V11: Structure Learning in Bayesian Networks

In lectures V9 and V10 we made the strong assumption
that we know in advance the network structure.

Today, we consider the task of learning in situations
where we do not know the structure of the BN in advance.

Instead, we will apply the strong assumption that our data set is fully observed.

As before, we assume that the data D are generated IID
from an underlying distribution P*(X).

We assume that P* is induced by some Bayesian network G* over X.

Example: coin toss

Consider an experiment where we toss 2 standard coins X and Y independently.

We are given a data set with 100 instances of this experiment
and would like to learn a model for this scenario.

A „typical“ data set may have the entries for X and Y:

27 head/head	22 head/tail
25 tail/head	26 tail/tail

In this empirical distribution, the 2 coins are apparently not fully independent.
(If X = tail, the chance for Y = tail appears higher than if X = head).

This is quite expected because the probability of tossing 100 pairs of fair coins
and getting exactly 25 outcomes in each category is only about 1/1000.

Thus, even if the coins are indeed indepdendent, we do not expect that
the observed empirical distribution will satisfy independence.

Example: coin toss

Suppose we get the same results in a very different situation.

Say we scan the sports section of our local newspaper for 100 days
and choose an article at random each day.

We mark $X = x^1$ if the word „rain“ appears in the article and $X = x^0$ otherwise.

Similarly, Y denotes whether the word „football“ appears in the article.

Our intuition whether the two random variables are independent is unclear.

If we get the same empirical counts as in the coins described before,
we might suspect that there is some weak connection.

In other words, it is hard to be sure whether the true underlying
model has an edge between X and Y or not.

Goals of the learning process

The goal of learning G* from the data is hard to achieve because

- the data sampled from P* are typically noisy and
- do not reconstruct P* perfectly.

We cannot detect with complete reliability which independencies are present in the underlying distribution.

Therefore, we must generally make a decision about our willingness to include in our learned model edges about which we are less sure.

If we include more of these edges, we will often learn a model that contains **spurious edges.**

If we include few edges, we may **miss independencies**.

The **decision** which **compromise** is **better** depends on the **application**.

Independence in coin toss example?

It seems that if we do make mistakes in the structure, it is better to have too many rather than too few edges. But the situation is more complex.

Let‘s go back to the coin example and assume that we had only 20 cases for X/Y:

3 head/head	6 head/tail
5 tail/head	6 tail/tail

When we assume X and Y as correlated, we find by MLE (where we simply count the observed numbers):

$P(X = H) = 9/20 = 0.45$

$P(Y = H \mid X = H) = 3/9 = 1/3$

$P(Y = H \mid X = T) = 5/11$

In the independent structure (no edge between X and Y), $P(Y = H) = 8/20 = 0.4$

Noisy data → prefer sparse models

All of these parameter estimates are imperfect, of course.

The ones in the more complex model are significantly more likely to be skewed *(dt: verzogen)* because each one is estimated from a much smaller data set.

E.g. P(Y = H | X = H) is estimated from only 9 instances
compared to 20 instances for the estimation of P(Y = H).

Note that the standard estimation error of MLE is $1/\sqrt{M}$.

When doing density estimation from limited data,
it is often better to prefer a sparser structure.

Overview of structure learning methods

Roughly speaking, there are 3 approaches to learning
without a prespecified structure:

(1) constraint-based structure learning

Finds a model that best explains the dependencies/independencies in the data.

(2) **Score-based** stucture learning (today)

We define a hypothesis space of potential models and a scoring function
that measures how well the model fits the observed data.
Our computational task is then to find the highest-scoring network.

(3) **Bayesian model averaging** methods

Generates an ensemble of possible structures.

Structure Scores

We will discuss 2 obvious choices of scoring functions:

- Maximum likelihood parameters (today)
- Bayesian scores (V12)

Maximum likelihood parameters

This function measures the probability of the data given a model.

→ try to find a model that would make the data as probable as possible.

A **model** is a **pair** $\langle G, \theta_G \rangle$.

Our **goal** is to find both a **graph** G and **parameters** θ_G
that **maximize** the **likelihood**.

Maximum likelihood parameters

In V9 we determined how to maximize the likelihood for a given structure G.

We will simply use these maximum likelihood parameters $\hat{\theta}_G$ for each graph.

$$\max_{G,\theta_G} L(\langle G, \theta_G \rangle : D) = \max_G \left[\max_{\theta_G} L(\langle G, \theta_G \rangle : D) \right]$$
$$= \max_G L\left(\langle G, \hat{\theta}_G \rangle : D\right)$$

To find the maximum likelihood (G, θ_G) pair, we should find the graph structure G that achieves the highest likelihood *when we use the MLE parameters* for G.

We define $\mathbf{score}_L(G : D) = l\left(\hat{\theta}_G : D\right)$

where $l\left(\hat{\theta}_G : D\right)$ is the logarithm of the likelihood function
and $\hat{\theta}_G$ are the maximum likelihood parameters for G.

Maximum likelihood parameters

Let us consider again the scenario of the 2 coins.

In model G_0, X and Y are assumed to be independent. In this case, we get

$$\text{score}_L(G_0 : D) = \sum_m \log \hat{\theta}_{x[m]} + \log \hat{\theta}_{y[m]}$$

In model G_1, we assume a dependency modelled by the arc X → Y. We get

$$\text{score}_L(G_1 : D) = \sum_m \log \hat{\theta}_{x[m]} + \log \hat{\theta}_{y[m]|x[m]}$$

where $\hat{\theta}_x$ is the maximum likelihood estimate for P(x)

and $\hat{\theta}_{y|x}$ is the maximum likelihood estimate for P(y | x).

The scores of the two models share a common component, the first term.

Maximum likelihood parameters

Thus, we can write the difference between the two scores as:

$$\text{score}_L(G_1 : D) - \text{score}_L(G_0 : D) = \sum_m \log \hat{\theta}_{y[m]|x[m]} - \log \hat{\theta}_{y[m]}$$

By counting how many times each conditional probability parameter appears in this term, we can change the summation index and write this as:

$$\text{score}_L(G_1 : D) - \text{score}_L(G_0 : D) = \sum_{x,y} M[x,y] \log \hat{\theta}_{y|x} - \sum_y M[y] \log \hat{\theta}_y$$

Let $\hat{P}$ be the empirical distribution observed in the data;
that is $\hat{P}(x,y)$ is the empirical frequency of *x,y* in D.

Then we can write $\mathrm{M}[x,y] = M \cdot \hat{P}(x,y)$ and $\mathrm{M}[y] = M \cdot \hat{P}(y)$

Moreover, $\hat{\theta}_{y|x} = \hat{P}(y|x) = \frac{\hat{P}(x,y)}{\hat{P}(x)}$ and $\hat{\theta}_y = \hat{P}(y)$

Mutual information

We get

$$\text{score}_L(G_1 : D) - \text{score}_L(G_0 : D) = M \sum_{x,y} \hat{P}(x,y) \log \frac{\hat{P}(x,y)}{\hat{P}(x)\hat{P}(y)} = M \cdot \mathbf{I}_{\hat{P}}(X;Y)$$

where $\mathbf{I}_{\hat{P}}(X;Y)$ is the **mutual information** between X and Y in the distribution $\hat{P}$.

The likelihood of model G_1 thus depends on
the mutual information between X and Y.

Note that higher mutual information implies
stronger dependency.

Thus, stronger dependency implies stronger preference
for the model where X and Y depend on each other.

Can this be generalized to general network structures?

Decomposition of Maximum likelihood scores

Proposition: the likelihood score decomposes as follows:

$$\text{score}_L(G:D) = M\sum_{i=1}^{n}\mathbf{I}_{\hat{P}}\left(X_i; Pa_{X_i}{}^{G}\right) - M\sum_{i=1}^{n}\hat{P}(x_i)\log\frac{1}{\hat{P}(x_i)}$$

$$= M\sum_{i=1}^{n}\mathbf{I}_{\hat{P}}\left(X_i; Pa_{X_i}{}^{G}\right) - M\sum_{i=1}^{n}\boldsymbol{H}_{\hat{P}}(X_i)$$

Proof: omitted

The likelihood of a network measures the strength
of the dependencies between variables and their parents.

We prefer networks where the parents of each variable are informative about it.

Maximum likelihood parameters

We can also express this result in a complementary manner.

Corollorary: Let $X_1, \ldots, X_n$ be an ordering of the variables that is consistent with edges in G. Then

$$\frac{1}{M}\text{score}_L(G:D) = \boldsymbol{H}_{\hat{P}}(X_1, \ldots, X_n) - \sum_{i=1}^{n} \mathbf{I}_{\hat{P}}\left(X_i; \{X_1, \ldots, X_{i-1}\} - Pa_{X_i}{}^{G} | Pa_{X_i}{}^{G}\right)$$

The first term on the right-hand-side does not depend on the structure, but the second term does.

The second term involves conditional mutual-information of variable X_i and the preceding variables given the parents of X_i.

Limitations of the maximum likelihood score

The likelihood score is a good measure
of the fit of the estimated BN and the training data.

Important, however, is the performance of the learned network on new instances.

It turns out that the MLE score never prefers simpler networks over more complex networks. The optimal ML network will always be a fully connected network.

Thus, the ML overfits the training data.

The model often does not generalize well to new data cases.

Structure search

The input to the optimization problem is:

- training set D
- scoring function (including priors, if needed)
- a set G of possible network structures

Our desired output:

- a network structure (from the set of possible structures) that maximizes the score.

We assume that we can decompose the score of the network structure G:

$$score(G:D) = \sum_i FamScore\left(X_i \middle| Pa_{X_i}{}^G : D\right)$$

as the sum of **family scores**.

FamScore(X | U : D) is a score measuring how well
a set of variables U serves as parents of X in the data set D.

Tree-structure networks

Structure learning of tree-structure networks is the simplest case.

Definition: in **tree-structured network structures** G,
each variable X has at most one parent in G.

The advantage of trees is that they can be learned efficiently in polynomial time.

Learning a tree model is often used as a starting point
for learning more complex structures.

Key properties to be used:
- decomposability of the score
- restriction on the number of parents

Score of tree structure

Instead of maximizing the score of a tree structure G,
we will try to **maximize** the **difference** between its **score**
and the score of the empty structure G_0.

$$\Delta(G) = score(G:D) - score(G_0:D)$$

$score(G_0:D)$ is simply a sum of terrms $FamScore(X_i:D)$ for each X_i.

That is the score of X_i if it does not have any parents.

The score $score(G:D)$ consists of terms $FamScore\left(X_i \middle| {Pa_{X_i}}^G : D\right)$.

Now there are 2 cases:

If ${Pa_{X_i}}^G = \emptyset$, then the terms for X_i in both scores cancel out.

Structure search

If $Pa_{X_i}{}^{G} = X_j$ we are left with the difference between the 2 terms.

$$\Delta(G) = \sum_{i, Pa_{X_i}{}^{G} \neq \emptyset} \left(FamScore\left(X_i \middle| Pa_{X_i}{}^{G} : D\right) - FamScore(X_i : D) \right)$$

If we define the weight

$$w_{j \to i} = FamScore\left(X_i \middle| X_j : D\right) - FamScore(X_i : D)$$

then we see that Δ(G) is the sum of weights on pairs X_i, X_j such that $X_j \to X_i$ in G

$$\Delta(G) = \sum_{X_j \to X_i \in G} w_{j \to i}$$

We have thus transformed our problem to one of finding
a **maximum weight spanning forest** in a directed weighted graph.

General case

For a general model topology that may also involve cycles,
we start by considering the search space.

We can think of the search space as a **graph**
over **candidate solutions** (different network topologies).

Nodes are connected by operators that transform one network into the other one.

If each state has **few neighbors**, the search procedure only
has to consider few solutions at each point of the search.

However, the search for an optimal (or high-scoring) solution
may be long and complex.

On the other hand, if each state has **many neighbors**, the search may involve
only a few steps, but it may be difficult to decide at each step which point to take.

General case

A good trade-off for this problem chooses reasonably few neighbors for each state but ensures that the „diameter“ of the search space remains small.

A natural choice for the neighbors of a state is a set of structures that are identical to it except for **small „local“ modifications**.

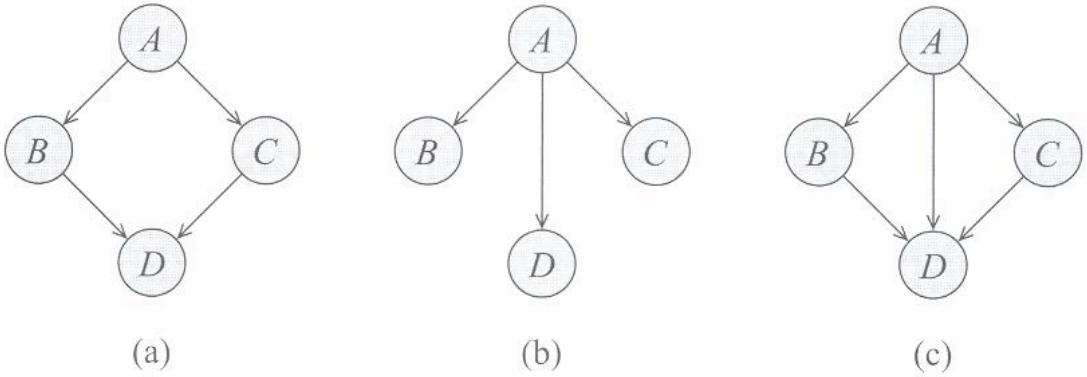
We will consider the following set of modifications of this sort:

- **Edge addition**
- **Edge deletion**
- **Edge reversal**

The **diameter** of the **search space** is then at most n^2.

(We could first delete all edges in G_1 that do not appear in G_2 and then add the edges of G_2 that are not in G_1. This is bounded by the total number of possible edges n^2).

Example requiring edge deletion



(a) Original model that generated the data
(b) and (c) Intermediate networks encountered during the search.

Let‘s assume that A is highly informative about B and C.

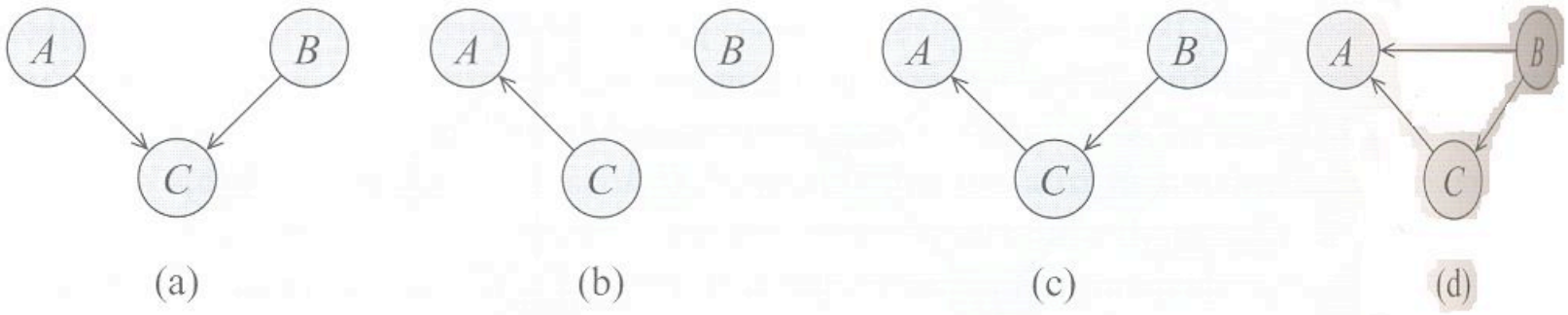
When starting from an empty network,
edges A → B and A → C would be added first.

Sometimes, we may also add the edge A → D. Since A is informative about B and C (which are the parents of D), A is also informative about D -> (b)

Later, we may also add the edges B → D and C → D -> (c)

Node A cannot provide additional information on top of what B and C convery.
Deleting A → D therefore makes the score optimal.

Example requiring edge reversal



(a) Original network, (b) and (c) intermediate networks during search.
(d) Undesirable outcome.

When adding edges, we do not know their direction because both directions give the same score.

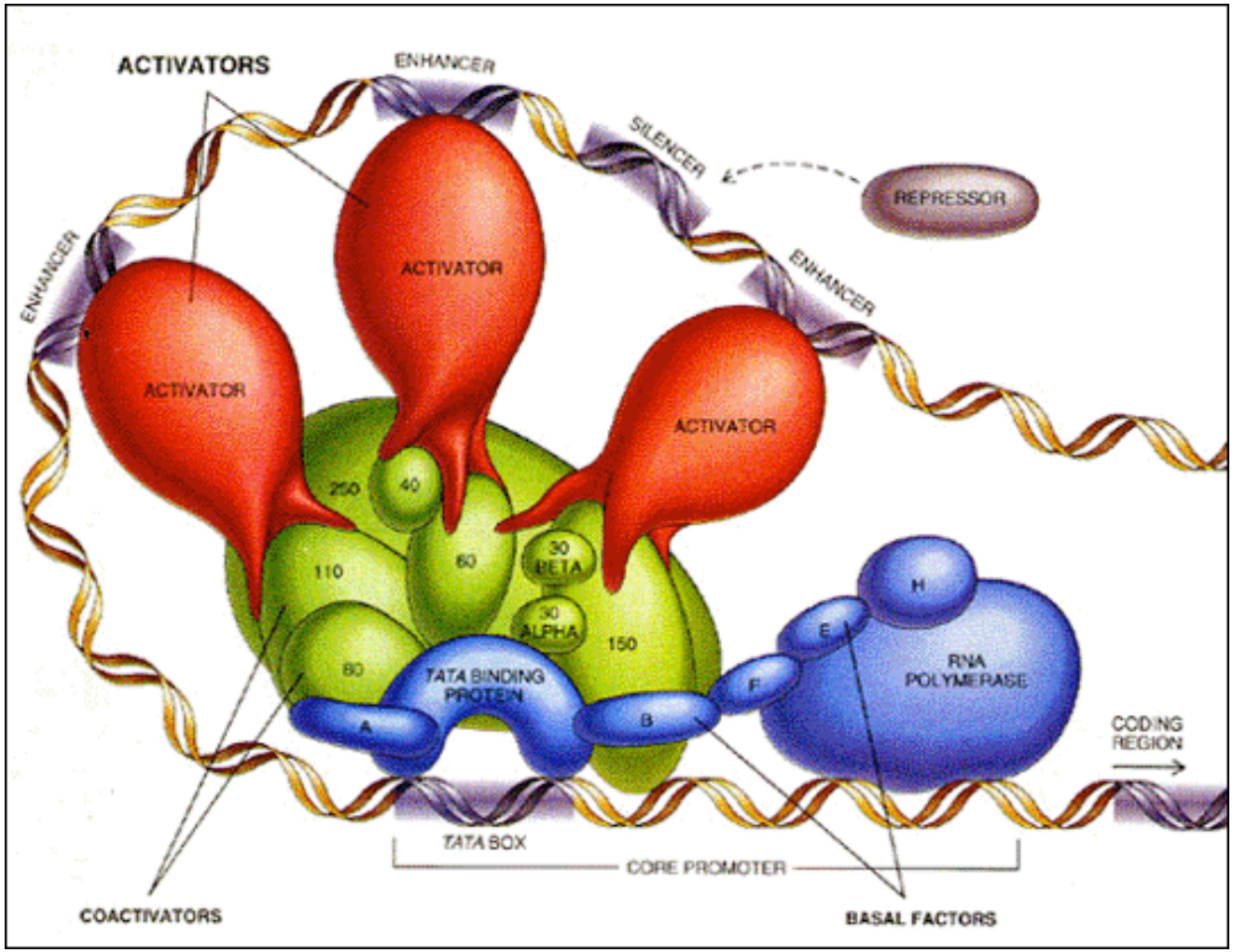
This is where edge reversal helps.

In situation (c) we realize that A and B together should make the best prediction of C. Therefore, we need to reverse the direction of the arc pointing at A.

We will continue with structure learning in V12

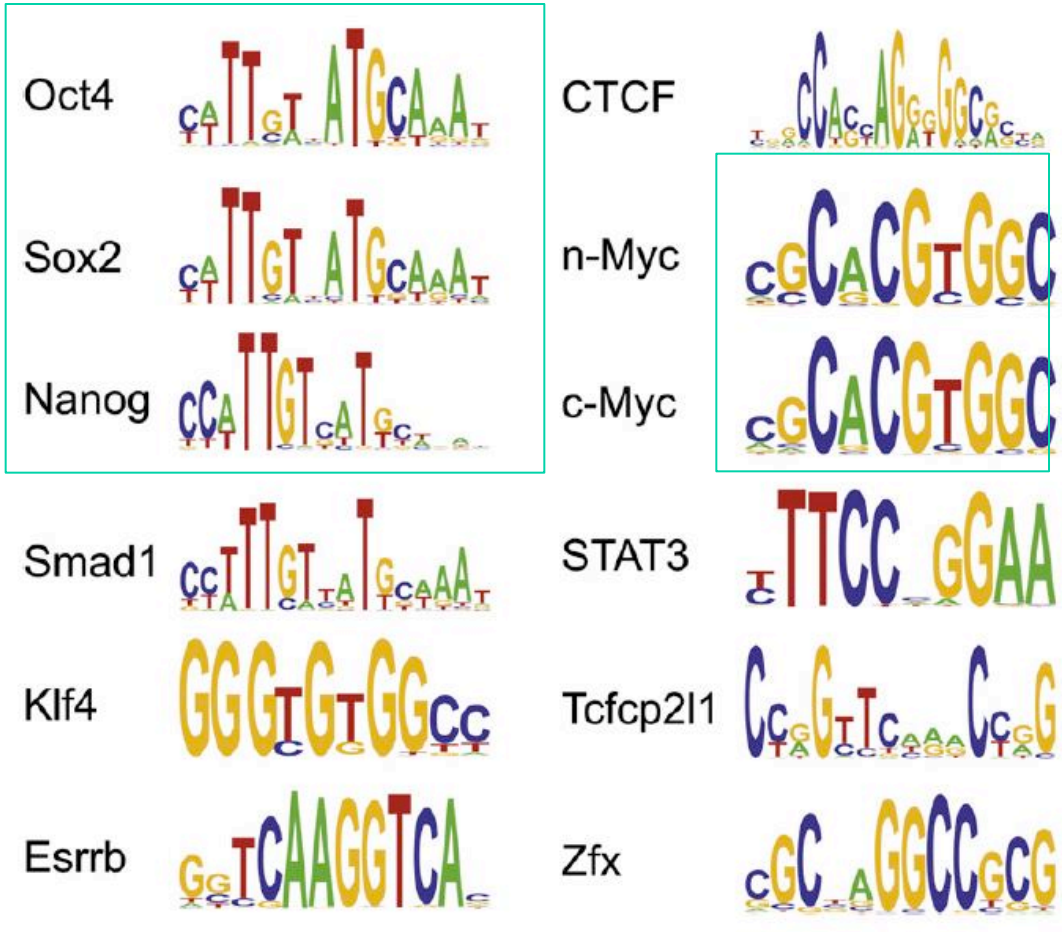
Who controls the developmental status of a cell?

Transcription

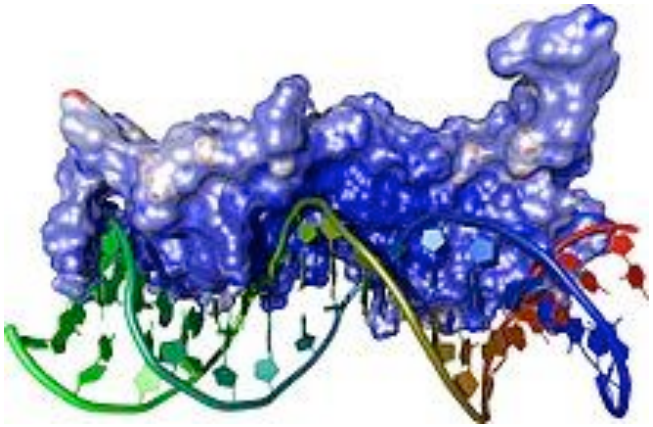


http://www.berkeley.edu/news/features/1999/12/09_nogales.html

Preferred transcription factor binding motifs



Chen et al., Cell 133, 1106-1117 (2008)



DNA-binding domain of a glucocorticoid receptor from *Rattus norvegicus* with matching DNA fragment.

www.wikipedia.de

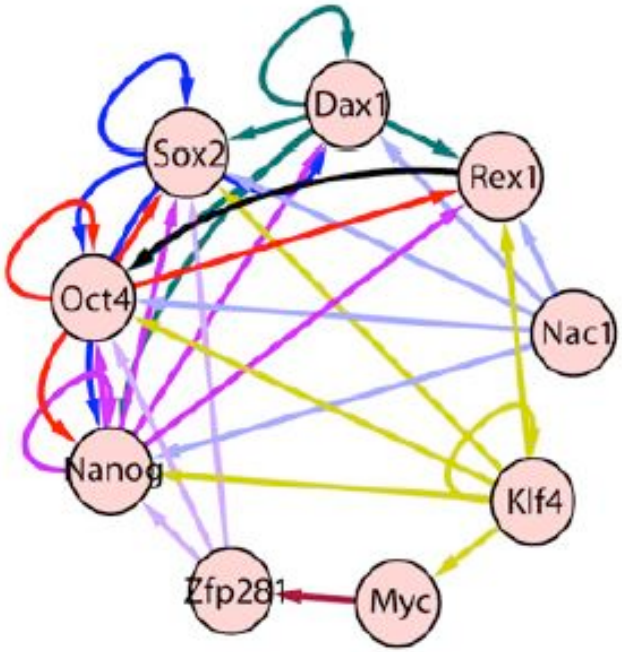
Gene regulatory network around Oc4 controls pluripotency

Tightly interwoven network of 9 transcription factors keeps ES cells in pluripotent state.

6632 human genes have binding site in their promoter region for at least one of these 9 TFs.

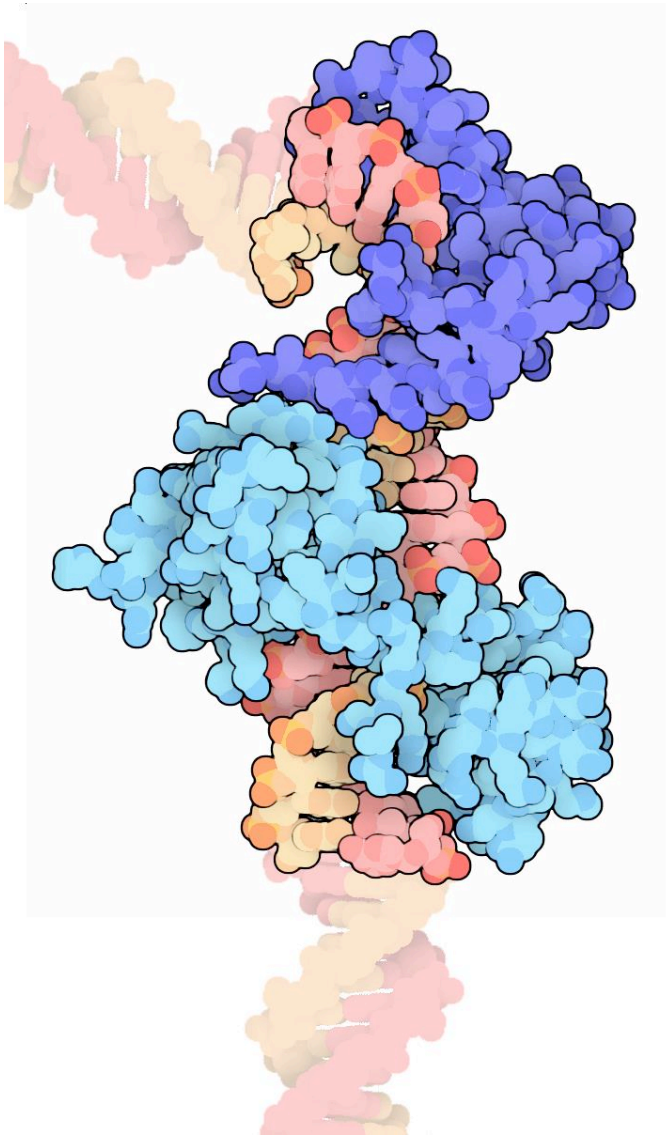
Many genes have multiple motifs.

800 genes bind ≥ 4 TFs.



Kim et al. Cell 132, 1049 (2008)

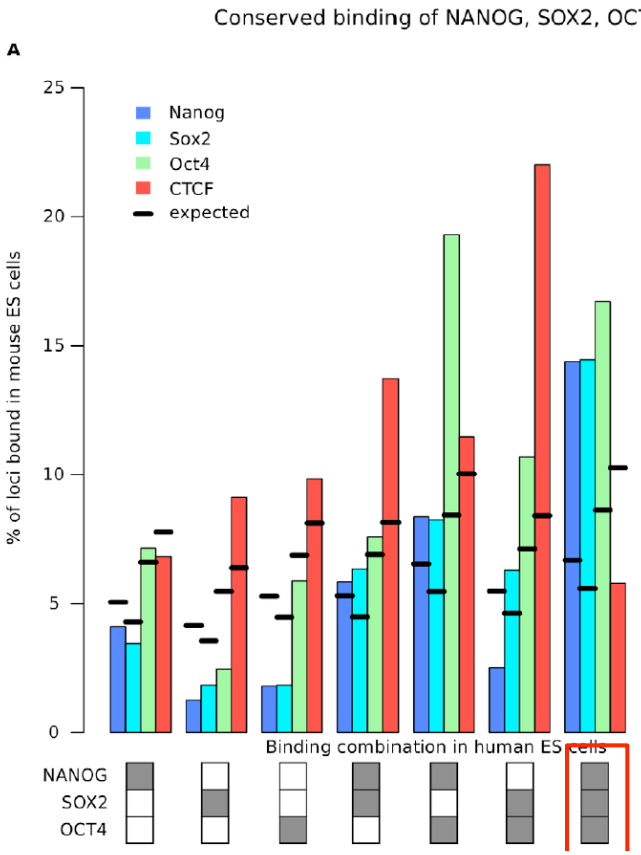
Complex of transcription factors Oct4 and Sox2



Idea: Check for conserved transcription factor binding sites in mouse and human

www.rcsb.org

Combined binding of Oct4, Sox2 and Nanog



Göke et al., PLoS Comput Biol 7, e1002304 (2011)

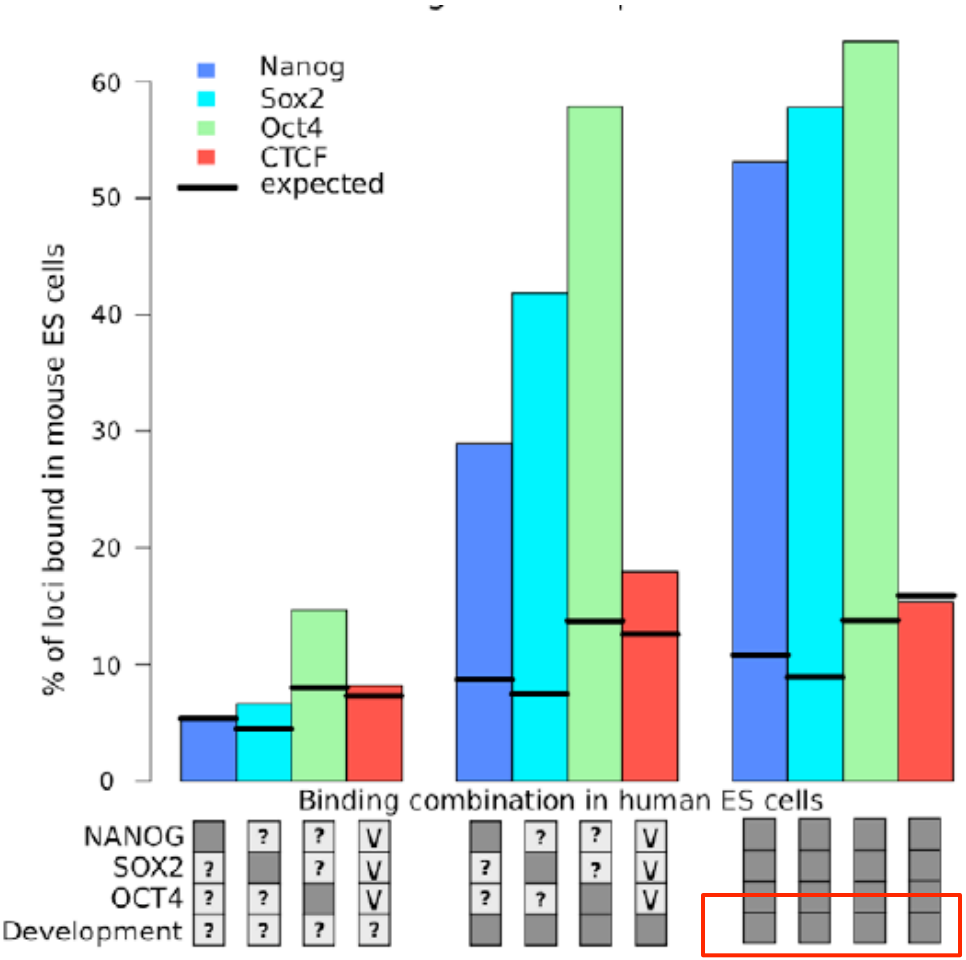
The combination of OCT4, SOX2 and NANOG influences conservation of binding events.

(A) Bars indicate the fraction of loci where binding of Nanog, Sox2, Oct4 or CTCF can be observed at the orthologous locus in mouse ES cells for all combinations of OCT4, SOX2 and NANOG in human ES cells as indicated by the boxes below.

Dark boxes indicate binding, white boxes indicate no binding (“AND” relation).

Combinatorial binding of OCT4, SOX2 and NANOG shows the largest fraction of conserved binding for Oct4, Sox2 and Nanog in mouse.

Increased Binding conservation in ES cells at developmental enhancers



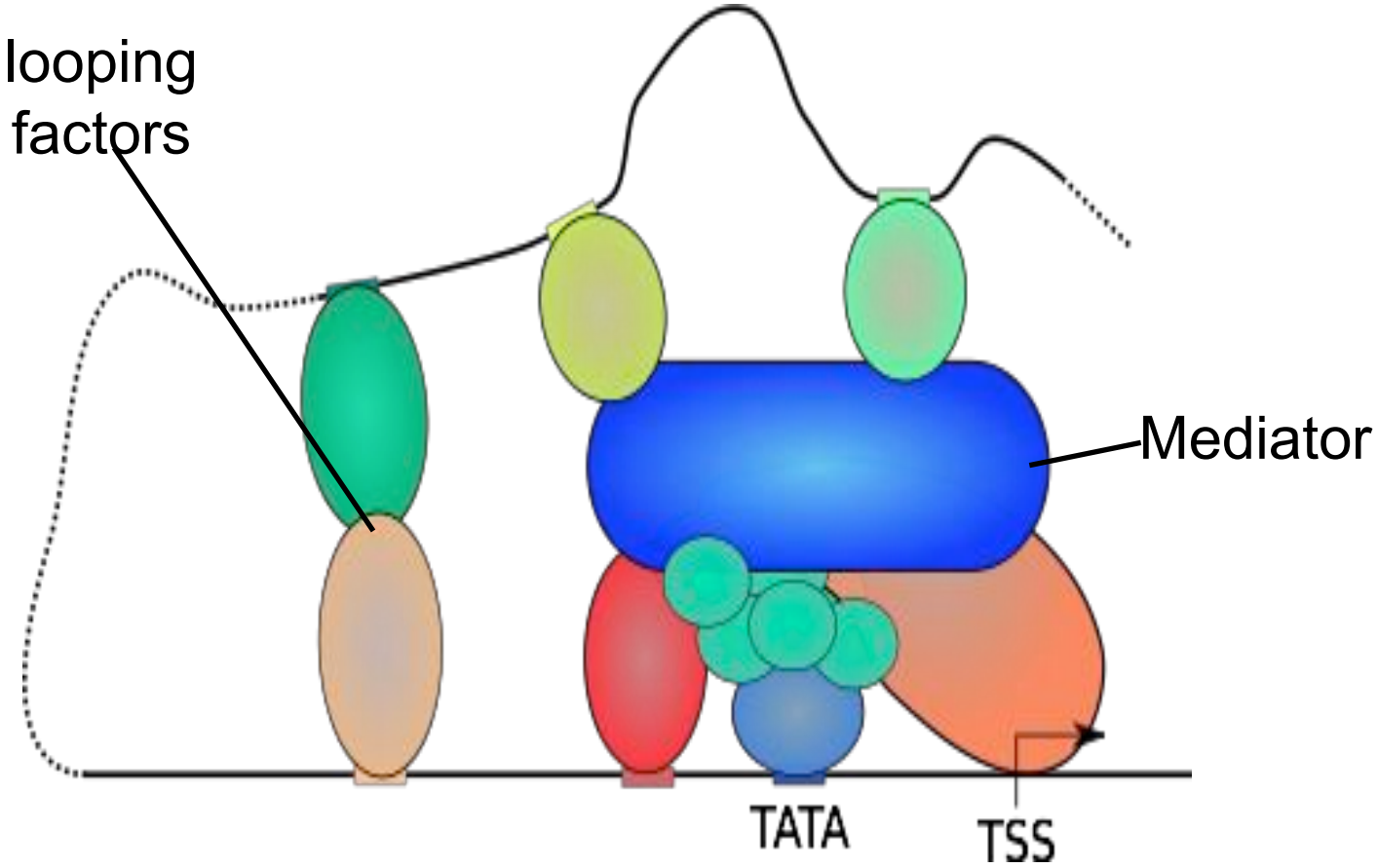
Fraction of loci where binding of Nanog, Sox2, Oct4 and CTCF can be observed at the orthologous locus in mouse ESC.

Combinations of OCT4, SOX2 and NANOG in human ES cells are discriminated by developmental activity as indicated by the boxes below.
Dark boxes : "AND" relation,
light grey boxes with "v" : "OR" relation, '
'?" : no restriction.

Combinatorial binding events at develop-mentally active enhancers show the highest levels of binding conservation between mouse and human ES cells.

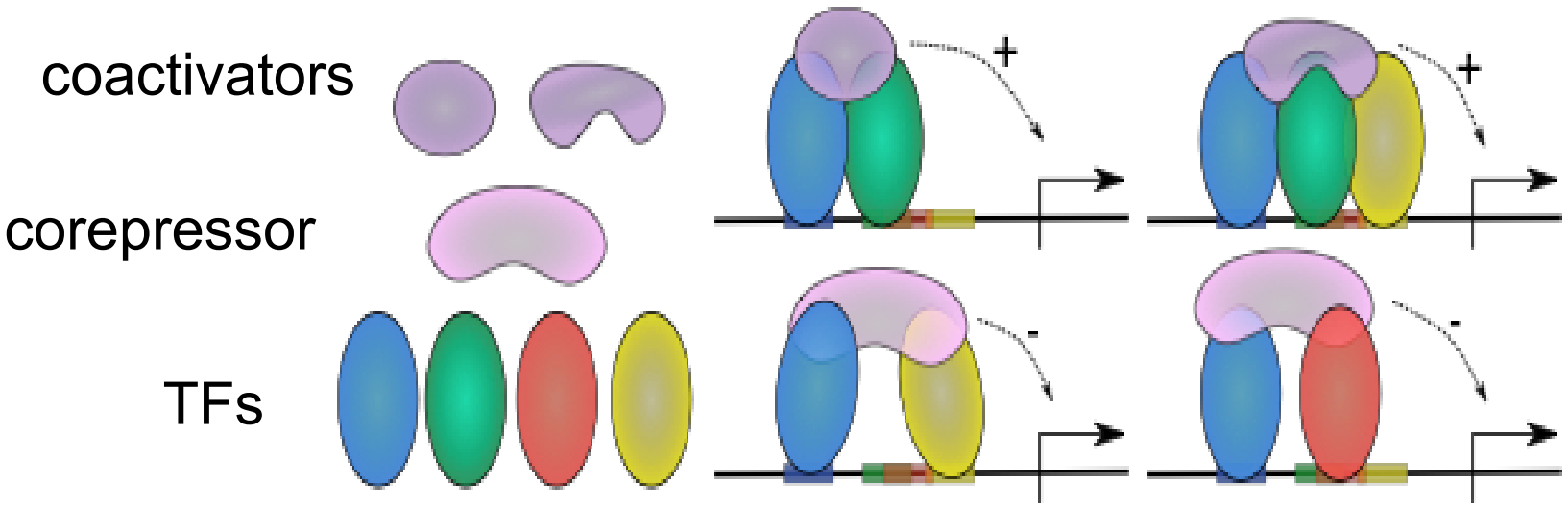
Göke et al., PLoS Comput Biol 7, e1002304 (2011)

Transcriptional activation



DNA-looping enables interactions for the distal promotor regions,
Mediator cofactor-complex serves as a huge linker

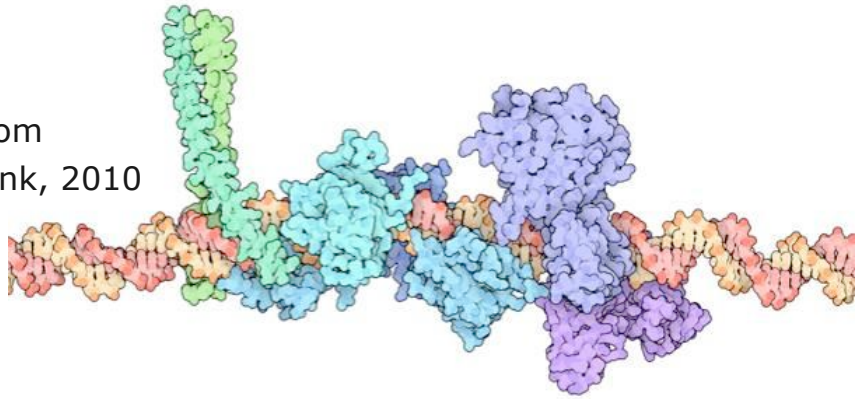
cis-regulatory modules



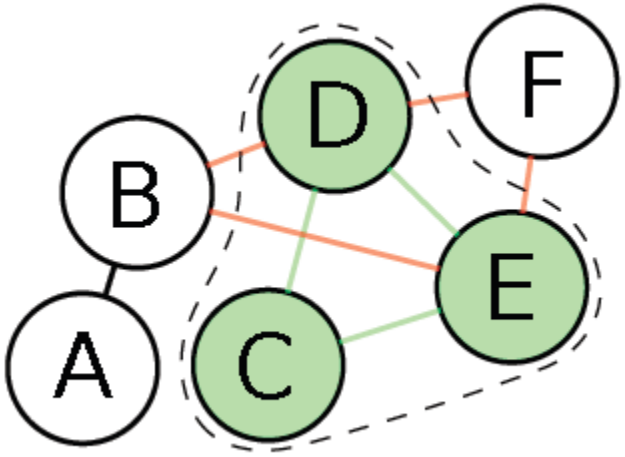
TFs are not dedicated activators or respressors!

It‘s the assembly that is crucial.

IFN-enhanceosome from
RCSB Protein Data Bank, 2010



Aim:
identify Protein complexes involving transcription factors



Borrow idea from ClusterOne method:

Identify candidates of TF complexes

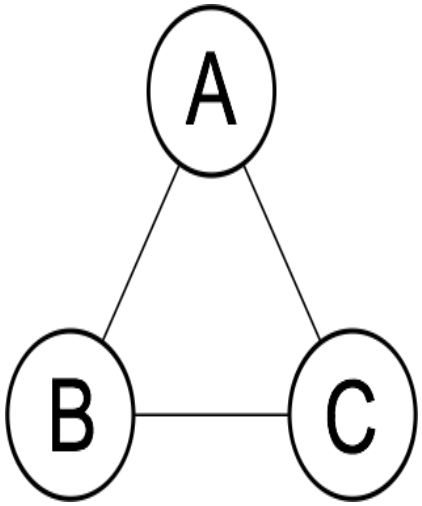
in protein-protein interaction graph

by optimizing the cohesiveness

$$f(V) = \frac{w^{in}(V)}{w^{in}(V) + w^{bound}(V)}$$

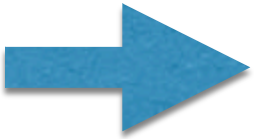
Thorsten Will,
Master thesis
(accepted for ECCB 2014)

DDI model

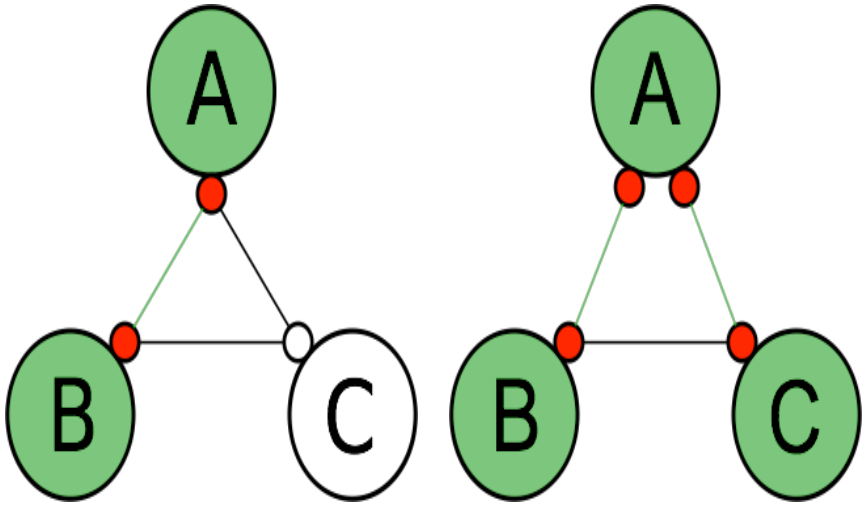


"protein-level" network

transition to domain-domain interactions



"domain-level" network

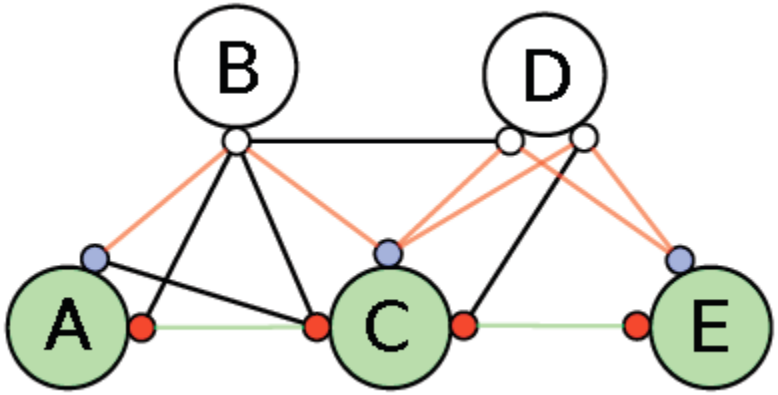


domain interactions can reveal which proteins can bind simultaneously if interactions per domain are restricted

Ozawa et al., BMC Bioinformatics, 2010
Ma et al., BBAPAP, 2012

underlying domain-domain representation of PPIs

Assumption: every domain can only participate in one interaction.

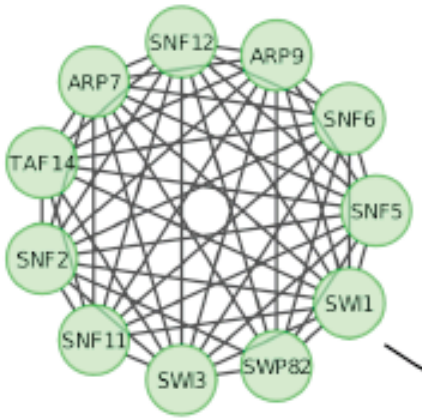


Green proteins A, C, E form actual complex.

Their red domains are connected by the two green edges.

B and D are incident proteins. They could form new interactions (red edges) with unused domains (blue) of A, C, E

data source used: Yeast Promoter Atlas, PPI and DDI



weighted protein-protein interaction data, such as

PrePPI

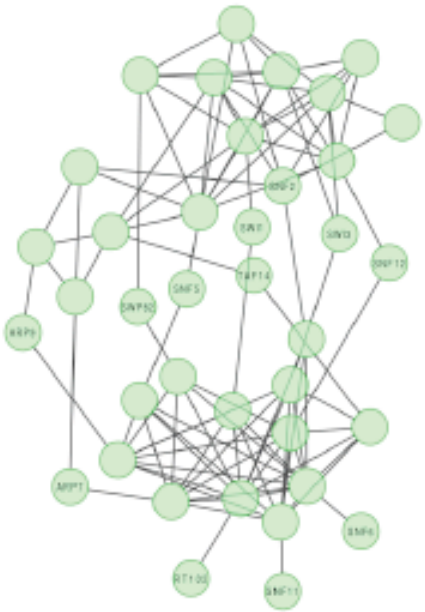
SIF format with UniProt IDs

seed proteins,
threshold for pairs,
max. depth of search

domain-aware cohesiveness optimization algorithm

transcription factor complex candidates

UniProt EMBL-EBI



domain-domain interaction network

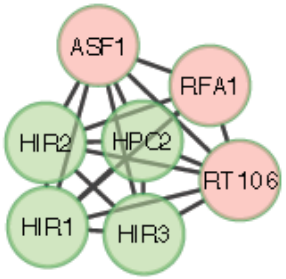
data retrieval and buildup automatically

Pfam InterPro DOMINE IDDI

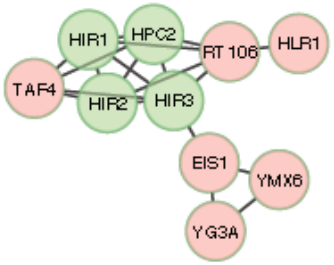
Daco identifies far more TF complexes than other methods

	DACO	Cl1ps	Cl1s	Cl1	MCD	MCL
TF complexes	1375	175/176	61/63	106/106	16/38	75/79
TF variants	412	134/138	59/61	80/80	16/38	75/79

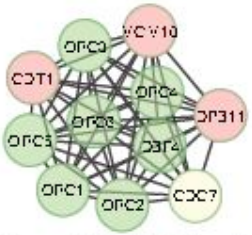
Examples of TF complexes – comparison with ClusterONE



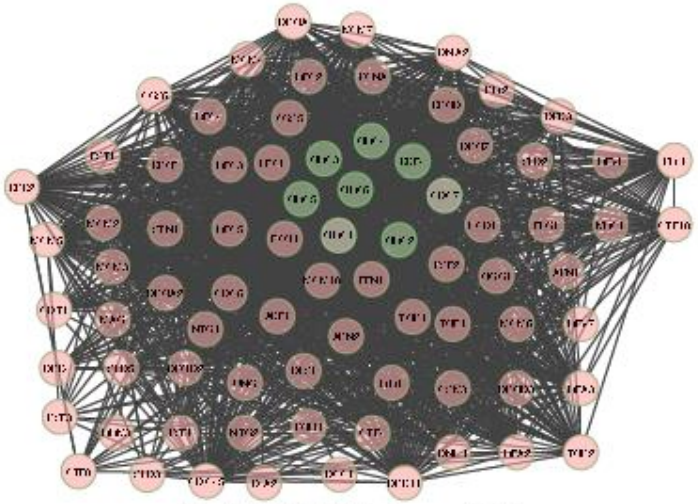
(a) HIR(SGD) / DACO



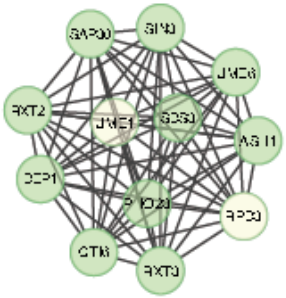
(b) HIR(SGD) / ClusterONE



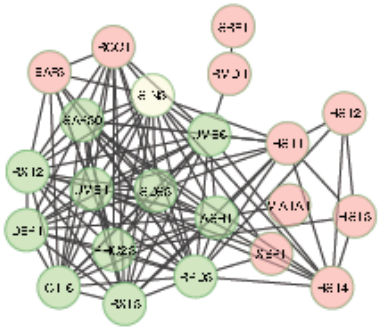
(e) ORC(MIPS) / DACO



(f) ORC(MIPS) / ClusterONE



(c) RPD3L(CYC2008) / DACO

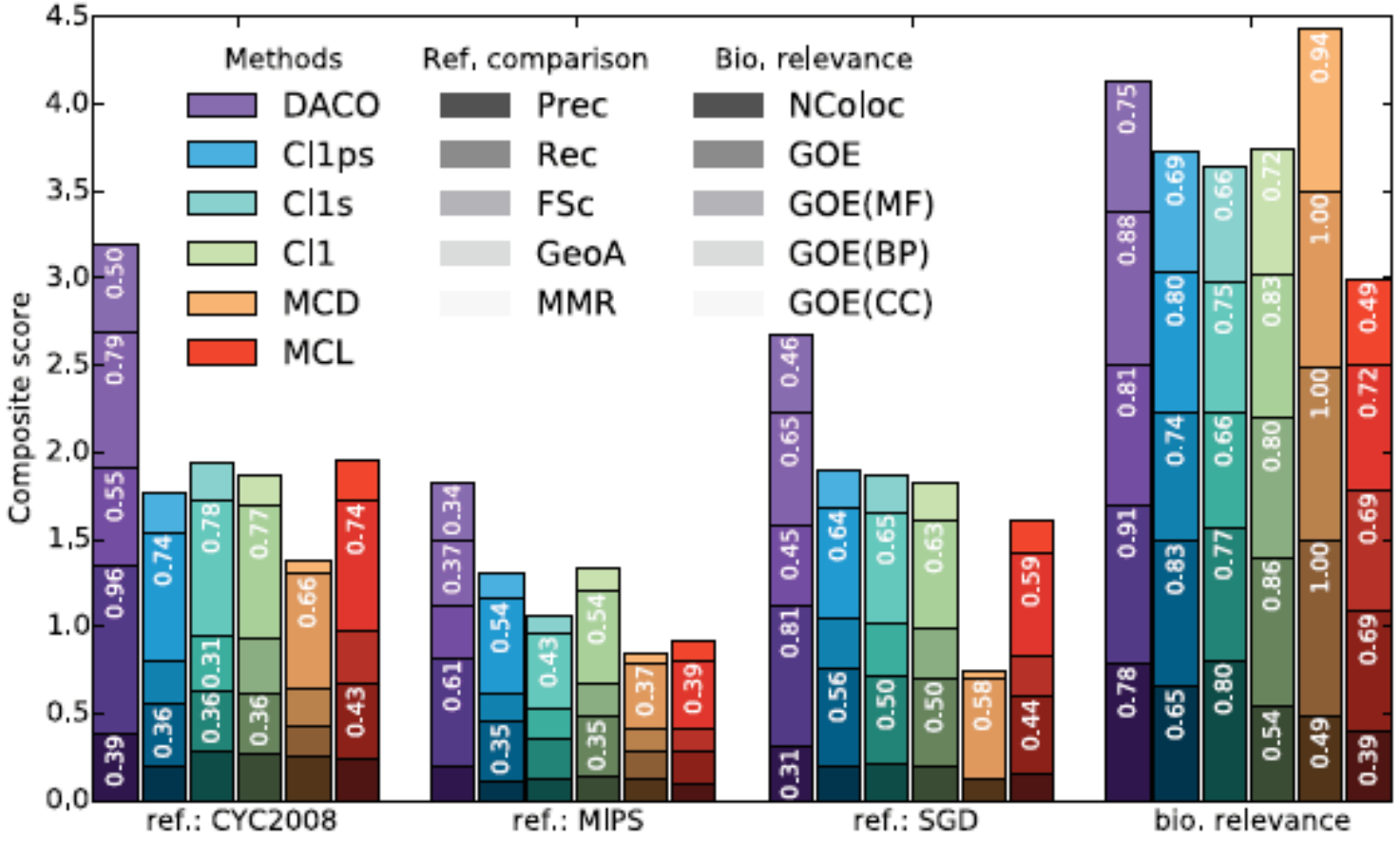


(d) RPD3L(CYC2008) / ClusterONE

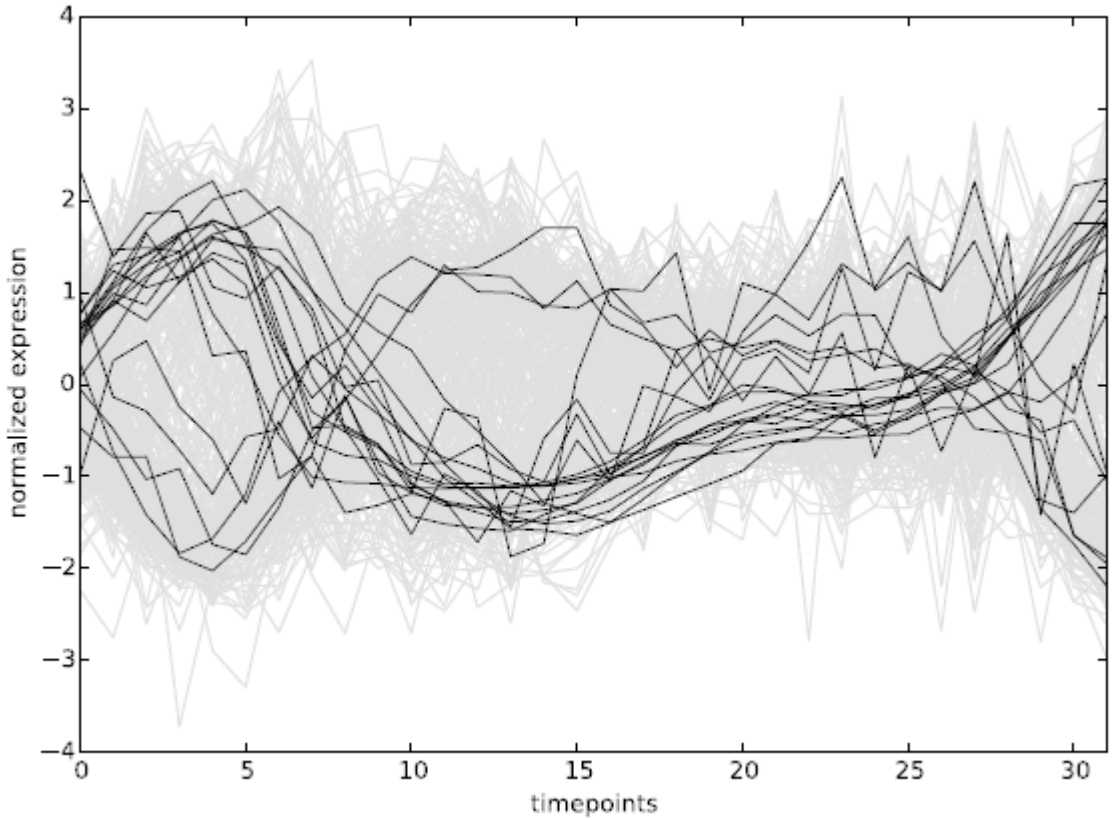
Green nodes: proteins in the reference that were matched by the prediction

red nodes: proteins that are in the predicted complex, but not part of the reference.

Performance evaluation



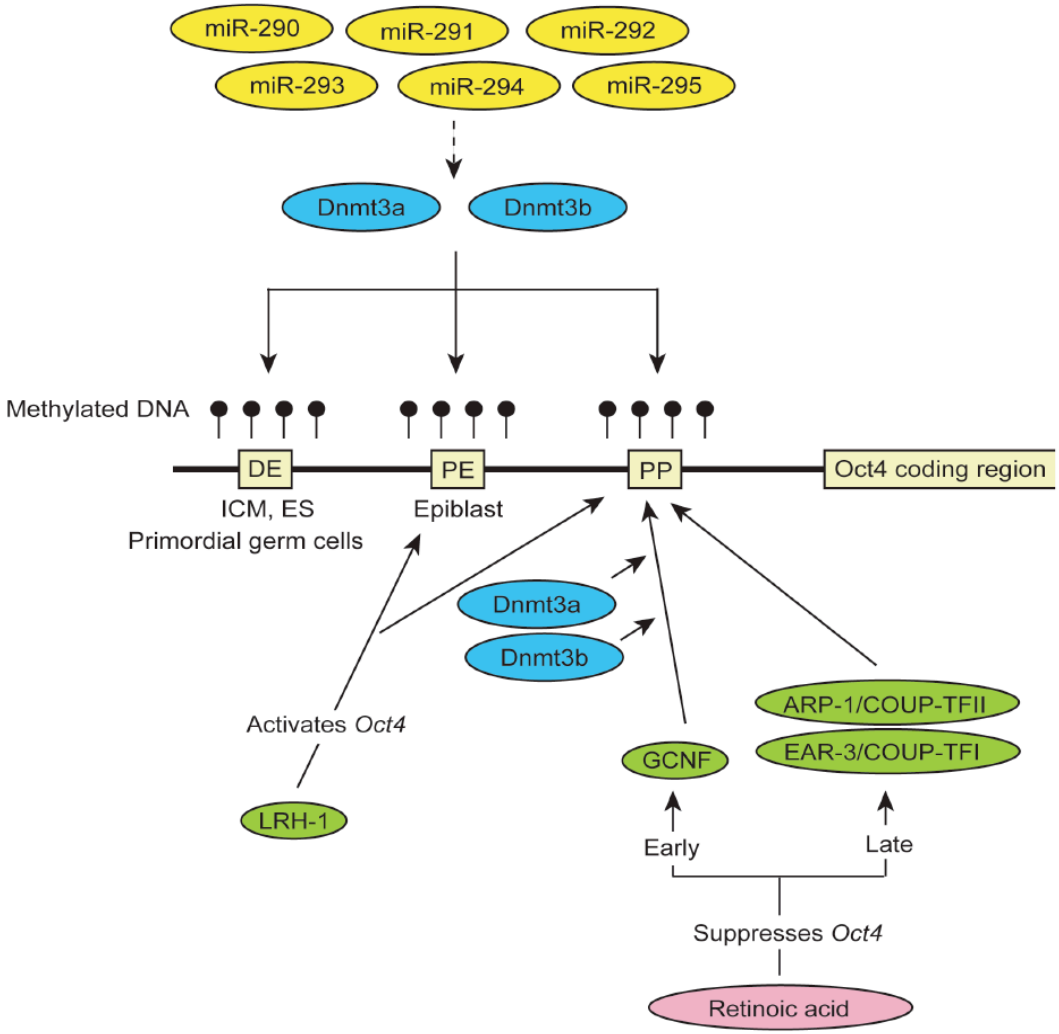
Are target genes of TF complexes co-expressed?



Functional role of TF complexes

TFs	P_{dECS}	bind. mode	targets	reg. influence	GO process enrichment ($P < 0.05$) in targets
MET4/MET32	0.0010	coloc.	19	+	methionine metabolic process
TBP/HAP5	0.0335	med.	47	+	/
GLN3/DAL80	0.0009	med.	28	/	allantoin catabolic process
DIG1/STE12/SWI6	0.0369	all	15	/	fungal-type cell wall organization
FHL1/RAP1	0.0001	coloc.	116	+	rRNA transport
RPH1/GIS1	0.0001	med.	100	-	hexose catabolic process
CBF1/MET32	0.0002	coloc.	33	o	sulfate assimilation
DIG1/STE12	0.0003	med.	34	-	response to pheromone
GCN4/RAP1	0.033	med.	62	+	/
MSN4/MSN2	0.0021	med.	105	+	oligosaccharide biosynthetic process
DAL80/GZF3	0.0044	med.	20	-	purine nucleobase metabolic process
SWI6/SWI4	0.0039	med.	53	+	regulation of cyclin-dependent protein serine/threonine kinase activity
STB1/SWI6	0.0275	all	47	+	/
TBP/SWI6	0.0159	med.	14	+	/
GLN3/GZF3	0.0120	adj.	31	/	allantoin catabolic process
MBP1/SWI6/SWI4	0.0307	med.	18	+	regulation of cyclin-dependent protein serine/threonine kinase activity
MBP1/SWI6	0.0124	adj.	25	/	cell cycle process

Complicated regulation of Oct4



Kellner, Kikyo, Histol Histopathol 25, 405 (2010)