Methods for Multi-Category Cancer Diagnosis from Gene Expression Data:

A Comprehensive Evaluation to Inform Decision Support System Development

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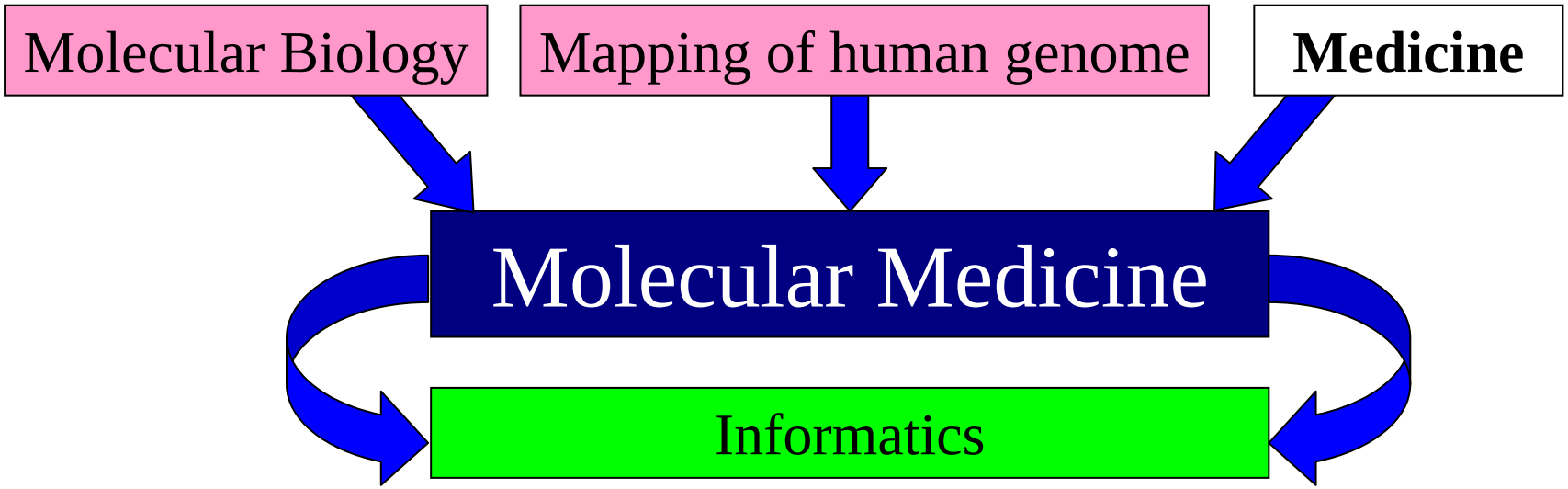
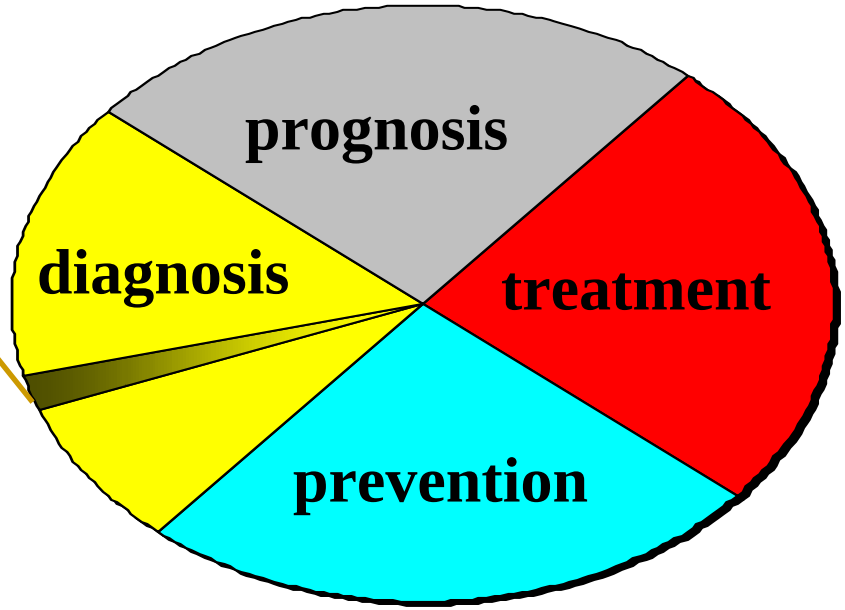
VANDERBILT UNIVERSITY

DSL Discovery Systems Laboratory

Research Problem

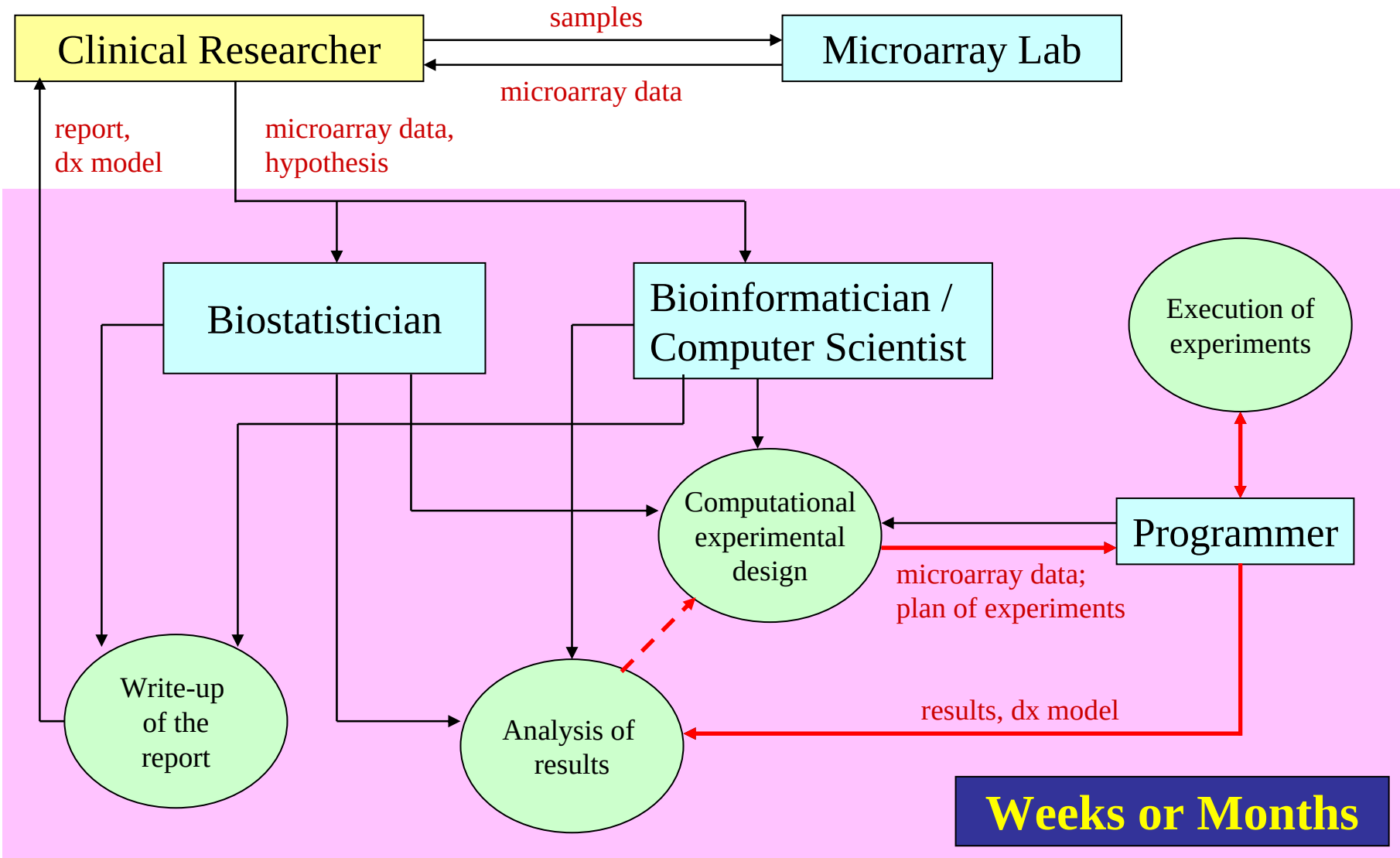


Development of an automated system for high-quality cancer diagnosis from microarray gene expression data

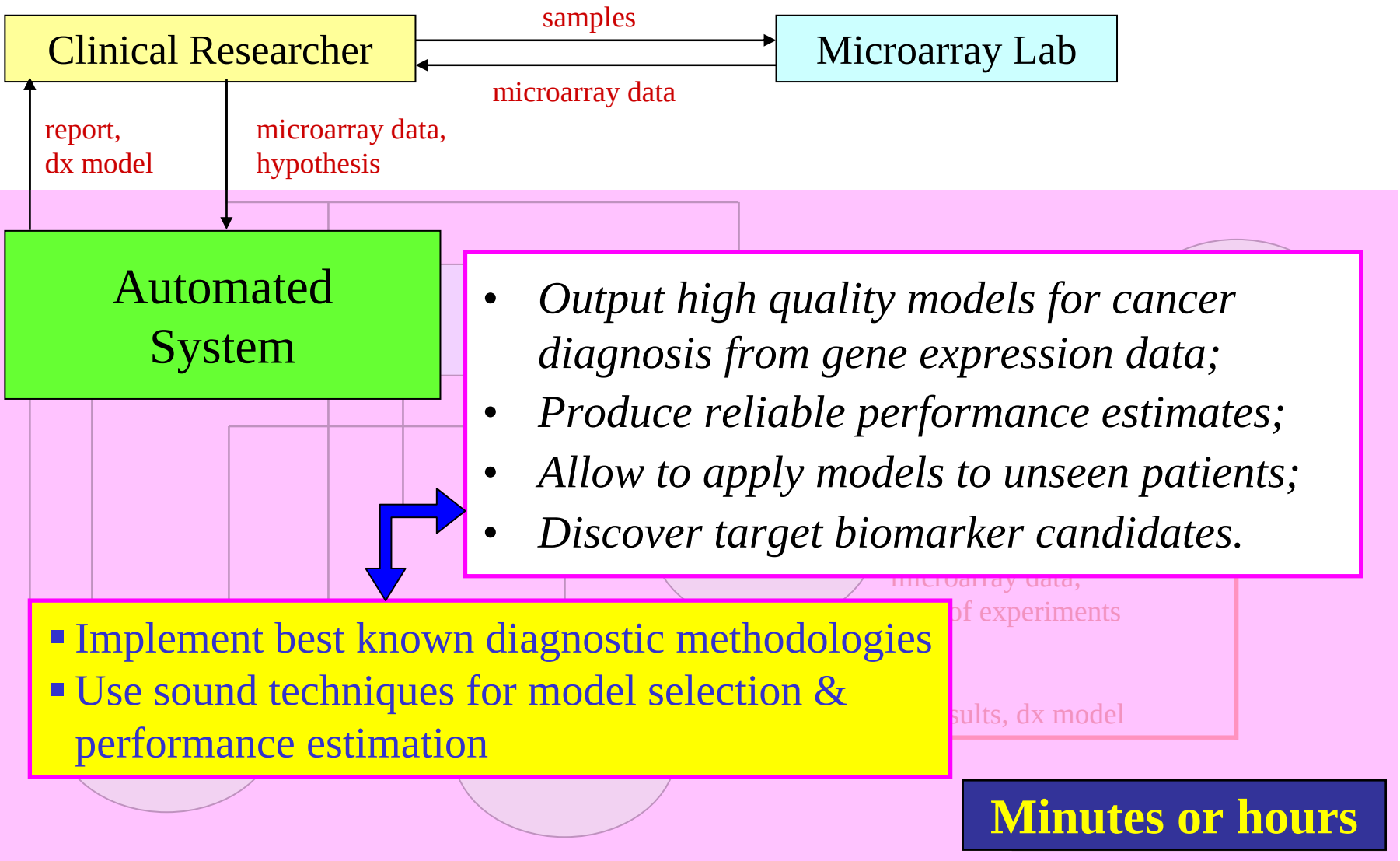


- *How the efforts to develop this system necessitated a large-scale evaluation of learning methods*
- *How evaluation findings informed the resulting system*

Building Cancer Diagnostic Models from Microarray Data



Automated Diagnostic System **GEMS**: **G**ene **E**xpression **M**odel **S**elector



Prior Research

193 primary studies

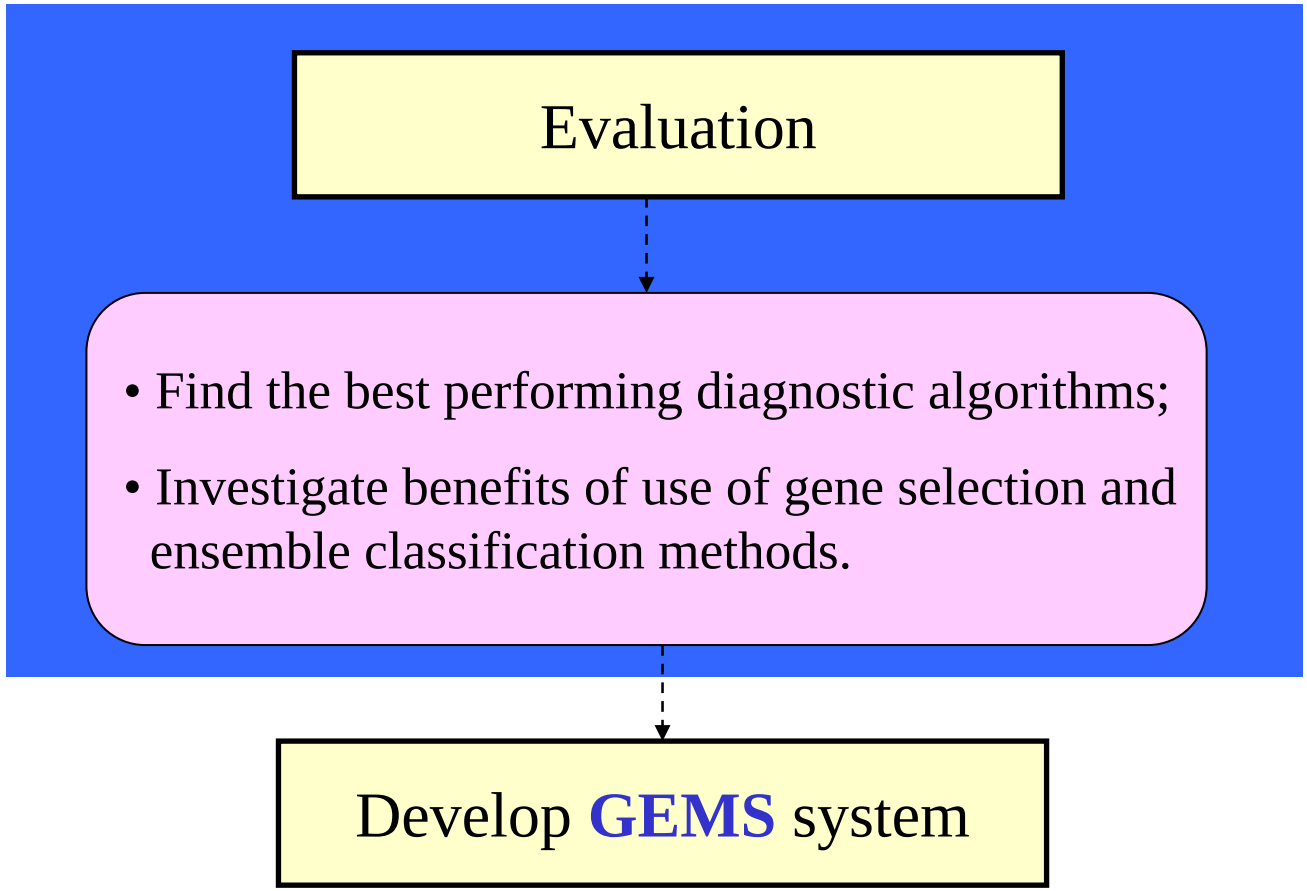
2 meta-analyses

20 software systems

- Limited range of methods & datasets per study
- No description of parameter optimization of learners
- Different experimental designs are employed
- Overfitting [*Ntzani et al.*, Lancet 2003]:
  - **74%** no validation
  - **13%** incomplete cross-validation
  - **13%** implemented cross-validation correctly
- The available meta-analyses are not aimed at identification of best performing methodologies
- Existing systems do not justify choices of diagnostic methods

Cannot specify a small set of best performing diagnostic algorithms;
Have to to perform evaluation *de novo*

Step I: Evaluation



Methods & Datasets

Cross-Validation Designs (2)

- 10-Fold CV
- LOOCV

Gene Selection Methods (4)

- S2N One-Versus-Rest
- S2N One-Versus-One
- Non-param. ANOVA
- BW ratio

Performance Metrics (2)

- Accuracy
- RCI

Statistical Comparison

- Randomized permutation testing

Classifiers (11)

MC-SVM
- One-Versus-Rest
- One-Versus-One
- DAGSVM
- Method by WW
- Method by CS

- KNN
- Backprop. NN
- Prob. NN
- Decision Trees

WV
- One-Versus-Rest
- One-Versus-One

Ensemble Classifiers (7)

Based on MC-SVM outputs
- Majority Voting
- MC-SVM OVR
- MC-SVM OVO
- MC-SVM DAGSVM
- Decision Trees

Based on outputs of all classifiers
- Majority Voting
- Decision Trees

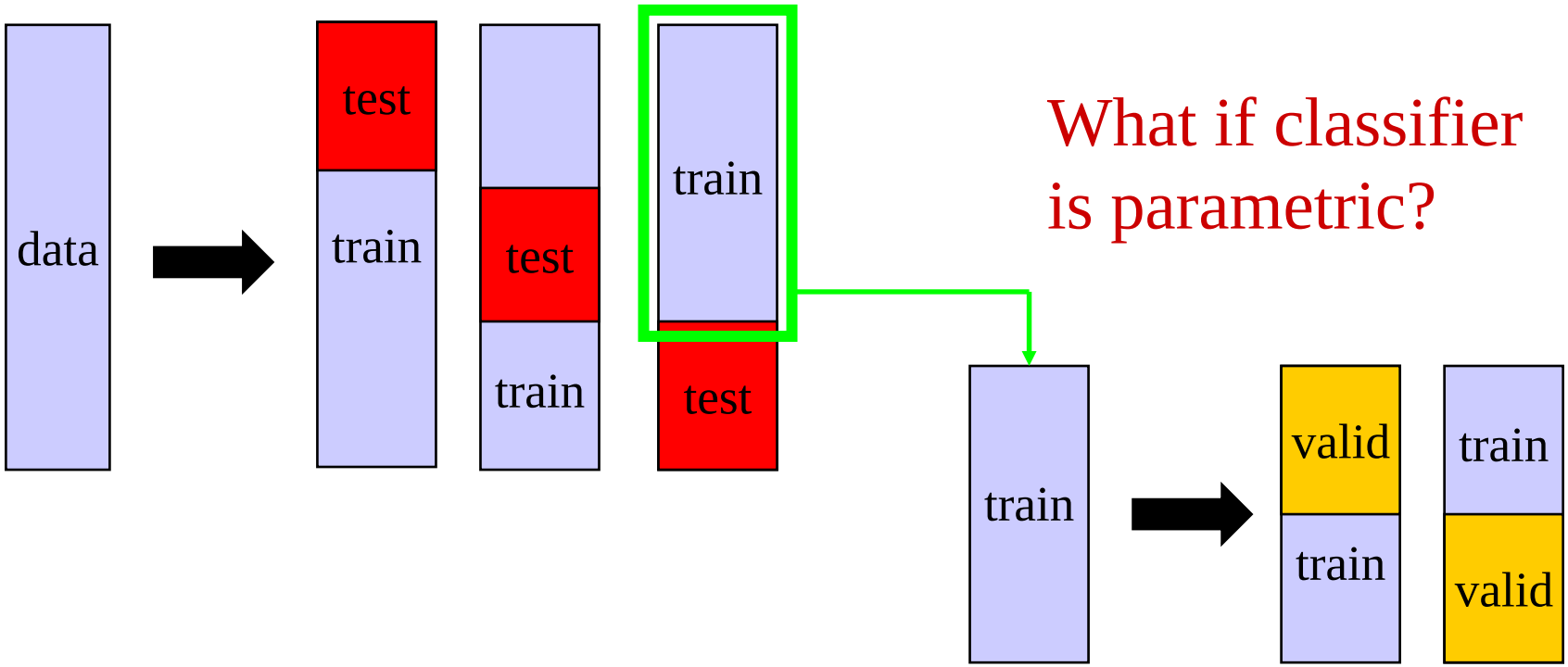
Gene Expression Datasets (11)

Multicategory Dx
- 11_Tumors
- 14_Tumors
- 9_Tumors
- Brain Tumor1
- Brain_Tumor2
- Leukemia1
- Leukemia2
- Lung_Cancer
- SRBCT

Binary Dx
- Prostate_Tumors
- DLBCL

Cross-Validation Design

Performance estimation by 10-fold Cross-Validation (**CV**) and Leave-One-Out Cross-Validation (**LOOCV**)

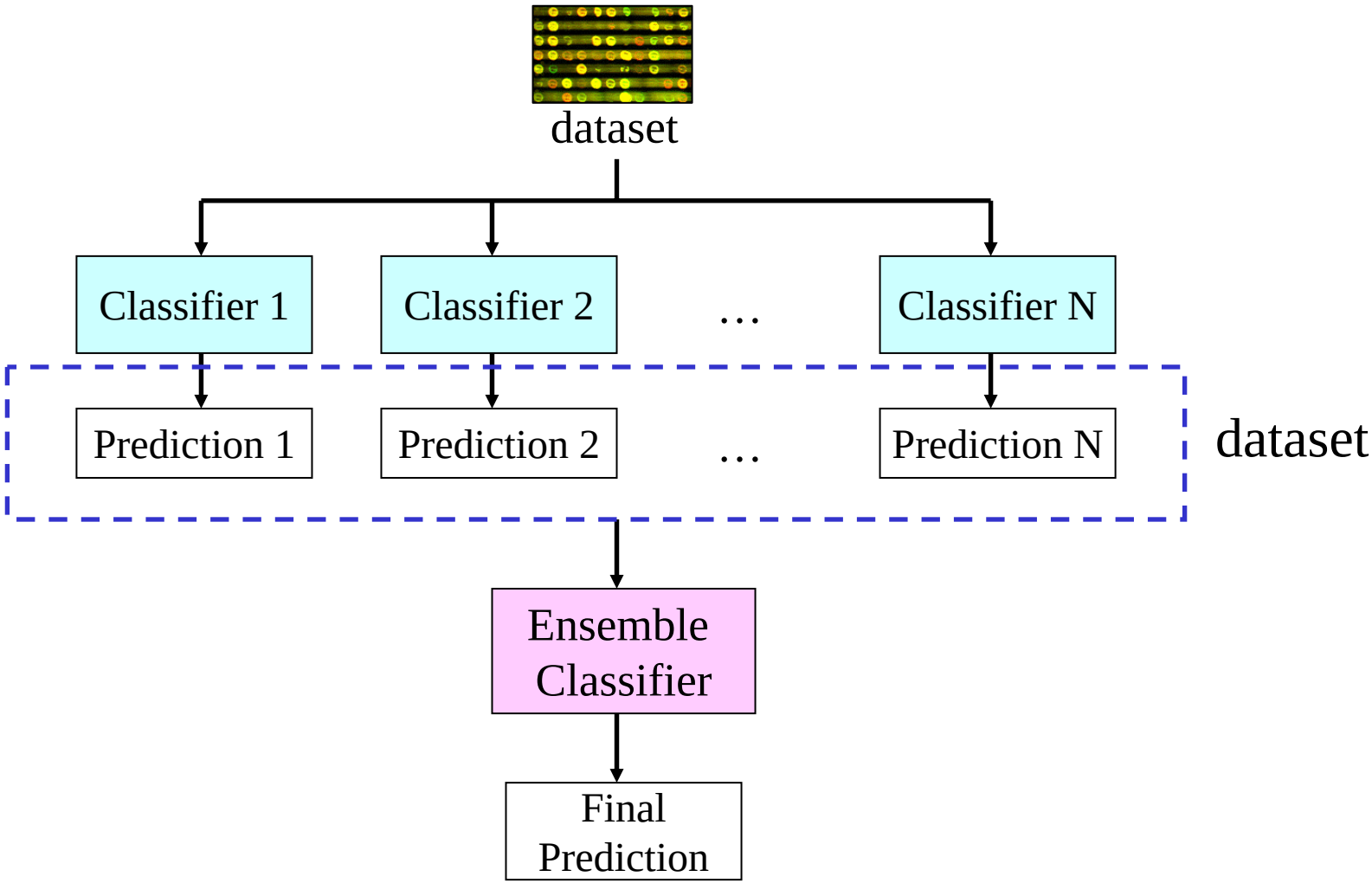


Model selection / parameter optimization by “nested” cross-validation

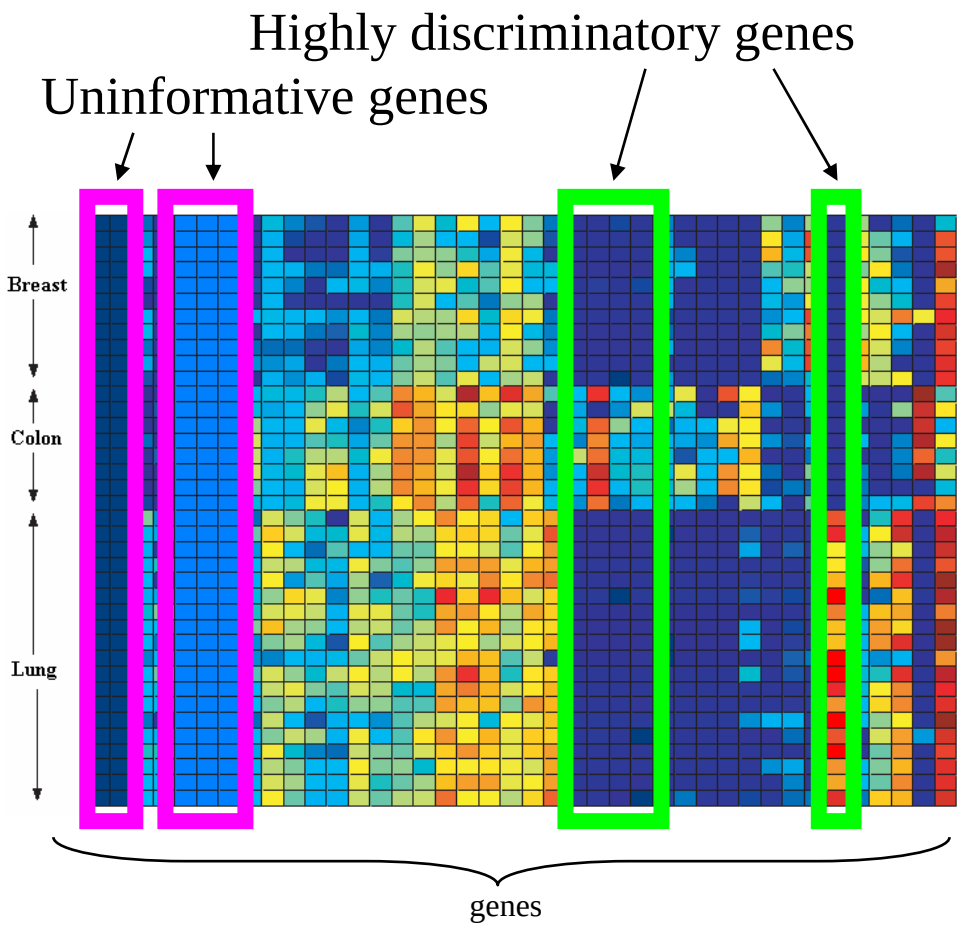
Classifiers

- K-Nearest Neighbors (KNN) — instance-based
- Backpropagation Neural Networks (NN) — neural networks
- Probabilistic Neural Networks (PNN) — neural networks
- Multi-Class SVM: One-Versus-Rest (OVR) — kernel-based
- Multi-Class SVM: One-Versus-One (OVO) — kernel-based
- Multi-Class SVM: DAGSVM — kernel-based
- Multi-Class SVM by Weston & Watkins (WW) — kernel-based
- Multi-Class SVM by Crammer & Singer (CS) — kernel-based
- Weighted Voting: One-Versus-Rest — voting
- Weighted Voting: One-Versus-One — voting
- Decision Trees: CART — decision trees

Ensemble Classifiers



Gene Selection Methods



1. Signal-to-noise (S2N) ratio in one-versus-rest (OVR) fashion;
2. Signal-to-noise (S2N) ratio in one-versus-one (OVO) fashion;
3. Kruskal-Wallis nonparametric one-way ANOVA (KW);
4. Ratio of genes between-categories to within-category sum of squares (BW).

Performance Metrics & Statistical Comparison

1. Accuracy
   + can compare to previous studies
   + easy to interpret & simplifies statistical comparison

2. Relative classifier information (RCI)
   + easy to interpret & simplifies statistical comparison
   + not sensitive to distribution of classes
   + accounts for difficulty of a decision problem

- Randomized permutation testing to compare accuracies of the classifiers (α=0.05)

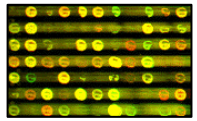
Microarray Datasets

Dataset name	Number of			Reference
	Sam-ples	Variables (genes)	Cate-gories	
11_Tumors	174	12533	11	Su, 2001
14_Tumors	308	15009	26	Ramaswamy, 2001
9_Tumors	60	5726	9	Staunton, 2001
Brain_Tumor1	90	5920	5	Pomeroy, 2002
Brain_Tumor2	50	10367	4	Nutt, 2003
Leukemia1	72	5327	3	Golub, 1999
Leukemia2	72	11225	3	Armstrong, 2002
Lung_Cancer	203	12600	5	Bhattacherjee, 2001
SRBCT	83	2308	4	Khan, 2001
Prostate_Tumor	102	10509	2	Singh, 2002
DLBCL	77	5469	2	Shipp, 2002

Total:

- ~1300 samples
- 74 diagnostic categories
- 41 cancer types and 12 normal tissue types

Staged Experimental Design



Dataset

Analysis without gene selection

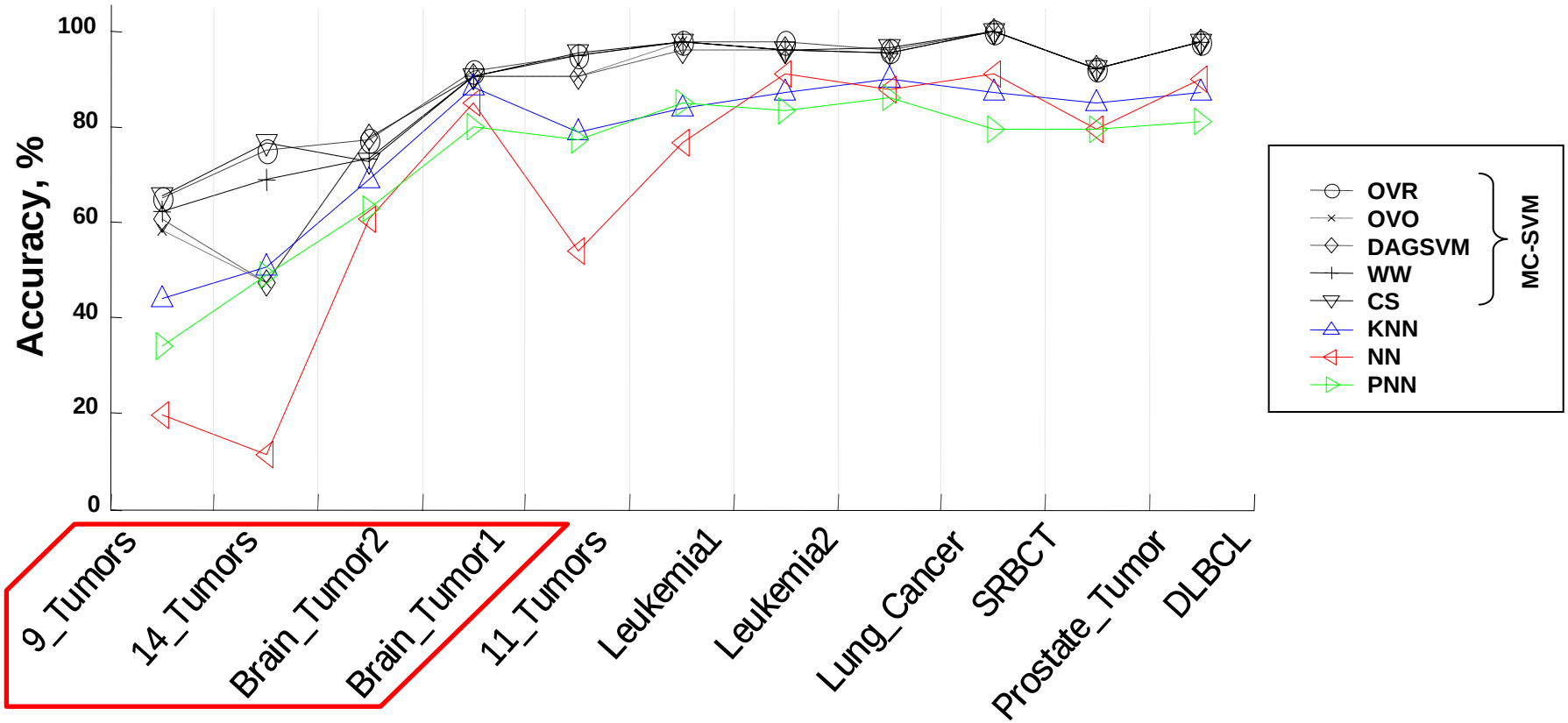
Performance

optimal or near-optimal

not optimal → Analysis with gene selection

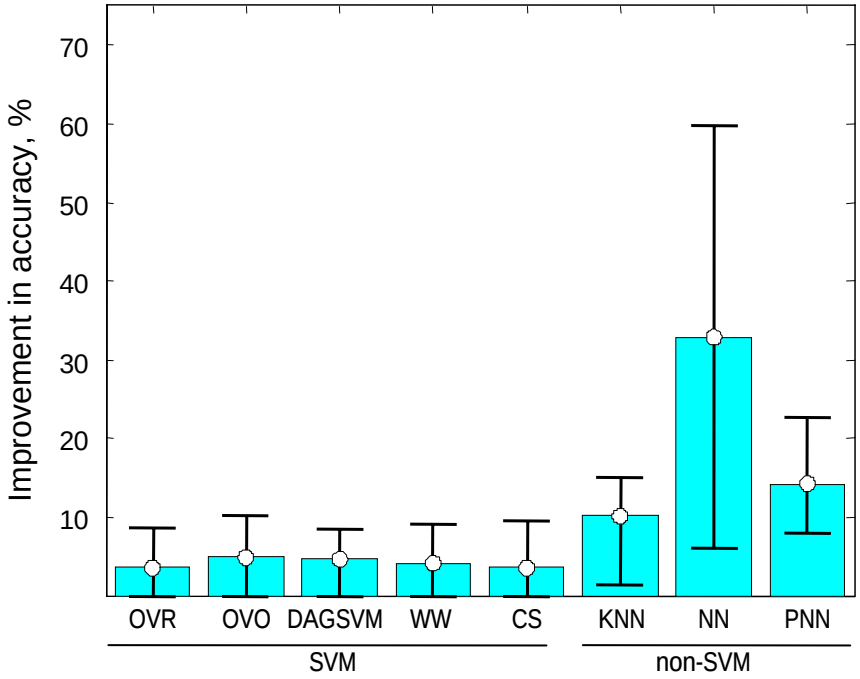
Performance

Results Without Gene Selection

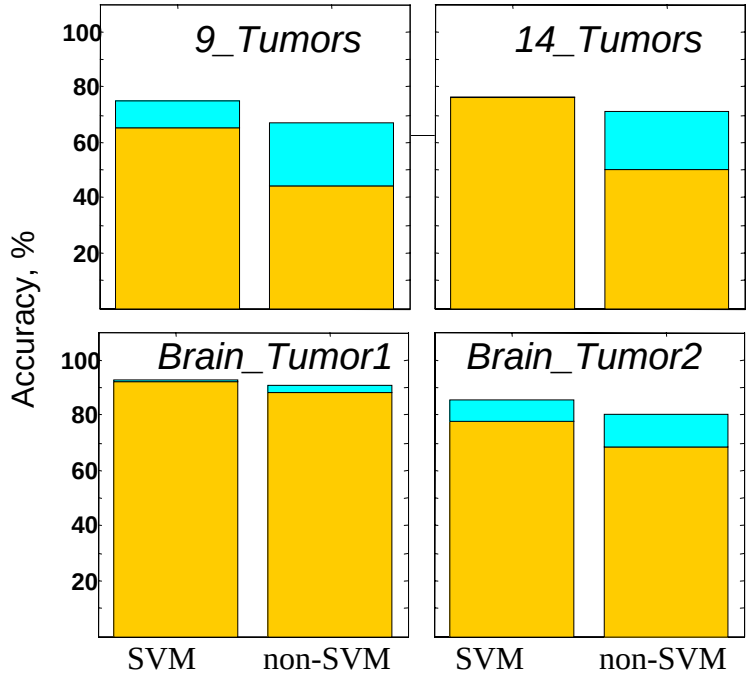


Results With Gene Selection

Improvement of diagnostic performance by gene selection (*averages for the four datasets*)

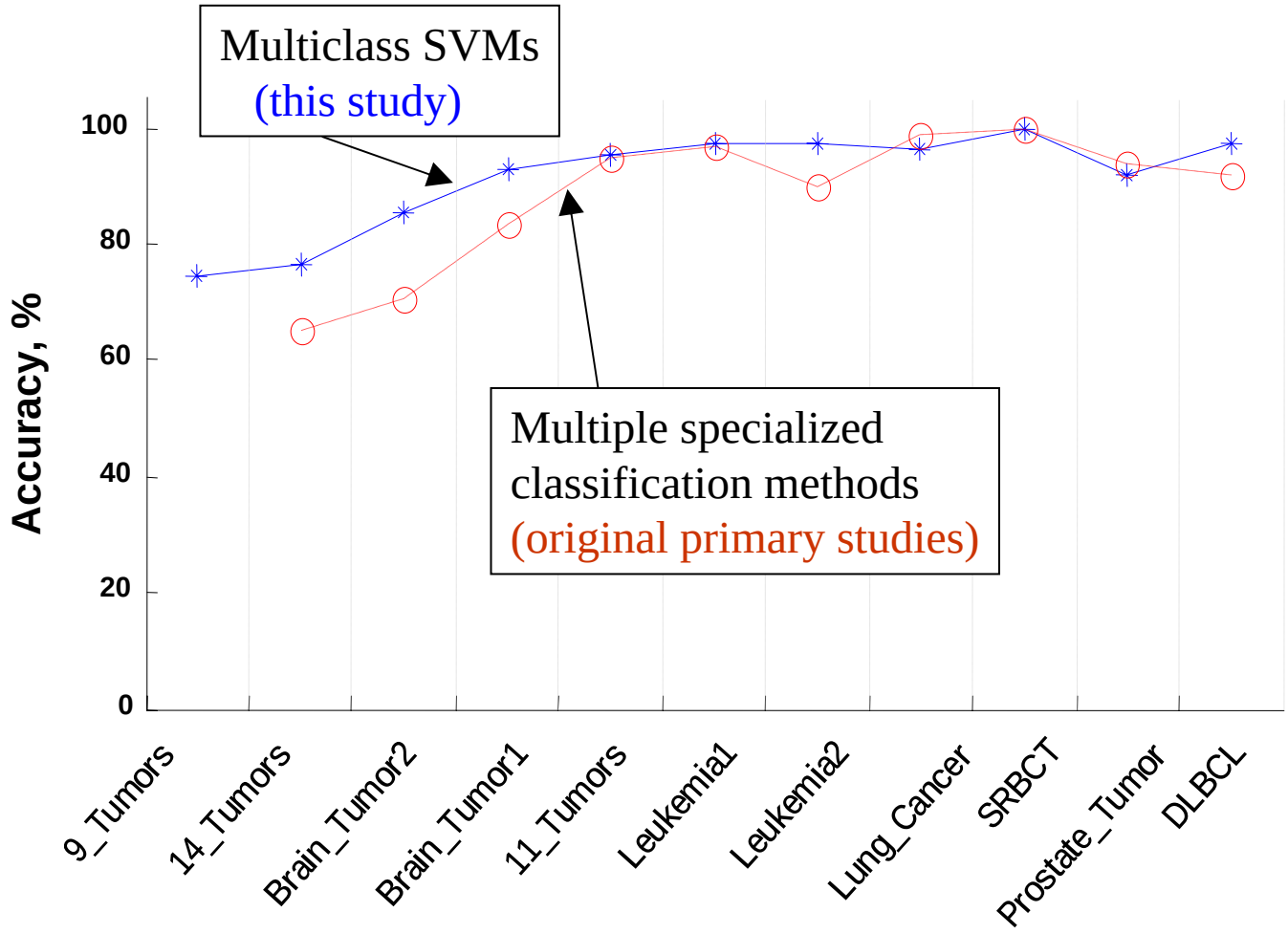


Diagnostic performance *before* and *after* gene selection



Average reduction of genes is 10-30 times

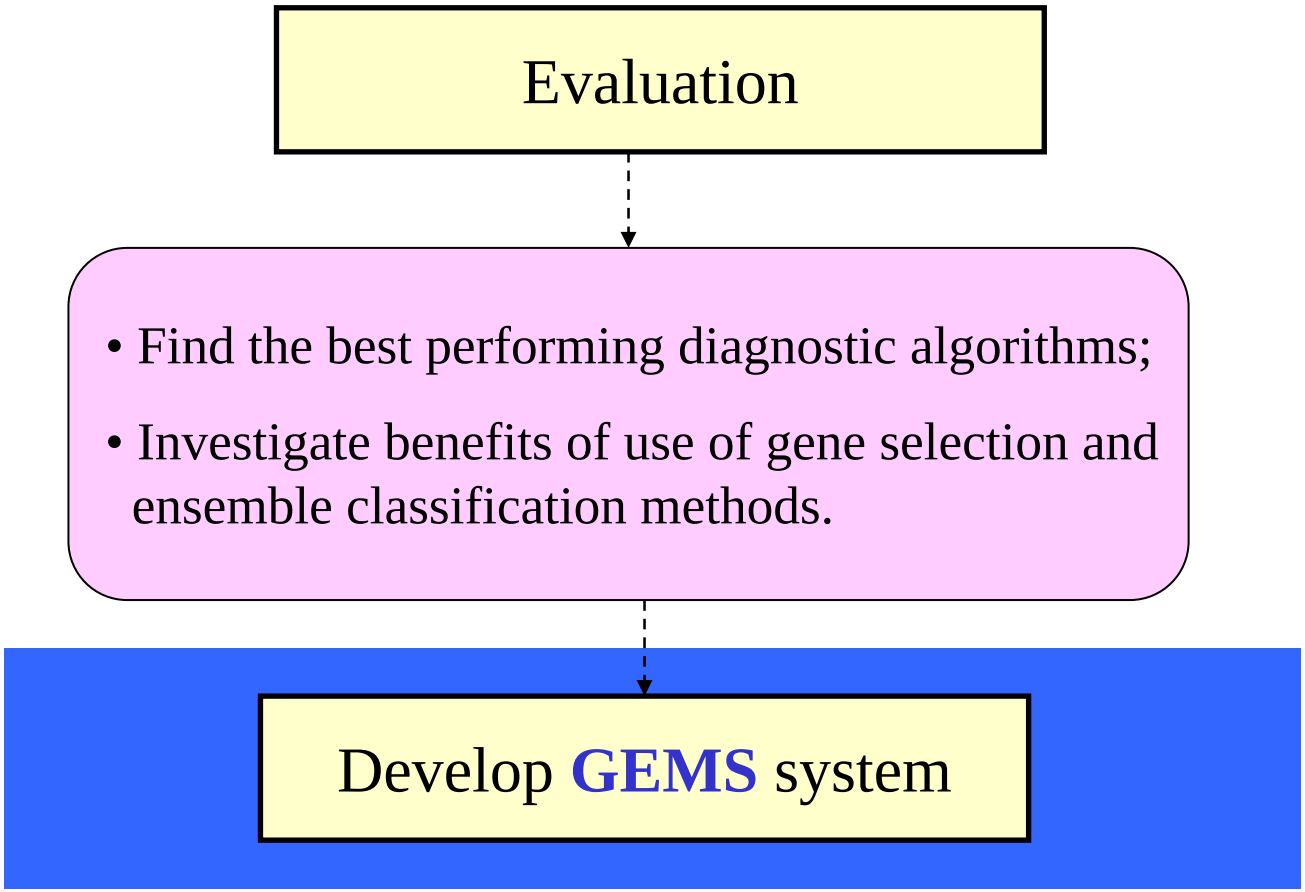
Comparison with Previously Published Results



Conclusions of Evaluation Stage

- Multi-class SVMs are the best family among the tested algorithms outperforming KNN, NN, PNN, DT, and WV.
- Gene selection in some cases improves classification performance of all classifiers, especially of non-SVM algorithms;
- Ensemble classification does not improve performance;
- Obtained results favorably compare with literature.

Step II: System Development Informed by Evaluation



Methods Implemented in GEMS

Cross-Validation Designs

- N-Fold CV
- LOOCV

Normalization Techniques

- [a, b]
- (x – MEAN(x)) / STD(x)
- x / STD(x)
- x / MEAN(x)
- x / MEDIAN(x)
- x / NORM(x)
- x – MEAN(x)
- x – MEDIAN(x)
- ABS(x)
- x + ABS(x)

Classifiers

MC-SVM
- One-Versus-Rest
- One-Versus-One
- DAGSVM
- Method by WW
- Method by CS

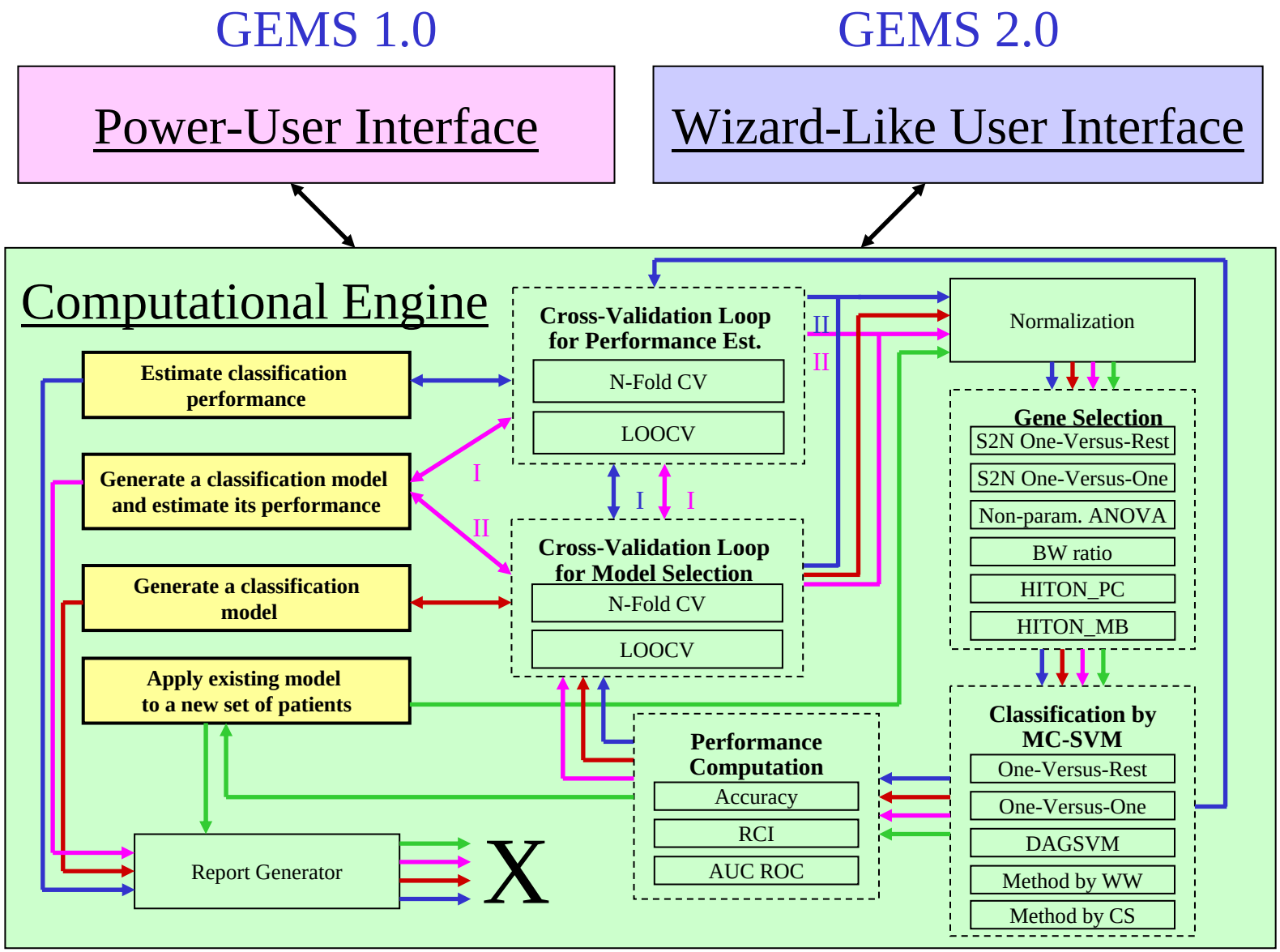
Performance Metrics

- Accuracy
- RCI
- AUC ROC

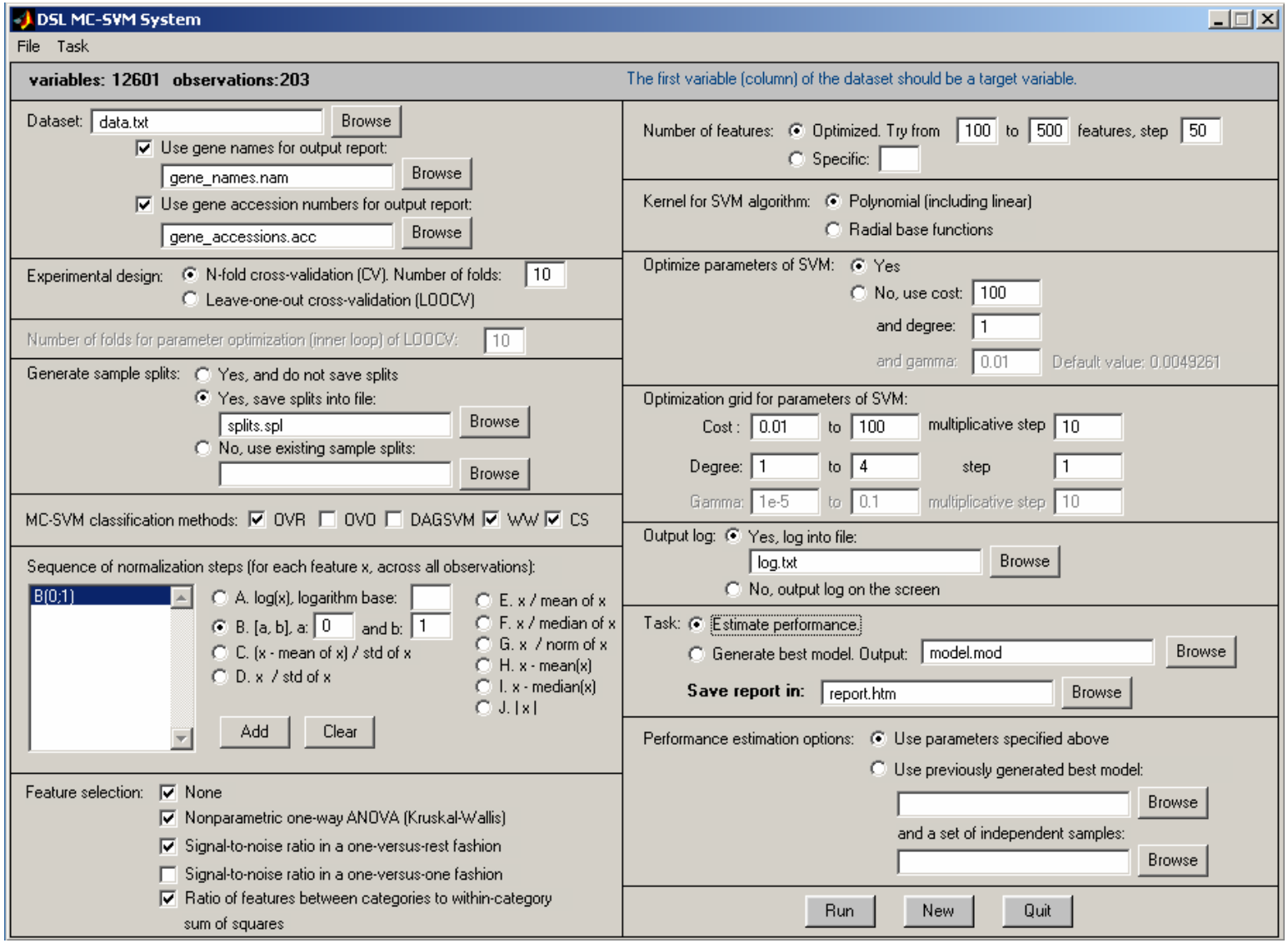
Gene Selection Methods

- S2N One-Versus-Rest
- S2N One-Versus-One
- Non-param. ANOVA
- BW ratio
- HITON_MB
- HITON_PC

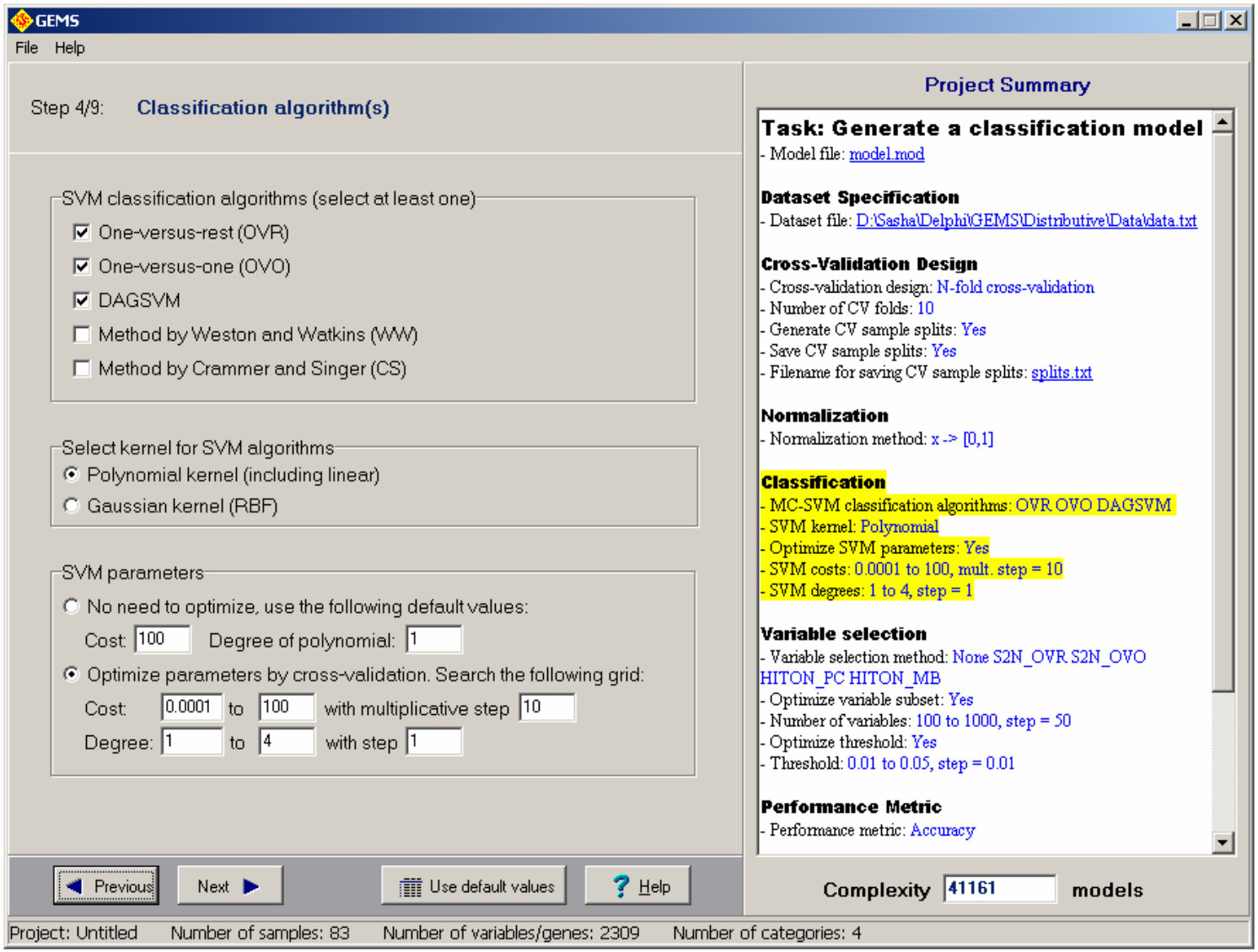
Software Architecture of GEMS



GEMS 1.0: Power-User Interface

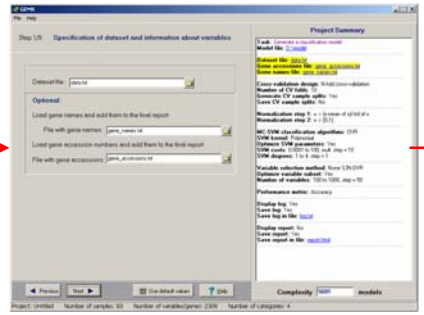


GEMS 2.0: Wizard-Like Interface

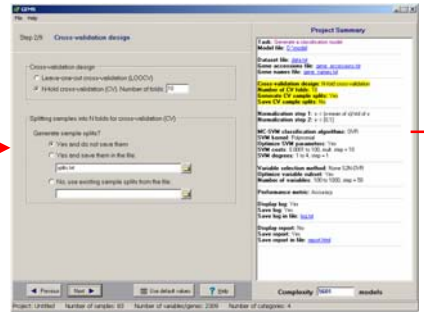


GEMS 2.0: Wizard-Like Interface

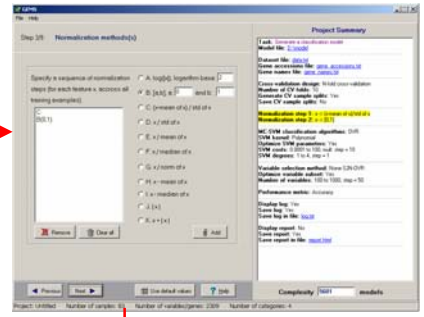
Task selection



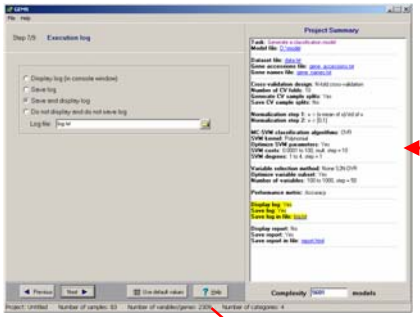
Dataset specification



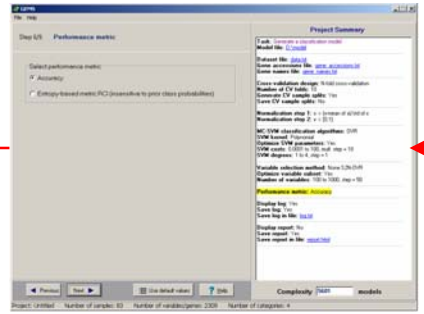
Cross-validation design



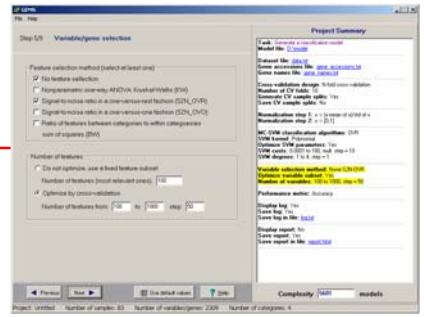
Normalization



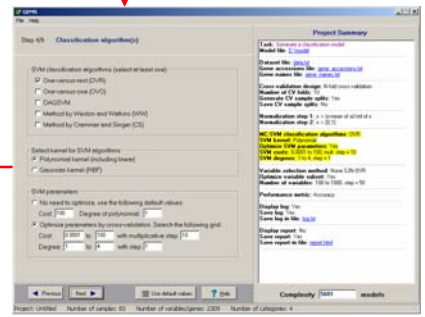
Logging



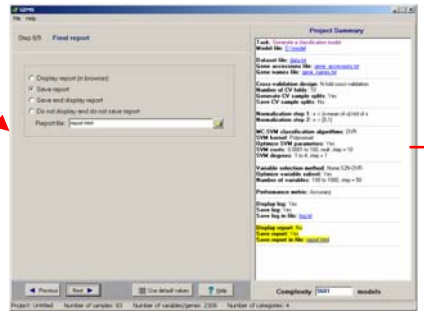
Performance metric



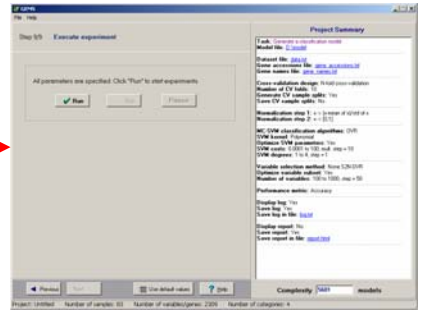
Gene selection



Classification



Report generation



Analysis execution

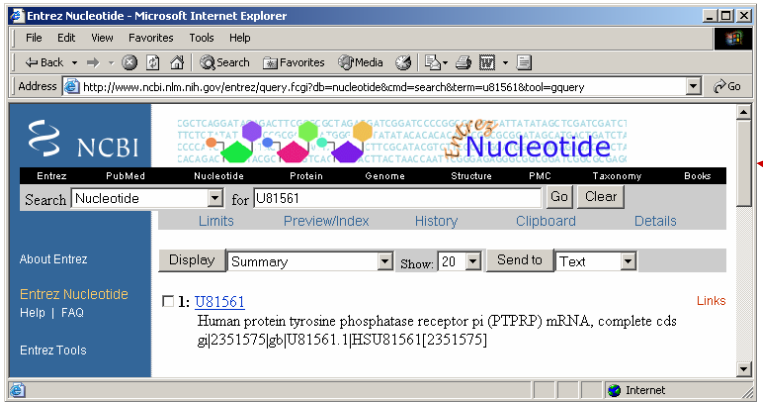
GEMS 2.0: Wizard-Like Interface

Input microarray gene expression dataset

File with gene names

File with gene accession numbers

Output model



Address D:\Sasha\Matlab\MC-SVM\Toolbox_Development\distributive\report.htm

GEMS : Experimental Report

Task:	Generate best model
Experiment execution time:	46 seconds
Number of samples:	203
Number of variables:	12601
Number of categories:	5
Validation accuracy:	96.5517%
Dataset filename:	D:\Sasha\Matlab\MC-SVM\Toolbox_Development\distributive\data\Lung_Cancer\data.txt
Gene names filename:	D:\Sasha\Matlab\MC-SVM\Toolbox_Development\distributive\data\Lung_Cancer\gene_names.nam
Gene accession numbers filename:	D:\Sasha\Matlab\MC-SVM\Toolbox_Development\distributive\data\Lung_Cancer\gene_accessions.acc
Model filename:	model.mod

Description of the best model for the current data-split:

- SVM method: **OVR**
- SVM cost: **100**
- SVM kernel: **poly**
- SVM kernel parameter (degree): **1**

Feature selection method: **Signal-to-noise ratio in a one-versus-rest fashion**

Optimal number of features: **100**

Ranking (1 is 'best')	Column index of features (in dataset file)	Gene names	Accession numbers
1	8485	Cluster Incl U81561:Human protein tyrosine phosphatase receptor pi (PTPRP) mRNA, complete cds /cds=(42,3038) /gb=U81561 /gi=2351575 /ug=Hs.74624 /len=4699	U81561
2	5850	RaP2 interacting protein 8	AF055026
3	3074	piccolo (presynaptic cytomatrix protein)	AB011131
4	8473	Cluster Incl U48437:Human amyloid precursor-like protein 1 mRNA, complete cds /cds=(41,1993) /gb=U48437 /gi=1709300 /ug=Hs.74565 /len=2336	U48437
5	4854	Cluster Incl N90862:zb11b06.s1 Homo sapiens cDNA, 3 end /clone=IMAGE-301715 /clone_end=3" /gb=N90862 /gi=1444189 /ug=Hs.172684 /len=605"	L76703
6	3876	cadherin, EGF LAG seven-pass G-type receptor 3, flamingo (Drosophila) homolog	AB011536
7	3192	S100 calcium-binding protein A11 (calgizzarin)	D38583

Additional Validation of GEMS (post implementation)

	GEMS	Published results	Reference
6_Tumors	97.2%	96.0%	Shedden, 2003
Leukemia3	98.4%	98.4%	Yeoh, 2002
Lung_Cancer2	100%	100%	Beer, 2002

- Analysis in GEMS: 15-30 minutes per dataset
- GEMS is performing as good or better than published studies

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First reported use of GEMS: *Classification and Biomarker Discovery from Head & Neck Cancer Microarray Data* (presented at 6th ICHNC)

Limitations & Ongoing Work

Molecular medicine is moving very fast and GEMS is evolving accordingly:

- Periodical literature review to ensure that GEMS implements the best methodologies & algorithms
- Large-scale evaluation of GEMS with various user types
- Evaluation of computational causal discovery capabilities
- New functionality for prognosis & response to treatment

Final Conclusions

- We created a system to support automatic development of high-quality cancer classification models & gene selection for biomarker discovery from gene expression data
- An extensive study of several methods in this domain informed system development
- The evaluation revealed the importance of multi-category SVM classifiers in this domain and task
- Results obtained by GEMS are as good or better than previously published results by human experts and require only a few minutes of user's time to complete
- GEMS is available for download from http://www.gems-system.org

For more details, see paper in proceedings, online supplement, and:

A. Statnikov, C.F. Aliferis, I. Tsamardinos, D. Hardin, S. Levy. "A Comprehensive Evaluation of Multicategory Classification Methods for Microarray Gene Expression Cancer Diagnosis", (to appear in *Bioinformatics*)

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http://www.gems-system.org