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Targeted Retrieval of Gene Expression Measurements Using Regulatory Models

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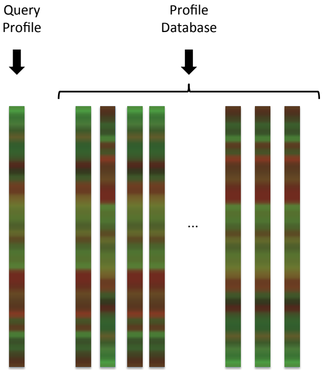
Funding: Tekes, Academy of Finland, PASCAL2

MLSB 2012

Motivation

- Large repositories of measurement data $\Longrightarrow$ use them!
- Goal: automated search for relevant experiments
- Considered task: given a gene expression profile, find “similar” profiles from a database



What is a suitable similarity measure?

- Shared keywords in the annotation (= knowledge-driven)
  (+) reliable, state of the art; (-) excludes new findings

  (Zhu *et al.*, Bioinformatics, 2008)

- Correlation of profiles (= data-driven)
  (+) easy to compute; (-) ignores gene dependencies

  (Engreitz *et al.*, BMC Bioinformatics, 2010)

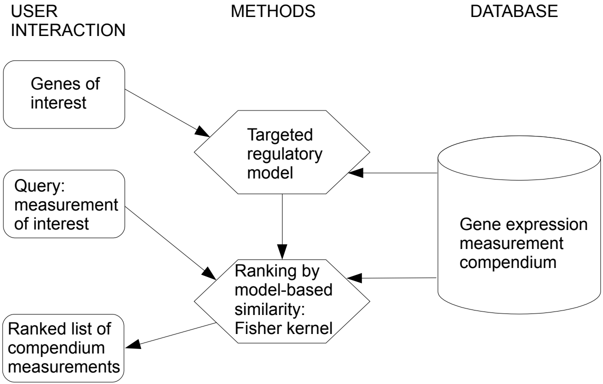
- Model-based similarity measure (= data-driven)
  (+) learns from database; (-) computationally expensive

  (Caldas *et al.*, Bioinformatics, 2009, 2012)

This approach: Model-based targeted retrieval

- Two main aspects
- **Targeted focus:** guide the model by genes of interest
  e.g. genes known to be related to a certain disease
  → adapt to users' needs, reduce computational effort
- **Similarity based on gene regulatory network models:**
  potential similarity of conditions at detailed biological level
  → improved interpretability by network activation patterns

System for targeted retrieval


USER INTERACTION

METHODS

DATABASE

Genes of interest

Query: measurement of interest

Ranked list of compendium measurements

Targeted regulatory model

Ranking by model-based similarity: Fisher kernel

Gene expression measurement compendium

- First step: learn regulatory model for user-provided genes
- Second step: retrieve measurements related to a query

Targeted gene expression model

- Conditional model: expression of target genes, given expression of other genes

$$P(X_{\mathcal{T}} | X_{-\mathcal{T}})$$

- Pseudo-likelihood approach:

$$\tilde{P}(X_{\mathcal{T}} | X_{-\mathcal{T}}) = \prod_{j \in \mathcal{T}} P(X_j | X_{-\{j\}}; \theta_j)$$

  i.e., independent model for each target gene

- Gene-specific model: Gaussian linear regression model

$$X_j = X_{-\{j\}} \beta + \epsilon, \quad \epsilon \sim \mathcal{N}(0, \sigma^2)$$

  sparse β estimate by L_1-norm regularization
  $\rightarrow$ target gene neighbors

Model-based similarity measure

- Fisher score representation of data point: $s_{\hat{\theta}}(x^{(i)})$:
  gradient of its log-likelihood at learned model parameters
  $\rightarrow$ direction in which to update the parameters after adding $x^{(i)}$ to the dataset ($\rightarrow$ summary of dataset $D + x^{(i)}$)

- Simple Fisher kernel: (Jaakkola and Haussler, NIPS 1998: using HMMs in classifiers)

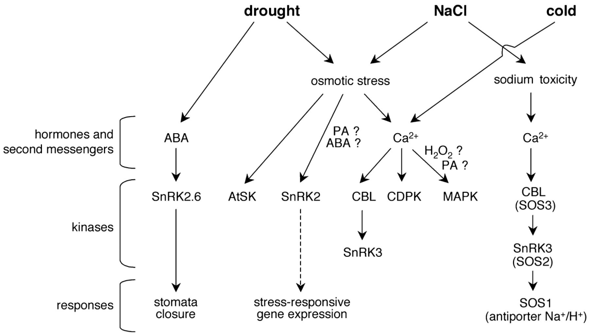
  $$K_{\hat{\theta}}(x^{(i_1)}, x^{(i_2)}) = s_{\hat{\theta}}(x^{(i_1)})^T s_{\hat{\theta}}(x^{(i_2)})$$

  $\rightarrow$ similarity of datasets $D + x^{(i_1)}$ and $D + x^{(i_2)}$ regarding model-based summary statistics

- Parameters of biological interest in our model:
  coefficients of target gene neighbors

Case study on plant osmotic stress

- Osmotic stress: dehydration of plant
- Causes: drought, salt, or cold conditions
- Relevance: important abiotic stress for crop productivity
- Cellular response:



Boudsocq M , Laurière C Plant Physiol. 2005;138:1185-1194

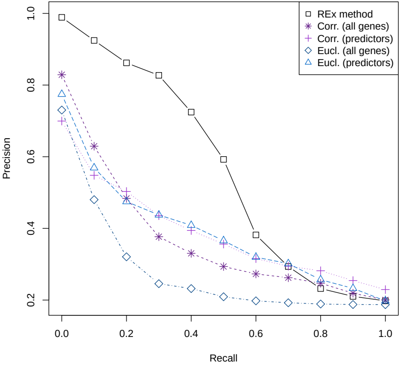
Case study on plant stress

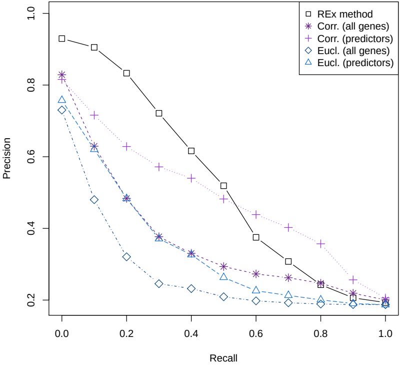
- Data: 141 differential expression profiles from 38 *A. thaliana* stress datasets, 6658 diff. expr. genes
- Task: retrieval of osmotic stress experiments (31 profiles from 5 datasets, $\geq$ 6 profiles per dataset)
- Target gene lists from two sources:
  - 10 water-stress related genes (TF DREB2A + targets)

    (Sakuma *et al.*, PNAS, 2006)
  - 41 genes annotated as 'drought-salt-cold'

    (STIFDB, Shameer *et al.*, Int J Plant Genomics, 2009)
  - *overlap: 4 genes*
- Experimental setup:
  - One left-out dataset as queries (cross-validation)
  - Unsupervised model training with all other profiles (including osmotic and non-osmotic)

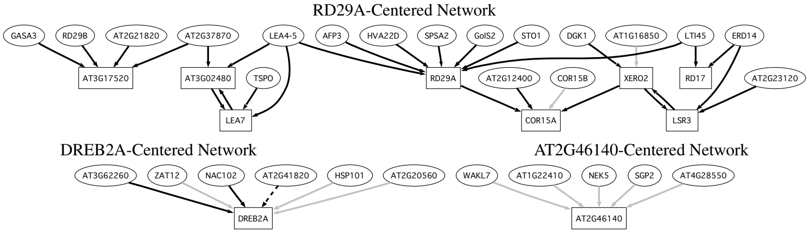
Precision-recall analysis


Target list: Sakuma-water


Target list: STIFDB

- Modeling targeted gene relationships helps

Osmotic stress network analysis



RD29A-Centered Network

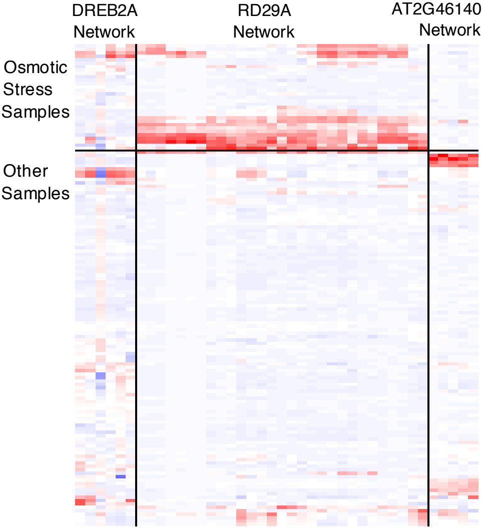
DREB2A-Centered Network

AT2G46140-Centered Network

- Top edges in bootstrapping

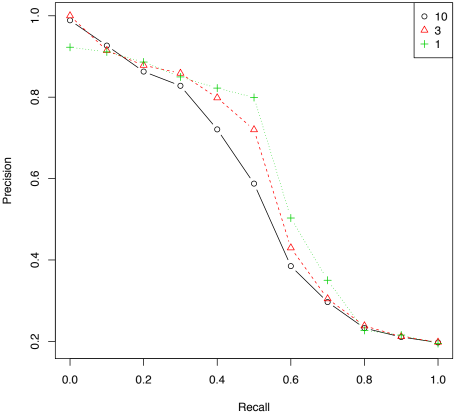
Target	Predictor	Stress-related annotation of predictor?
RD17	LTI45	yes (also included in STIFDB)
COR15A	COR15B	yes (also included in STIFDB)
XERO2	LSR3	yes (also included in Sakuma-water)
RD29A	LTI45	yes (also included in STIFDB)
AT3G02480	LEA7	yes (also included in Sakuma-water)
AT1G52690	AT3G02480	yes (also included in Sakuma-water)
LSR3	XERO2	yes (also included in Sakuma-water)
LSR3	ERD14	yes (also included in STIFDB)
AT3G17520	RD29B	yes (response to water deprivation)
RD17	ERD14	yes (also included in STIFDB)
DREB2A	AT3G62260	– (protein phosphatase 2C)
DREB2A	ZAT12	yes (involved in cold acclimation)

Model-based comparison of measurements



Discriminative target genes

- Test performance of optimal subsets of size *k*



- Best subset of size 1: RD29A (**r**esponsive to **d**ehydration)
- Best subset of size 3: RD29A, LEA7, COR15A

Discussion

- Summary: targeted retrieval using regulatory model
- Purpose: investigating specific commonalities between biological conditions based on (putative) gene relationships
- Efficiency: gene-specific models can be pre-computed
- Open questions:
  - Given promising performance with simple model, what is the most suitable model for retrieval? (also supervised options, prior knowledge, . . .)
  - Is the conceptual idea feasible for applications with heterogeneous data? (different platforms, species, measurement types, . . .)