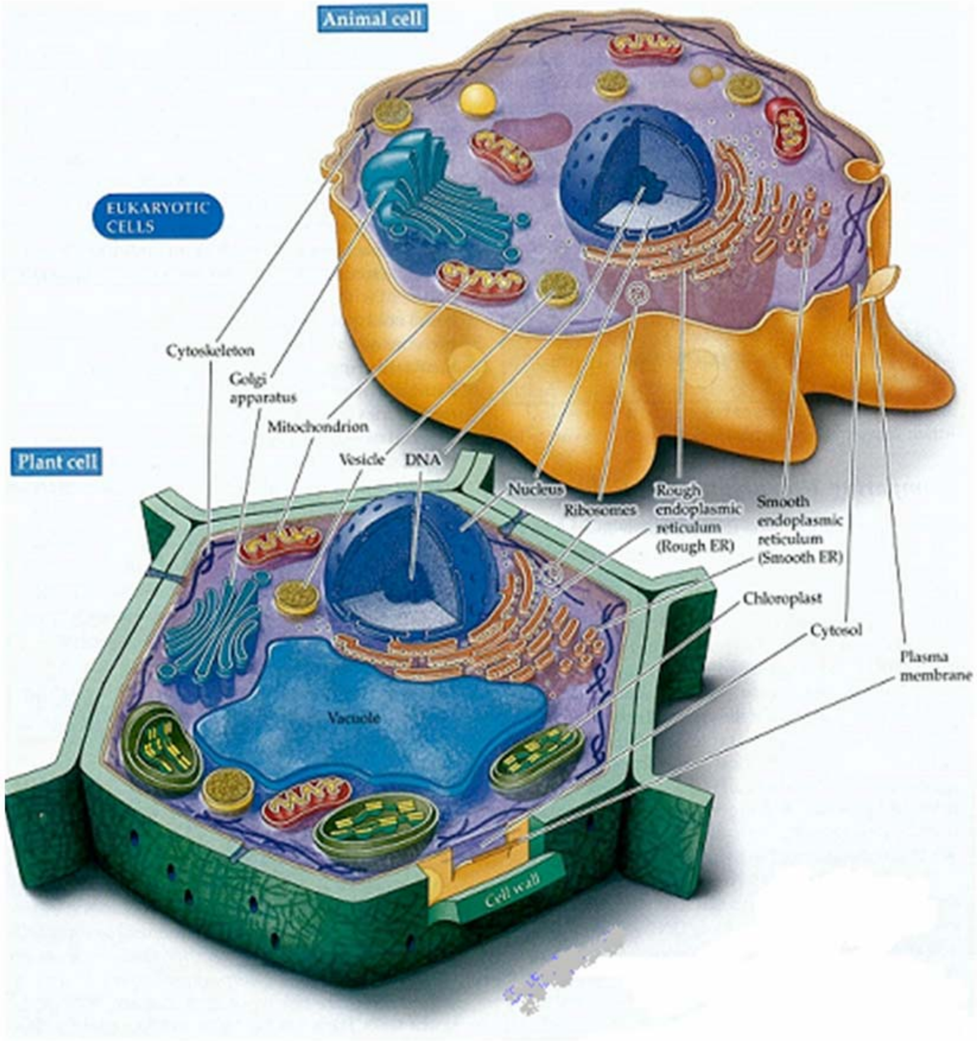
Outline

- Background
- Localization Prediction Methods
- Ensemble Methods (Theory)
- Supervised Ensemble Methods
  - Ensemble using a Voting Schema
  - Ensemble based on Decision Tree
- Data and Results
- Conclusions

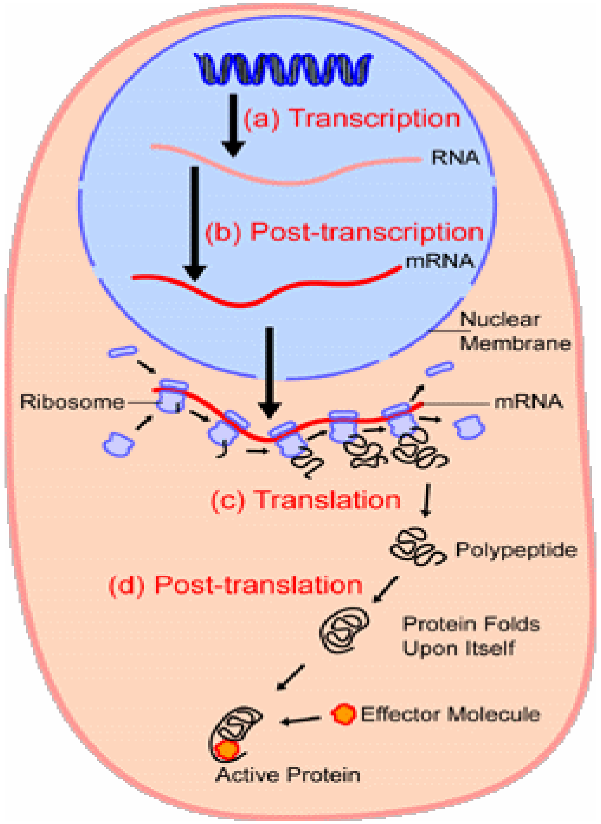
Background

- cells are organized in regions and compartments
- different regions serve different functionalities
- certain functionalities are performed by specific proteins
- proteins are adapted to the specific biophysical environment of its proper compartment



Background

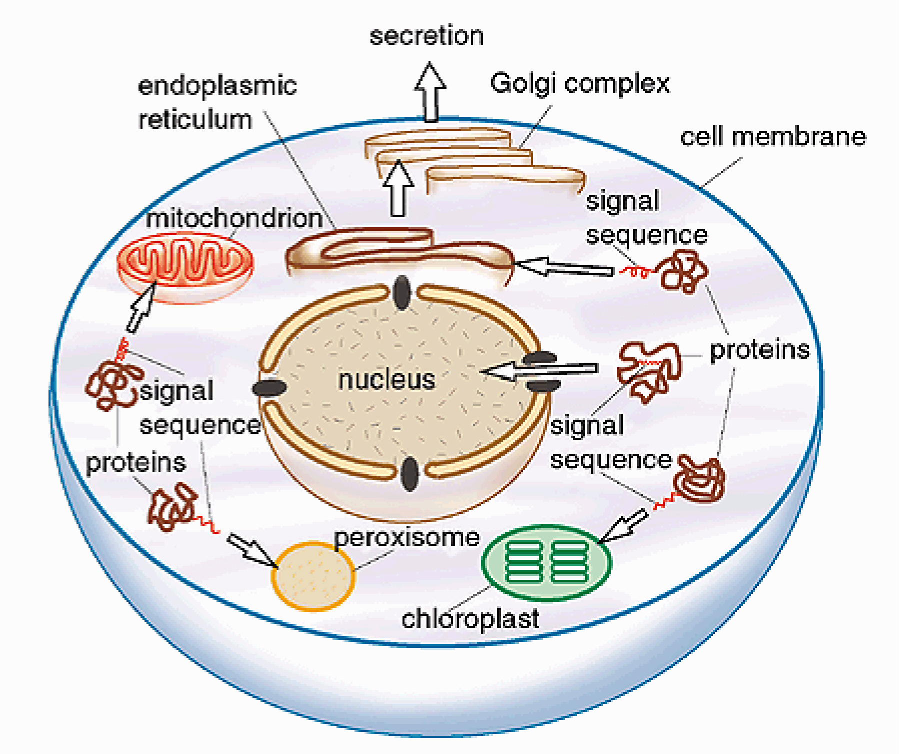
- proper function of a protein requires correct localization
- co-translational or post-translational transport of proteins into specific subcellular localizations
- highly regulated and complex cellular process

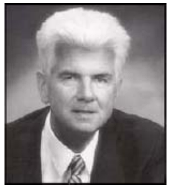


Localization Prediction Methods: Basis for Predictions

Prediction methods for subcellular localization are based on:

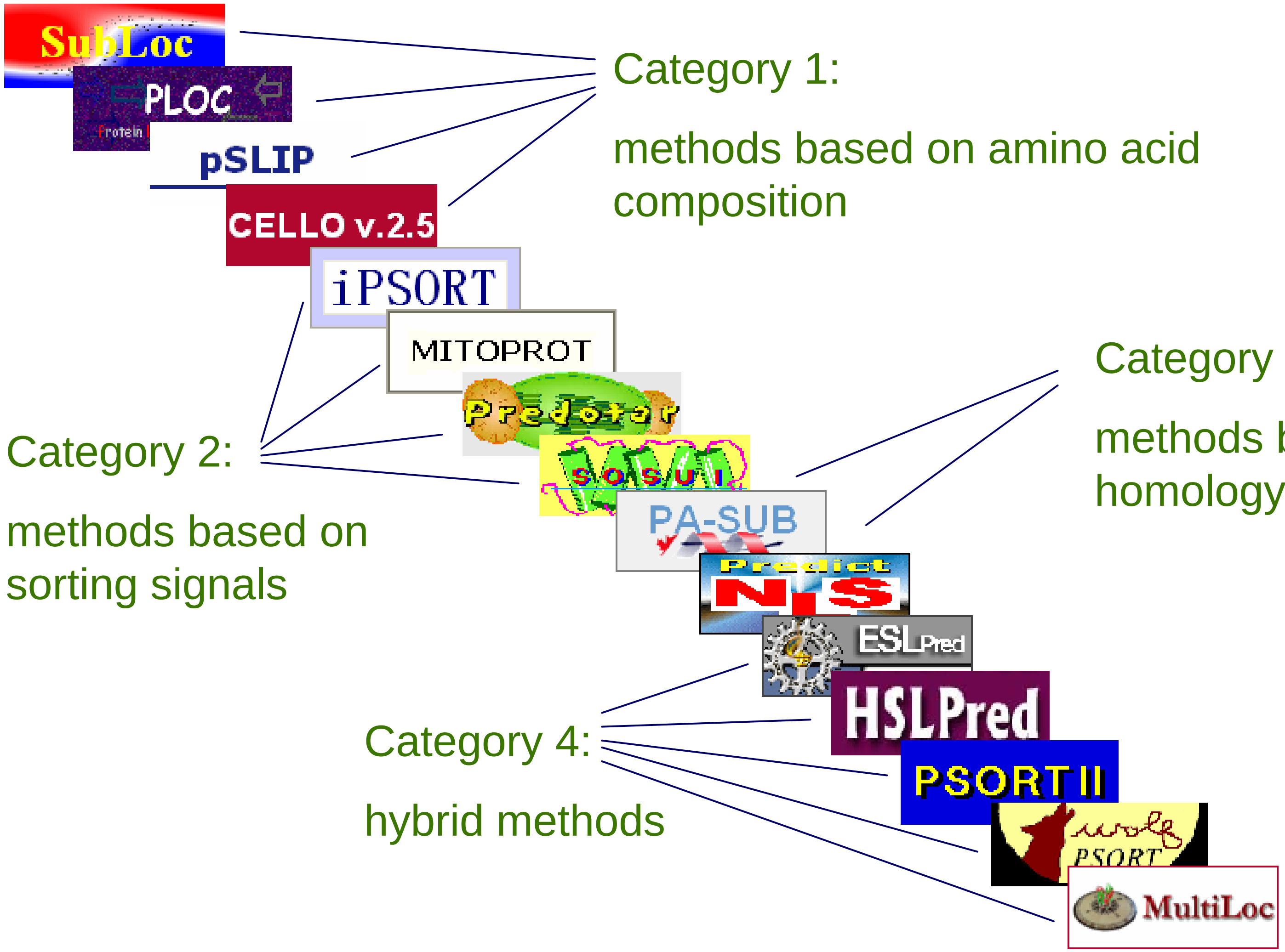
- adaptation of a protein to a certain region is reflected in amino-acid composition (surface exposed to specific milieu)
- transport and localization is guided e.g. by peptide signals
- homology of proteins





Nobel prize 1999 Günter Blobel
“proteins have intrinsic signals that govern their transport and localization in the cell”

Localization Prediction Methods: Using Different Information



Category 1:

methods based on amino acid composition

Category 2:

methods based on sorting signals

Category 3:

methods based on homology search

Category 4:

hybrid methods

Localization Prediction Methods: Different Computational Basis

- naïve Bayes
- Bayes networks
- k-nearest neighbor methods
- SVM
- neural networks
- rules

Localization Prediction Methods: Different Limitations of Methods

- Localization coverage
  - e.g. “SubLoc” predicts 4 localizations
  - “PLOC” predicts 12 localizations
- Taxonomic coverage
  - e.g. “HSLPred” predicts for human proteins
  - “PLOC” predicts for plant, animal and fungi proteins
- Sequence coverage
  - e.g. “ESLPred (2004)” and “SubLoc (2001)” used data set generated by another method “NNPSL” in 1998

Localization Prediction Methods: Different Limitations of Methods

- different means to assess the accuracy in publications
- inexact assignment of localizations for methods based on sorting signals
  - secretory pathway → E.R. / Golgi / Lysosome / Extracellular
- strong dependence on the quality of N-terminal sequence assignment for methods based on sorting signals
- strong dependence on the existence of homologous protein for methods based on homology search

Ensemble Methods: Theory (unsupervised)

- Ensemble methods combine several self-contained classifiers to gain better accuracy.
- Prerequisites to enhance accuracy by combination of base classifiers:
  - the single base classifier is “accurate” (i.e., better than random)
  - the base classifiers differ:
    - statistical variance (different prediction models perform equally well on training data)
    - computational variance (using different heuristics to overcome computational restrictions)
    - different bias
  - effect: the base classifiers make different (uncorrelated) errors

Ensemble Methods: Theory (unsupervised)

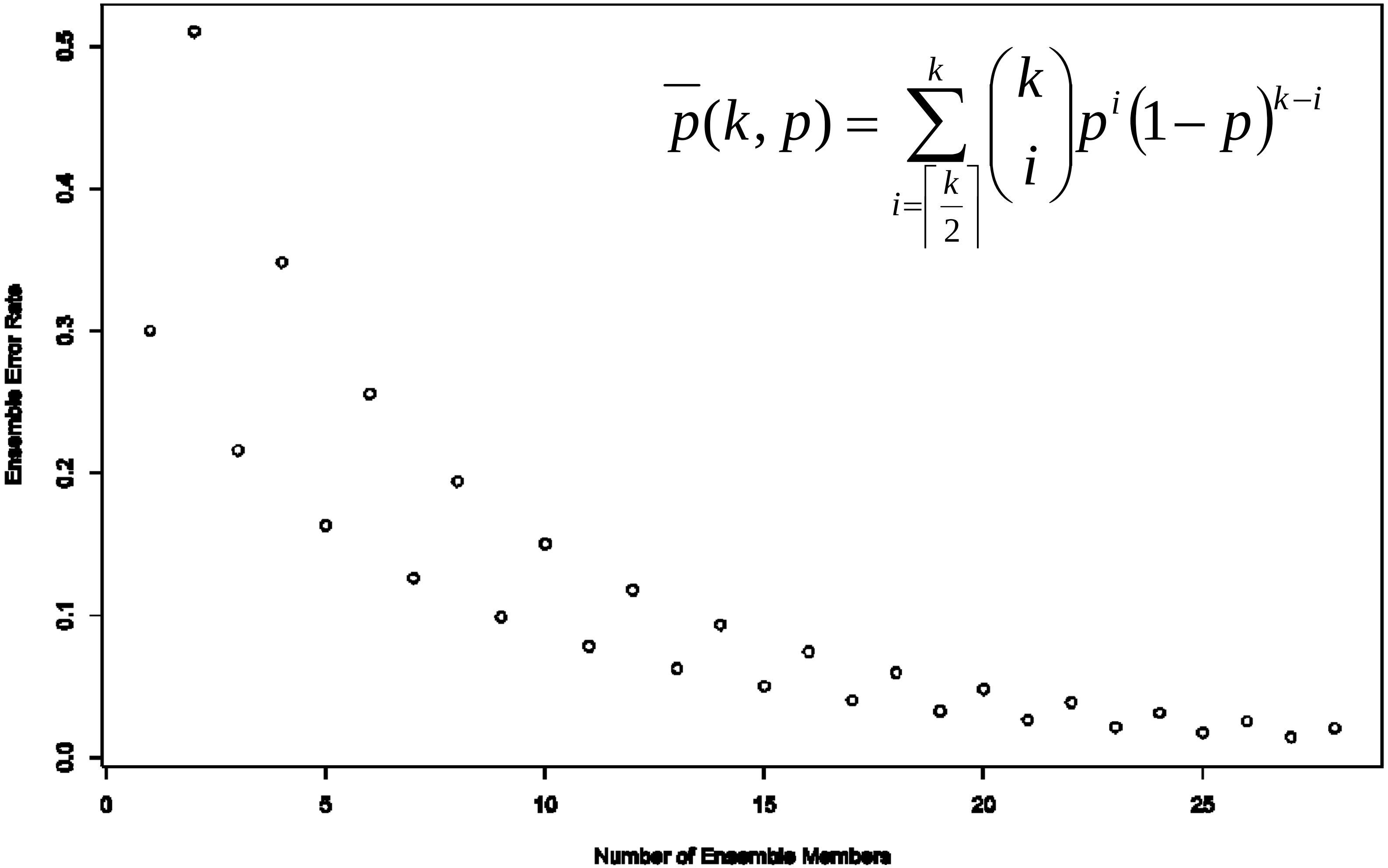
- ensemble of *k* hypotheses for dichotomous problem
- error rate of each hypothesis is $p < 0.5$
- ensemble is wrong if (and only if) more than $\left\lceil \frac{k}{2} \right\rceil$ members are wrong
- overall error rate of ensemble:

  area under binomial distribution, where $k \geq \left\lceil \frac{k}{2} \right\rceil$

  (i.e., at least k/2 hypotheses are wrong)

Ensemble Methods: Example

- example: single error rate *p = 0.3* equally for each member



$$\overline{p}(k,p) = \sum_{i=\left\lceil \frac{k}{2} \right\rceil}^{k} \binom{k}{i} p^{i} (1-p)^{k-i}$$

Ensemble Methods: Selection of Base Methods

- diversity of used information and computational methods makes localization prediction methods ideal base classifiers for ensembles
- prerequisites:
  - comparison of methods with different coverage: derive reliability index
  - assess accuracy of methods by comparable statistics
  - choose representative methods for different categories and algorithmic approaches

Ensemble Methods: Selection of Base Methods

Category	Method	Foundation	Algorithm
1	SubLoc	aa	SVM
	PLOC	dipeptide	SVM
	CELLO v.2.5	n-peptide	SVM
2	iPSORT	detecting sorting signals	AA-index
	Predotar	detecting sorting signals	NN
3	PA-SUB	BLAST against Swiss-Prot	Naive Bayes
4	PSORT II	aa+signal+motif+structure	k-NN
	wolf PSORT	aa+length+signal	k-NN
	MultiLoc	aa+signal+motif+structure	SVM
	ESLPred	aa+di+properties+psi-BLAST	SVM
	HSLPred	aa+di+gap+properties+psi-BLAST	SVM

Ensemble Methods: Exclusion of Some Methods

Category	Method	Foundation	Algorithm
too simple foundation, lower rank in preliminary tests			SVM
1	PLOC Protein localization prediction	dipeptide	SVM
	CELLO v.2.5	n-peptide	SVM
2	iPSORT	detecting sorting signals	AA-index
	Predotar	detecting sorting signals	NN
based on virtually all SWISSPROT entries that provide a localization			
	PSORT II	extension WoLFPSORT is used	k-NN
4	WoLF PSORT	aa+length+signal	k-NN
	MultiLoc	aa+signal+motif+structure	SVM
	ESLPred	aa+di+properties+psi-BLAST	SVM
	HSLPred	aa+di+gap+properties+psi-BLAST	SVM

Ensemble Methods:
From Unsupervised to Supervised

- preliminary tests and evaluations: several prediction methods unsuitable for unsupervised ensembles
- problem:
  - low accuracy for some localization classes
  - some errors may be correlated
- approach: supervised ensembles based on prior knowledge of the performance of the single methods

Method 1:

voting scheme based on prior evaluation of base classifiers

Method 2:

decision tree learns reliability of the single methods for single predictions

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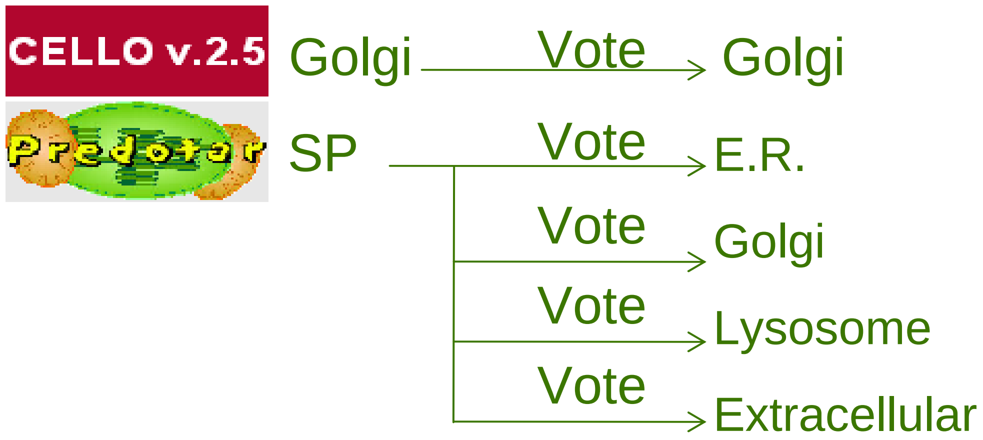
Supervised Ensemble Method 1: Voting Schema

- Each method gives its vote to one or several localizations

e.g.



CELLO v.2.5 Golgi $\xrightarrow{\text{Vote}}$ Golgi

Predotar SP $\xrightarrow{\text{Vote}}$ E.R.

$\xrightarrow{\text{Vote}}$ Golgi

$\xrightarrow{\text{Vote}}$ Lysosome

$\xrightarrow{\text{Vote}}$ Extracellular

- Score calculation for each localization according to the gained votes and the weight of each vote

For a certain localization *i*: $\text{score}_i = \sum_{j=1\ldots N} (\text{Vote}_j * (N - \text{Rank}_j + 1))$

N : number of methods used by the ensemble method

Rank_j : rank of method j during comparison

$\text{Vote}_j = 1$ if method j gives the vote to the localization i, otherwise $\text{Vote}_j = 0$.

Supervised Ensemble Method 2: Decision Tree

- Decision Trees learn to map prediction vectors of the base classifiers to a single prediction:

$$(localization\ index)^N \rightarrow localization\ index$$

- Example: decision tree for taxonomic group “plant” learns rules like *“If CELLO predicts class 6 and WoLFPSORT predicts class 4, then class 4 is correct.”*
- The prediction servers and the learned models are available online via http://www.dbs.ifi.lmu.de/research/locpred/ensemble/

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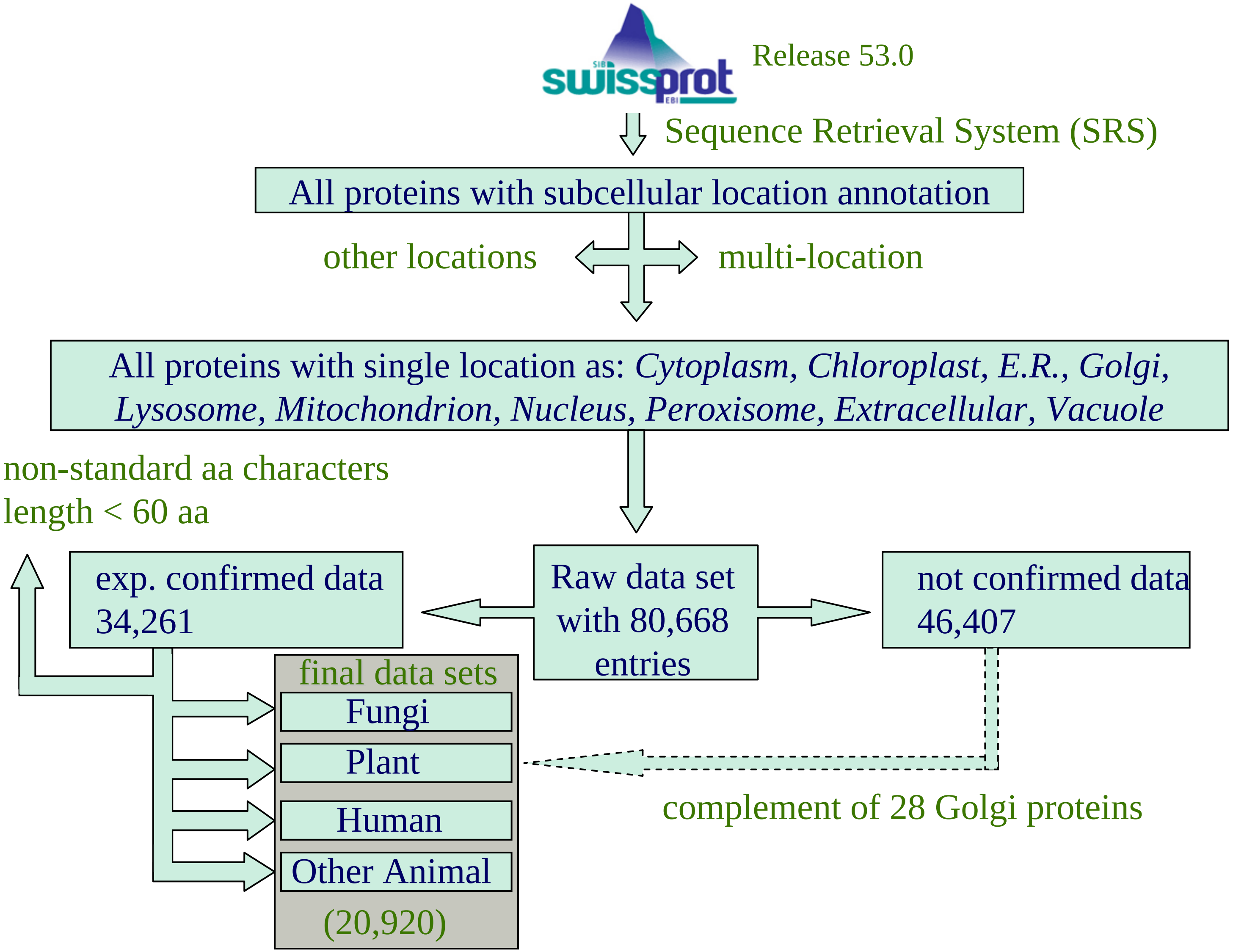
Data Preparation



Release 53.0

Sequence Retrieval System (SRS)

All proteins with subcellular location annotation

other locations

multi-location

All proteins with single location as: *Cytoplasm, Chloroplast, E.R., Golgi, Lysosome, Mitochondrion, Nucleus, Peroxisome, Extracellular, Vacuole*

non-standard aa characters
length < 60 aa

exp. confirmed data
34,261

Raw data set
with 80,668
entries

not confirmed data
46,407

final data sets

Fungi

Plant

Human

Other Animal

(20,920)

complement of 28 Golgi proteins

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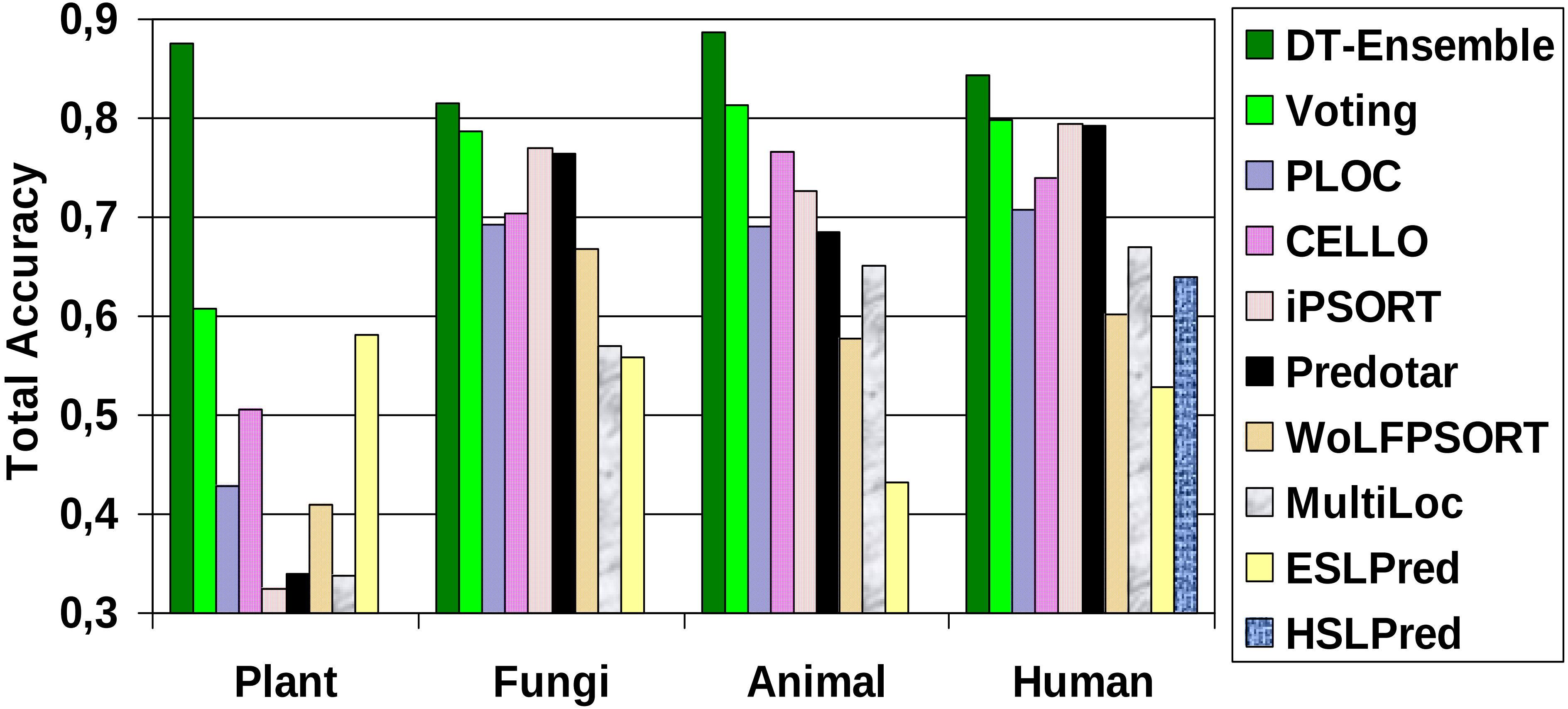
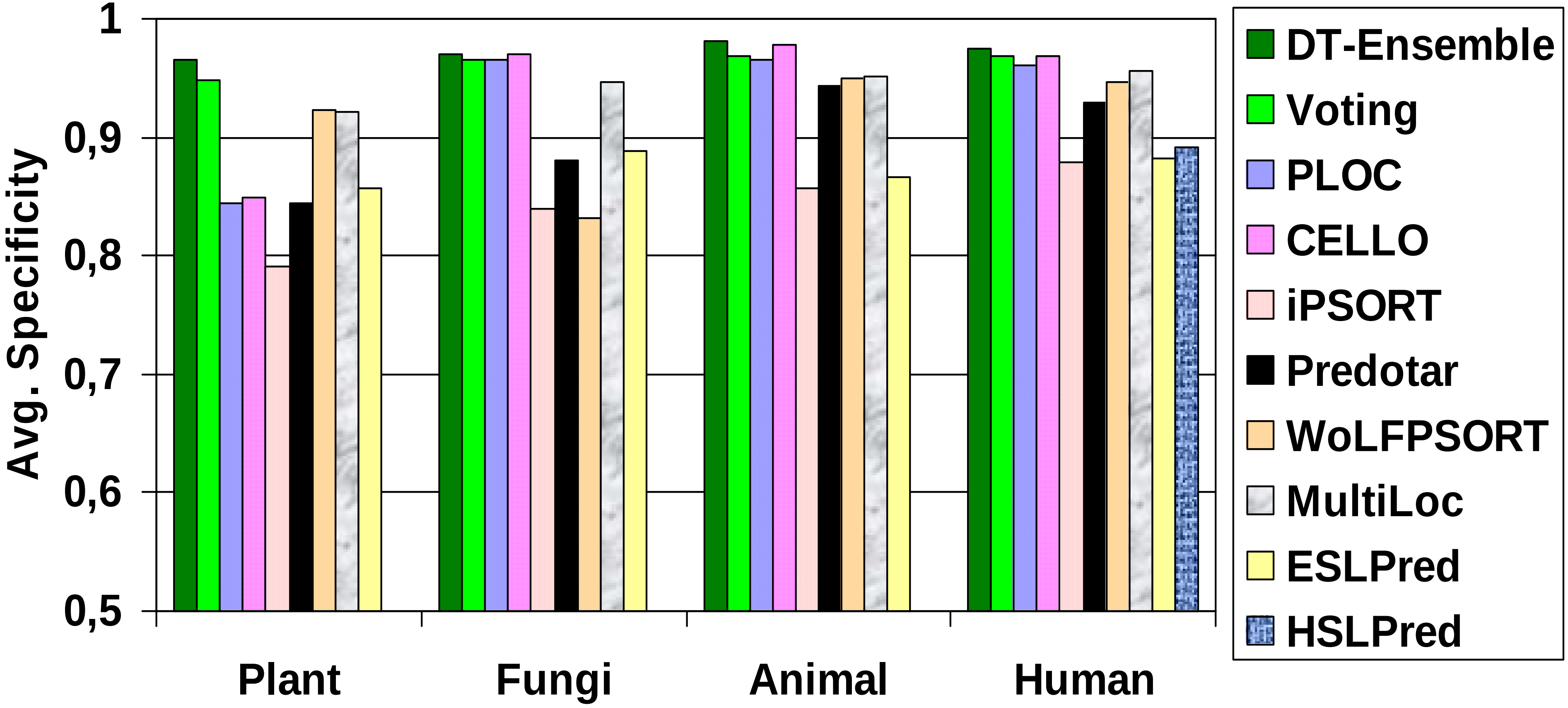
Results: Accuracy



Results: Specificity



Conclusions

- Localization prediction methods use different kind of information and different computational approaches.
- Combination of several methods to an ensemble yields considerably increased accuracy.
- Methods are seemingly unsuitable for unsupervised ensemble methods.
- Two supervised ensemble methods:
  - voting schema, based on prior knowledge (evaluation of single methods)
  - decision tree (trained to learn ideal combination of single methods for specific localization classes)
- Decision tree models provide further insight in reliability of single methods for specific localization classes.