Regulation Analysis using Restricted Boltzmann Machines

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Patrick Michl
Heidelberg University

RUPRECHT-KARLS-
UNIVERSITÄT
HEIDELBERG

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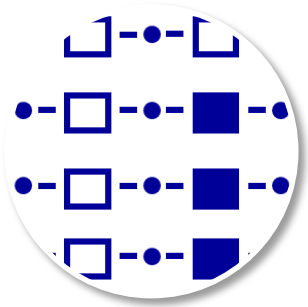
IN THE HELMHOLTZ ASSOCIATION

Agenda



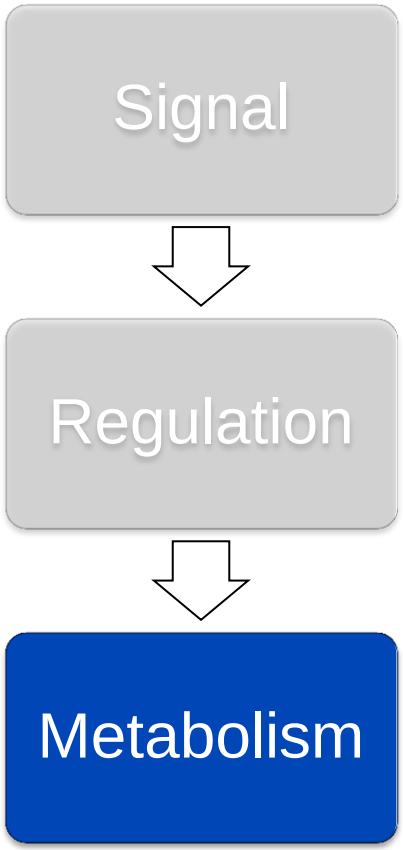
Biological Problem
Analysing the regulation of metabolism

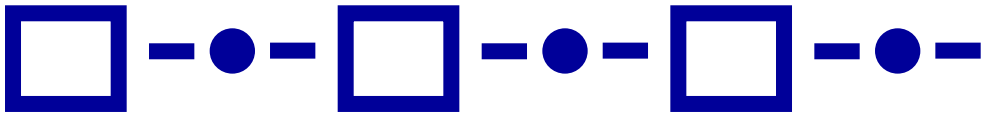
Machine Learning

Implementation

Biological Problem

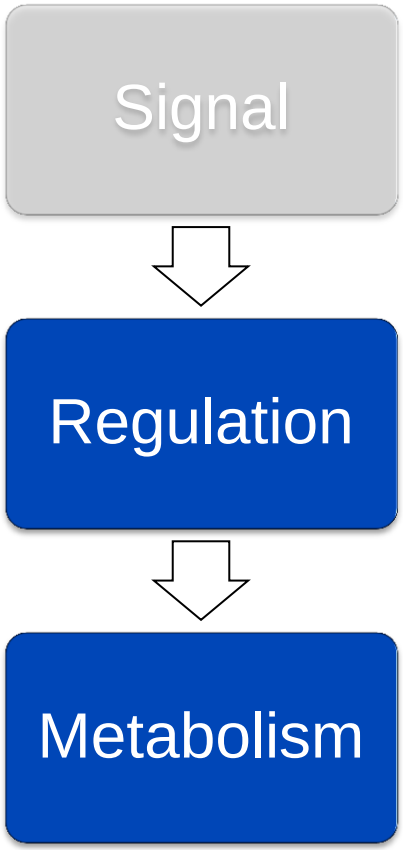
Analysing the regulation of metabolism

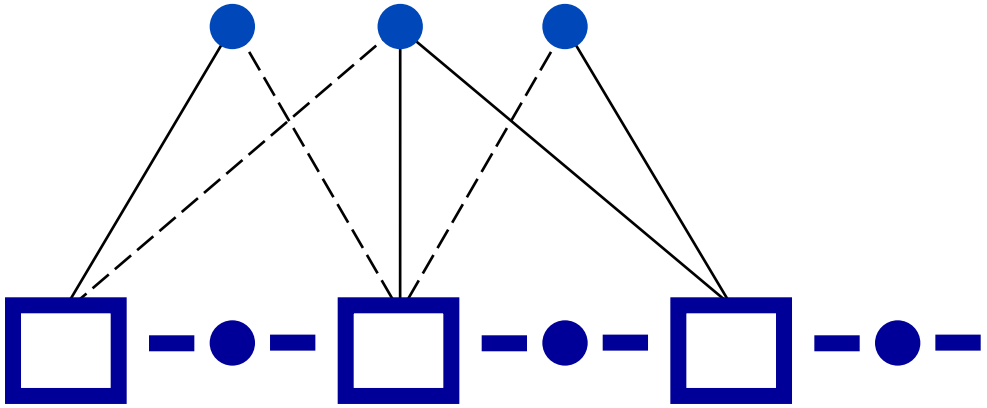




A **linear metabolic pathway** of enzymes (E) …

Biological Problem
Analysing the regulation of metabolism

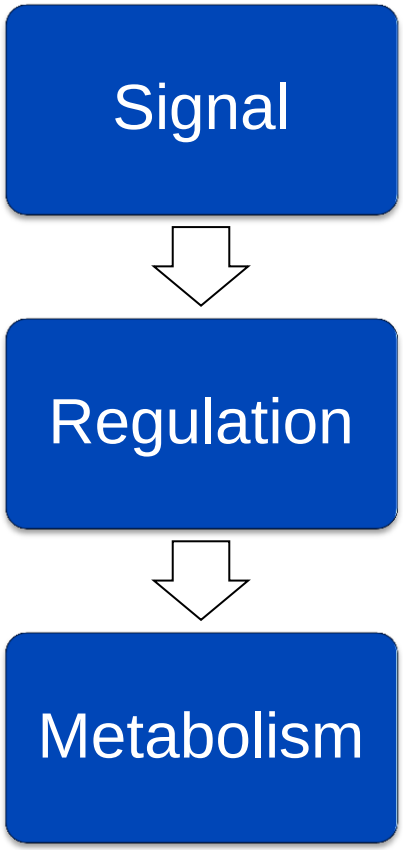


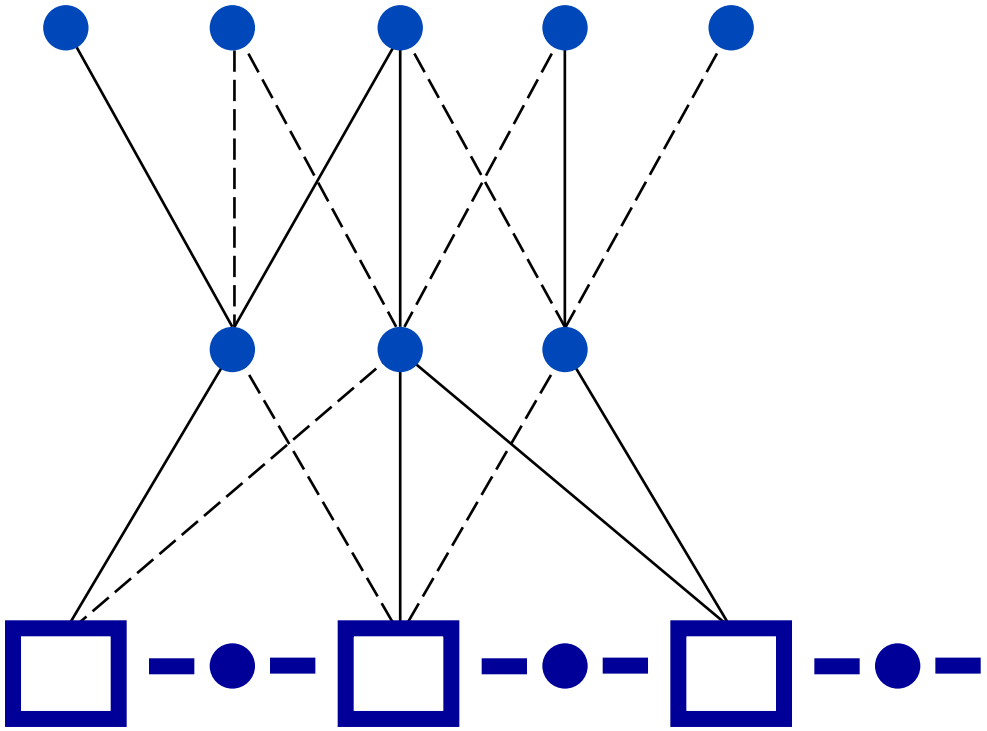


… is regulated by **transcription factors** (TF) …

Biological Problem

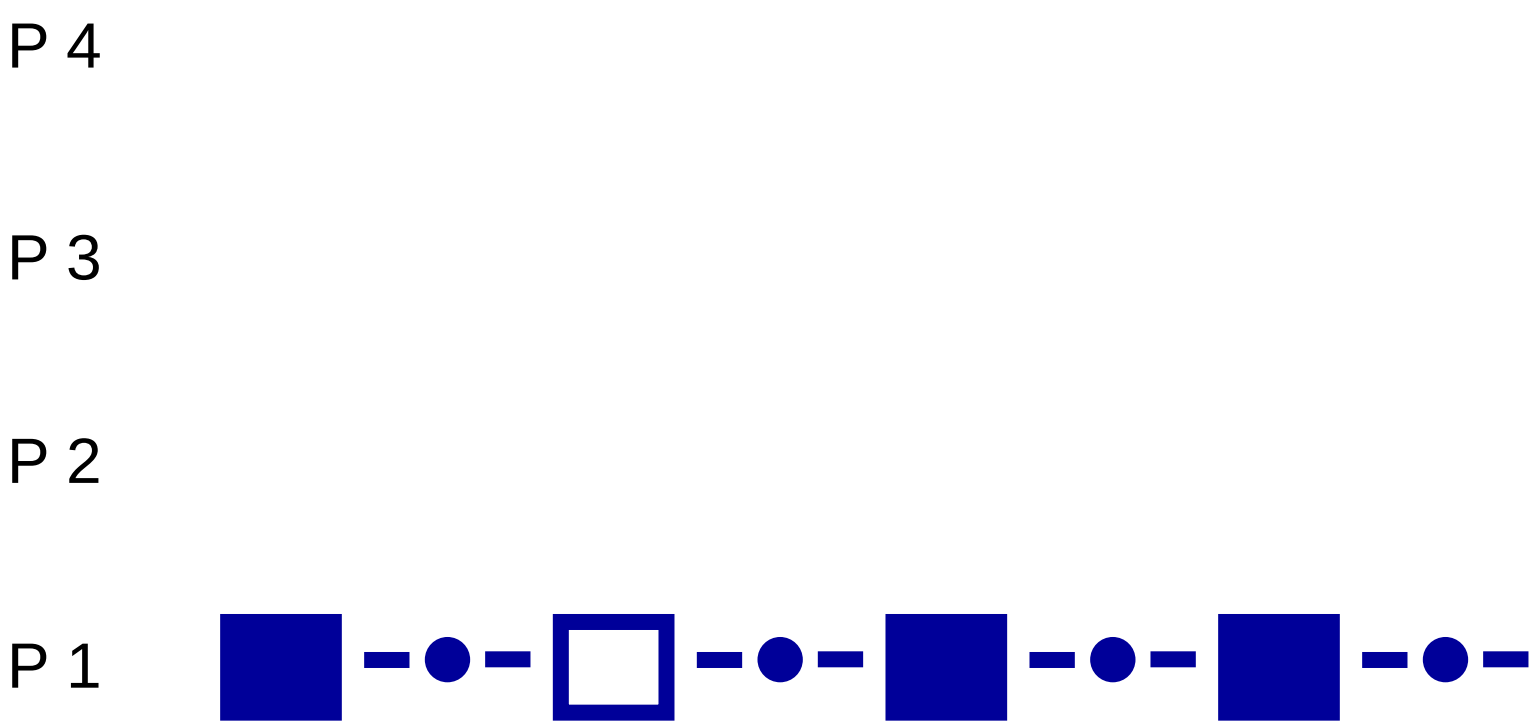
Analysing the regulation of metabolism





… which respond to **signals** (S)

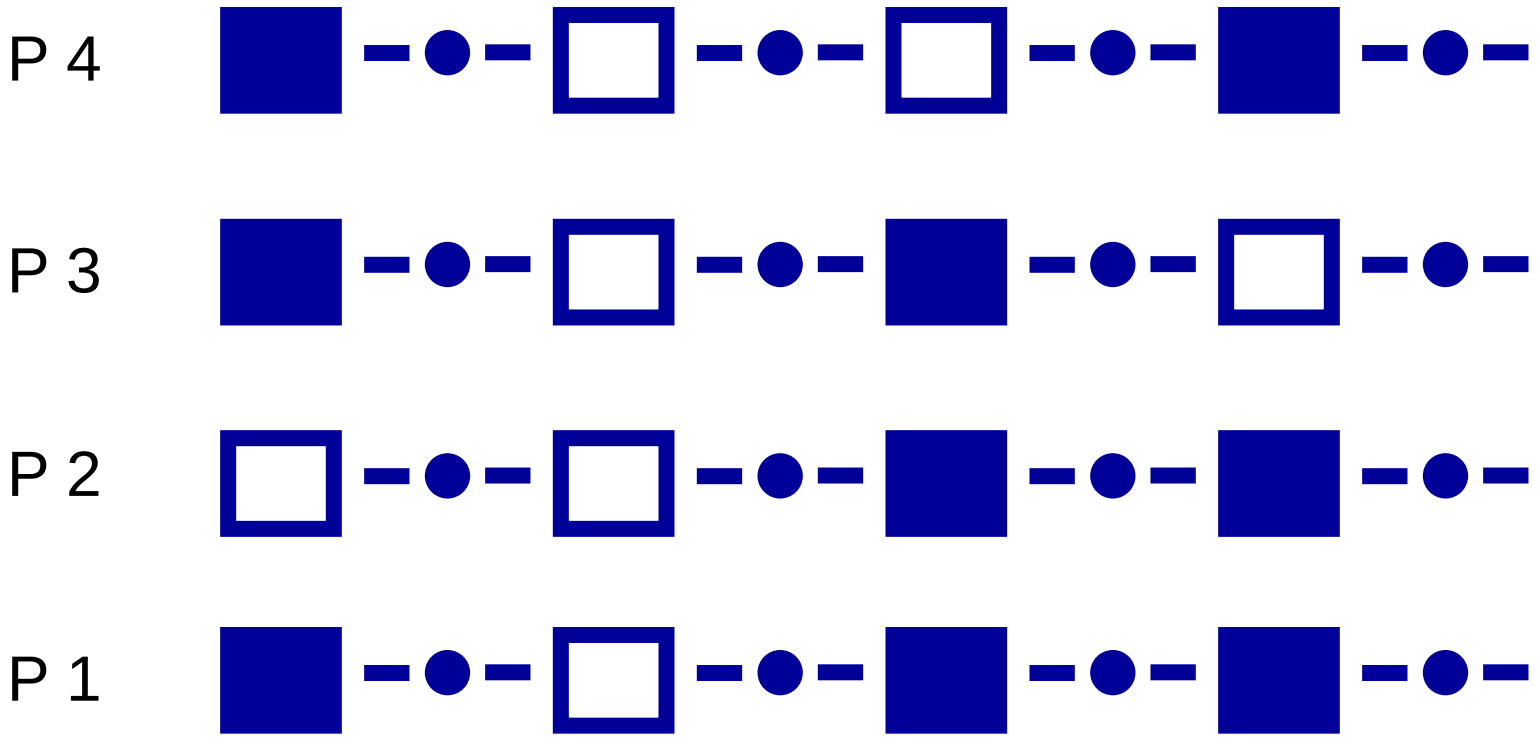
Biological Problem
Analysing the regulation of metabolism



Upregulated linear pathways …

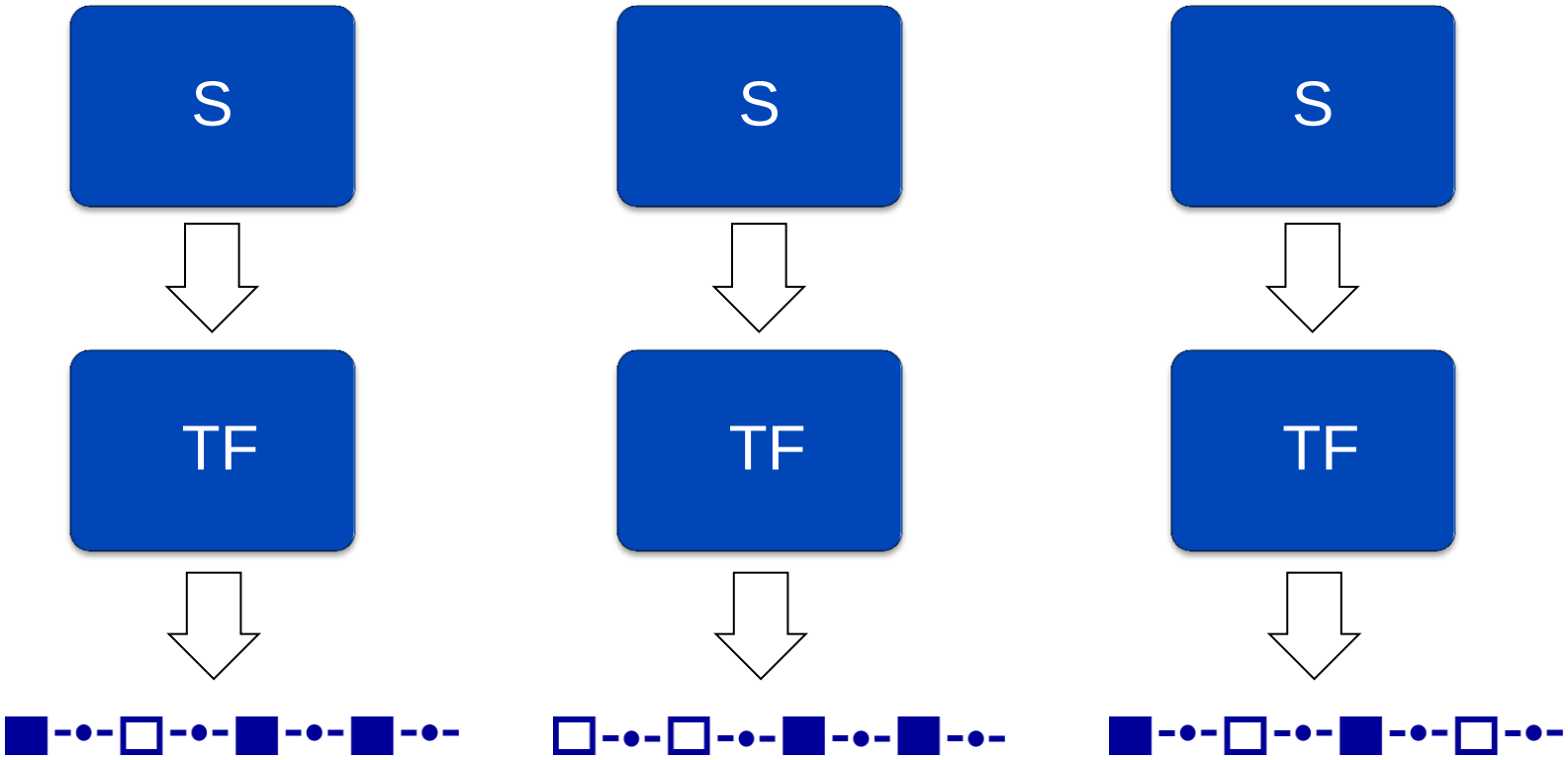
Biological Problem

Analysing the regulation of metabolism



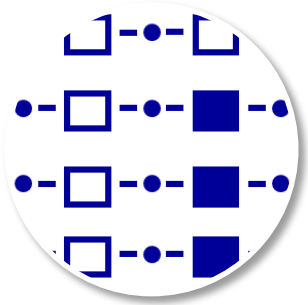
… can appear in **different patterns**

Biological Problem
Analysing the regulation of metabolism

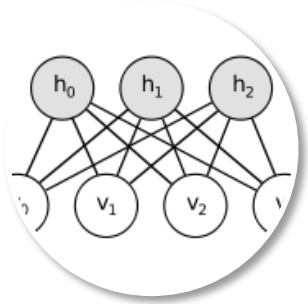


Which transcription factors and signals cause this patterns?

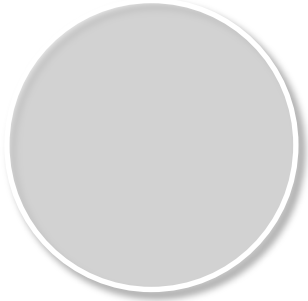
Agenda



Biological Problem
Analysing the regulation of metabolism

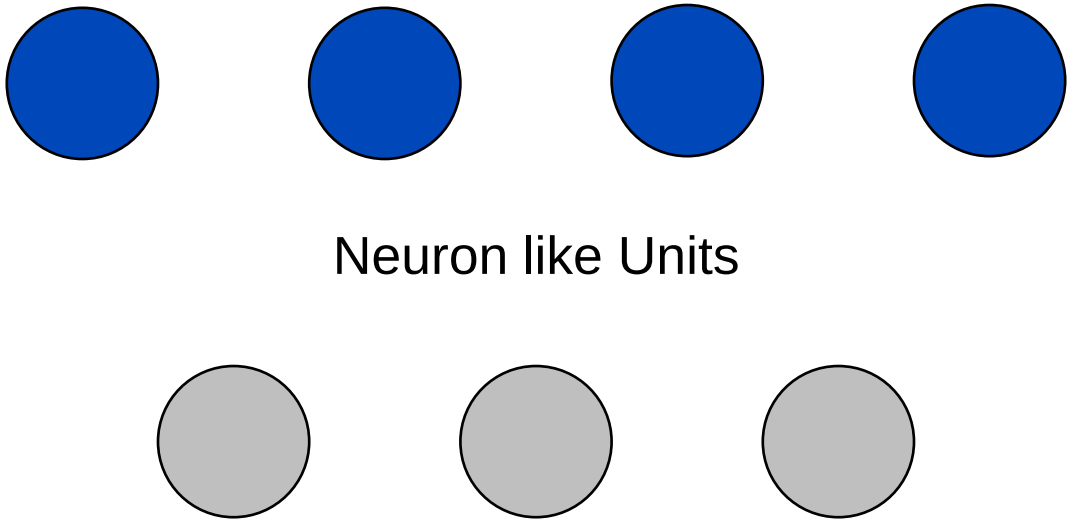


Machine Learning
Restricted Boltzmann Machines (RBM)



Implementation

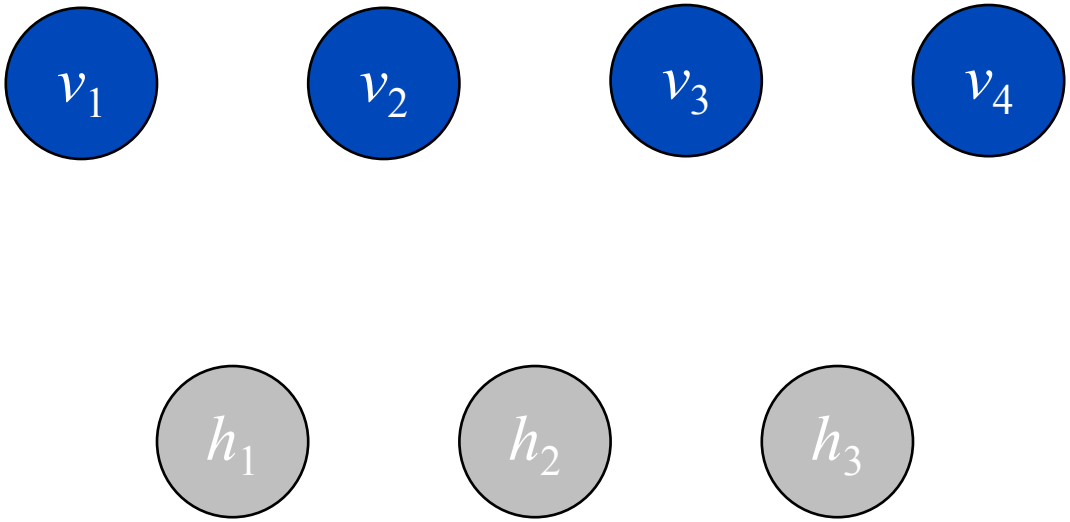
Restricted Boltzmann Machines



Neuron like Units

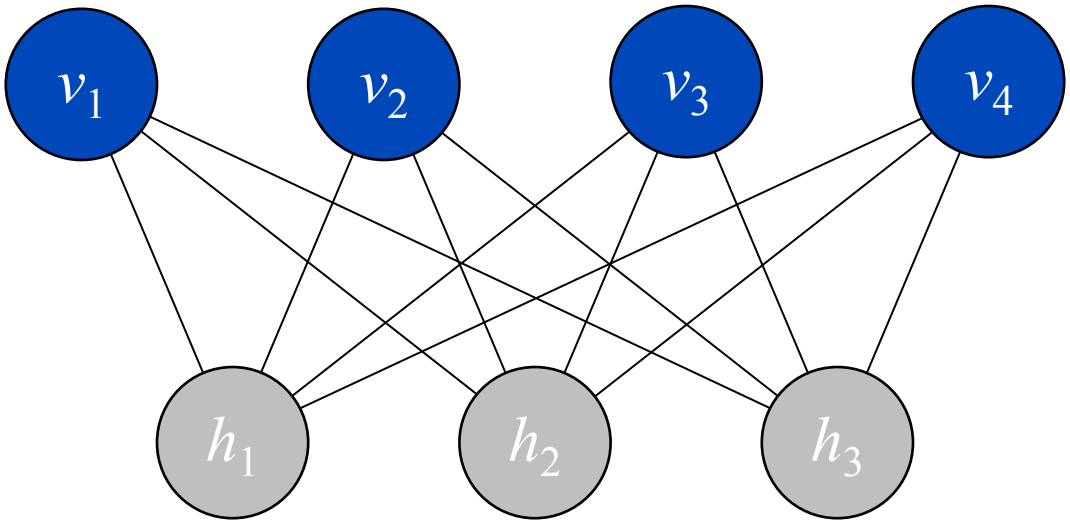
A Restricted Boltzmann Machine (RBM) is an **ANN** …

Restricted Boltzmann Machines



… with two layers: **visible units** (*v*) and **hidden units** (*h*)

Restricted Boltzmann Machines



Visible units are **strictly** connected with hidden units

Restricted Boltzmann Machines

$V :=$ set of visible units

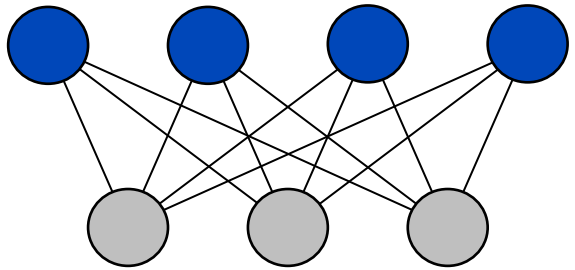
$H :=$ set of hidden units

$s_v :=$ value of $v, \forall v \in V$

$s_h :=$ value of $h, \forall h \in H$

$s_v \in \{0, 1\}, \forall v \in V$

$s_h \in \{0, 1\}, \forall h \in H$

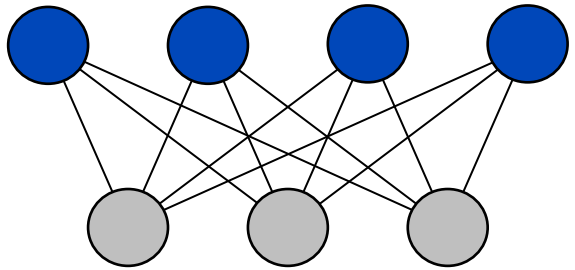


In the most common model all units have **binary values** …

Restricted Boltzmann Machines

$V :=$ set of visible units

$H :=$ set of hidden units



$s_v :=$ value of $v, \forall v \in V$

$s_h :=$ value of $h, \forall h \in H$

$s_v \in \{0, 1\}, \forall v \in V$

$s_h \in \{0, 1\}, \forall h \in H$

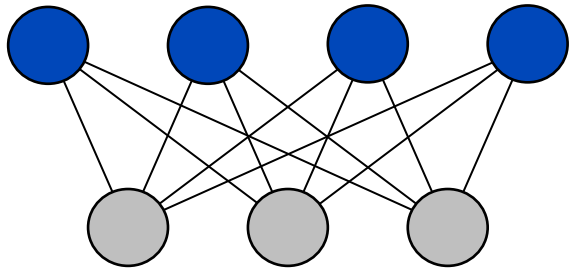
$\theta_v :=$ threshold of $v, \forall v \in V$

$\theta_h :=$ threshold of $h, \forall h \in H$

… and **arbitrary tresholds** which allow us …

Restricted Boltzmann Machines

$w_{v,h} :=$ weight of $edge(v,h)$



Local Energy

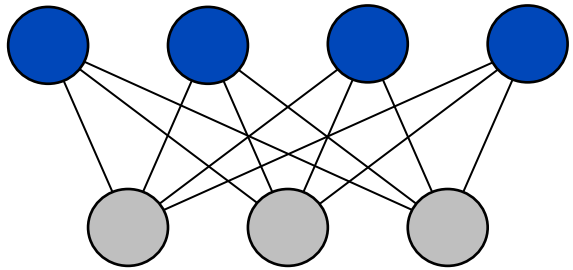
$$E_v := -\sum_h w_{v,h} s_v s_h + \theta_v s_v$$

$$E_h := -\sum_v w_{v,h} s_v s_h + \theta_h s_h$$

… to define **energy** functions: **Local** energies E_v and E_h …

Restricted Boltzmann Machines

$w_{v,h} :=$ weight of $edge(v,h)$



Local Energy

(1)

$$E_v := -\sum_h w_{v,h} s_v s_h + \theta_v s_v$$

$$E_h := -\sum_v w_{v,h} s_v s_h + \theta_h s_h$$

Global Energy

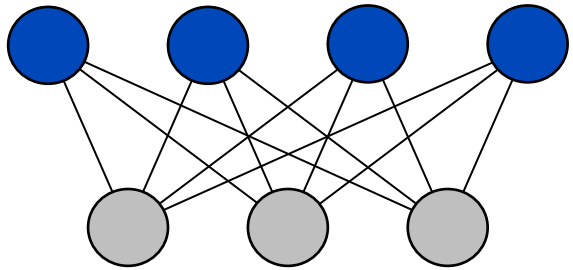
$$E := \sum_v E_v + \sum_h E_h$$

… and the **global** Energy *E*. We want to minimize *E*

Restricted Boltzmann Machines

Energy Delta for visible units

$$\Delta Ev = E_{v,\,off} - E_{v,\,on}$$
$$= \ldots$$

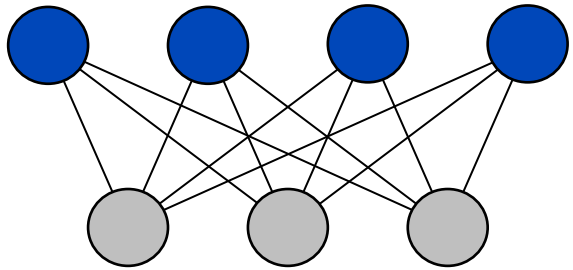


If we aproximate a **Boltzmann Distribution** for E_v …

Restricted Boltzmann Machines

Energy Delta for visible units

$$\Delta Ev = E_{v,\,off} - E_{v,\,on}$$
$$= -k_B T\ ln\ \mathrm{P}[v,\mathrm{off}]$$
$$-(-k_B T\ ln\ \mathrm{P}[v,\mathrm{on}])$$

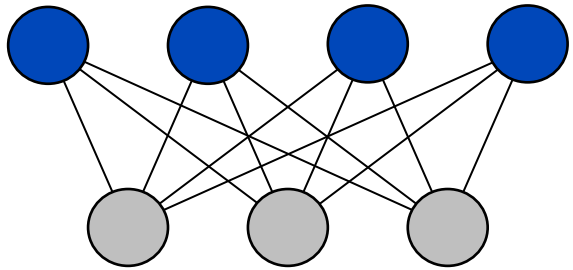


… we can use the **Boltzmann Factor** …

Restricted Boltzmann Machines

Energy Delta for visible units

$$\Delta Ev = E_{v,\,off} - E_{v,\,on}$$
$$= -k_B T\ ln\ \mathrm{P}[v,\mathrm{off}]$$
$$-(-k_B T\ ln\ \mathrm{P}[v,\mathrm{on}])$$



$$\mathrm{P}[v,\mathrm{off}] = 1 - \mathrm{P}[v,\mathrm{on}]$$

$$\mathrm{P}[v,\mathrm{on}] = \frac{1}{1 + e^{-\frac{\Delta Ev}{k_B T}}}$$

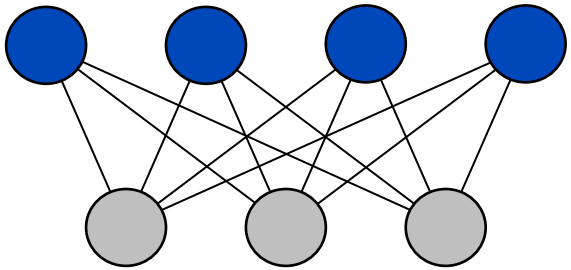
… to get a term for the **probability** [*v*, on]

Restricted Boltzmann Machines

Probalilities

$$\mathrm{P}[v,\mathrm{on}] = \frac{1}{1 + e^{-\frac{\Delta Ev}{k_B T}}} \quad (2)$$

$$\mathrm{P}[h,\mathrm{on}] = \frac{1}{1 + e^{-\frac{\Delta Eh}{k_B T}}}$$

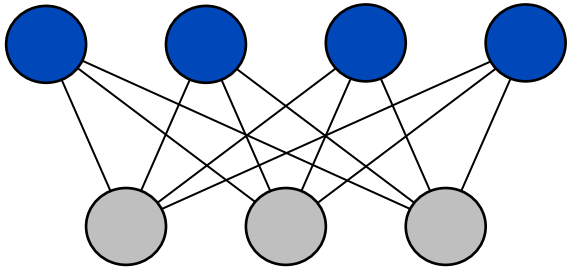


… and similary for hidden units

Restricted Boltzmann Machines

Simulated Annealing

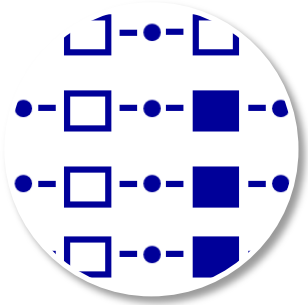
```
set T= T_Max

while (T> T_Min)
    forall v
        if (P[v,on] > rand(0,1)) set s_v = 1
    forall h
        if (P[h,on] > rand(0,1)) set s_h = 1
    set Tsmaller
```



$$E \rightarrow \min$$

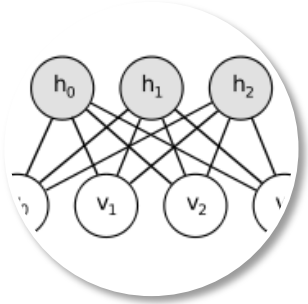
With (1) an (2) we can perform **Simulated Annealing**

Agenda



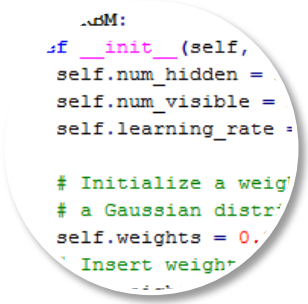
Biological Problem

Analysing the regulation of metabolism



Machine Learning

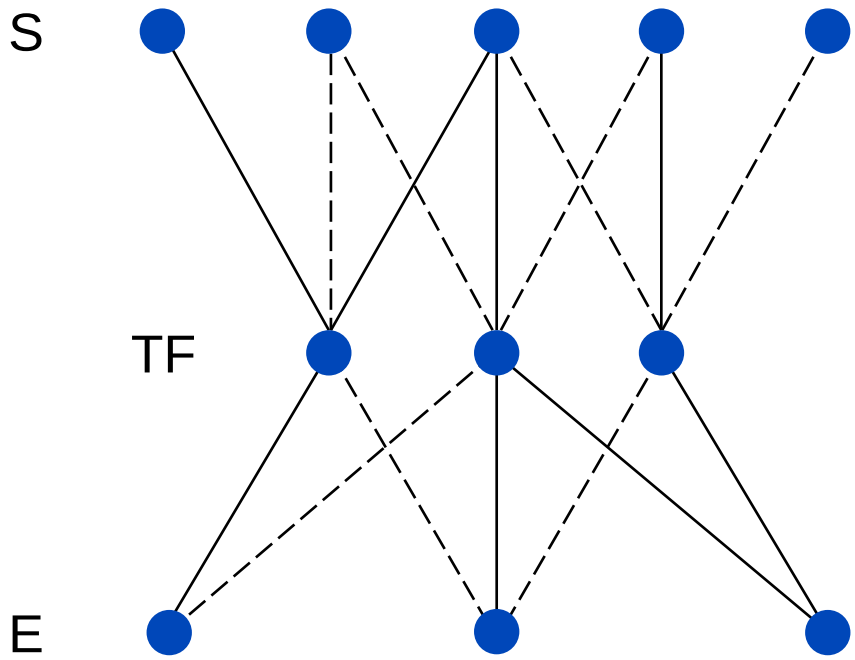
Restricted Boltzmann Machines (RBM)



Implementation

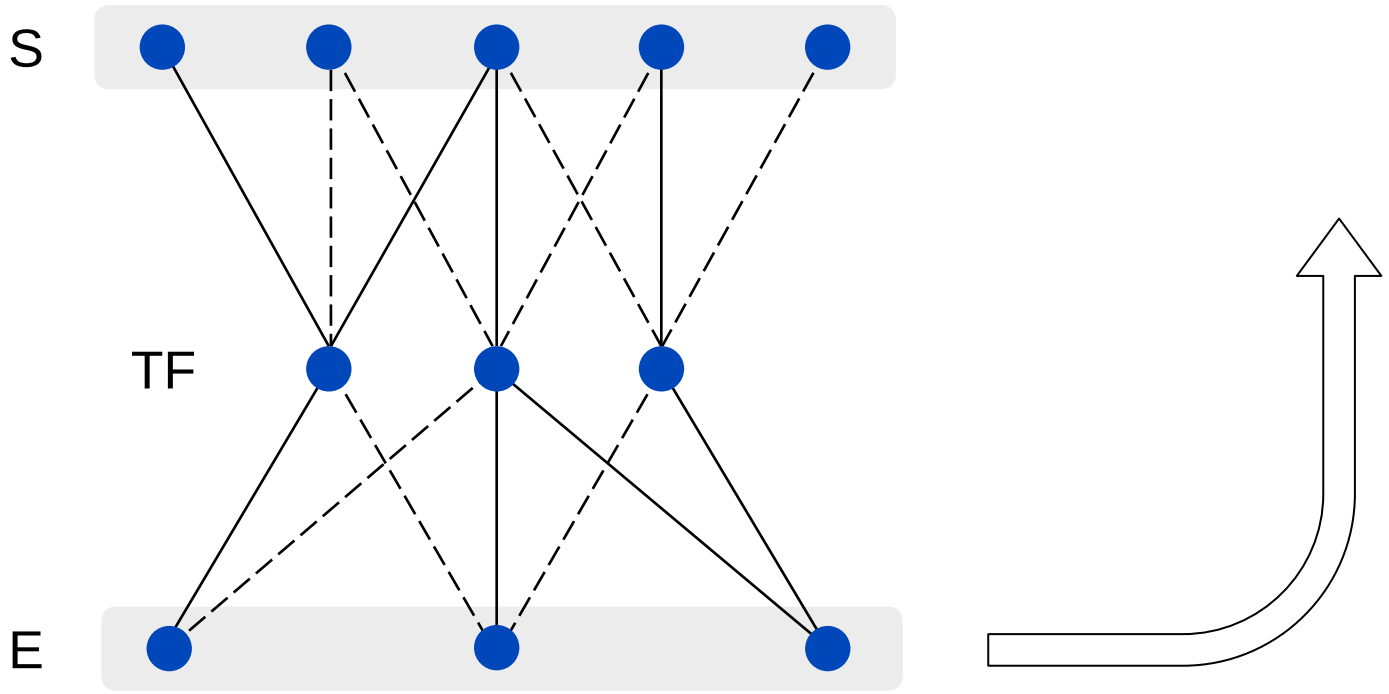
Modeling the Problem / Example

Modeling Regulation as RBM



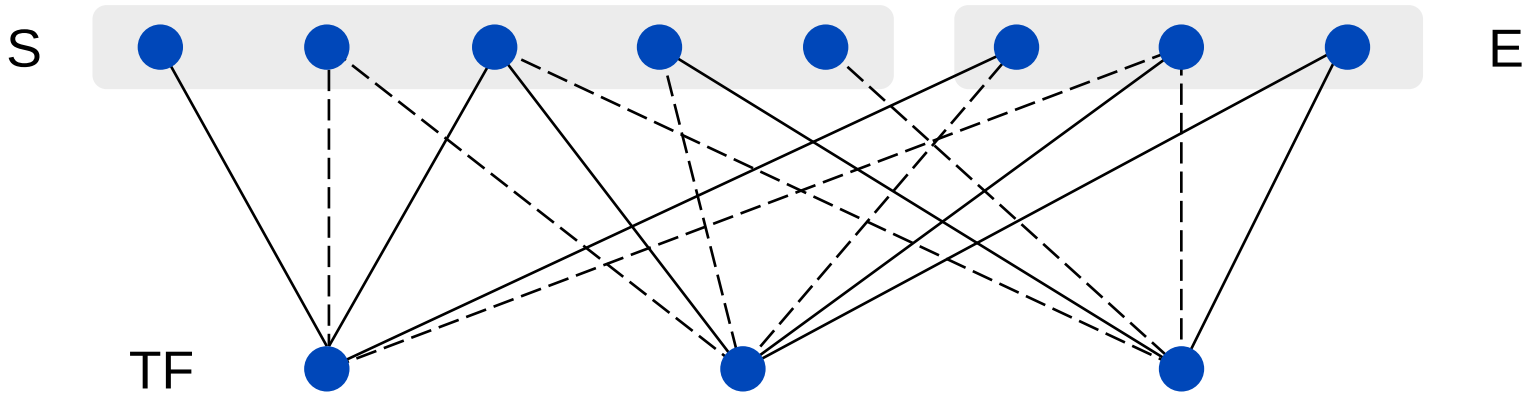
To **model** regulation as an RBM …

Modeling Regulation as RBM



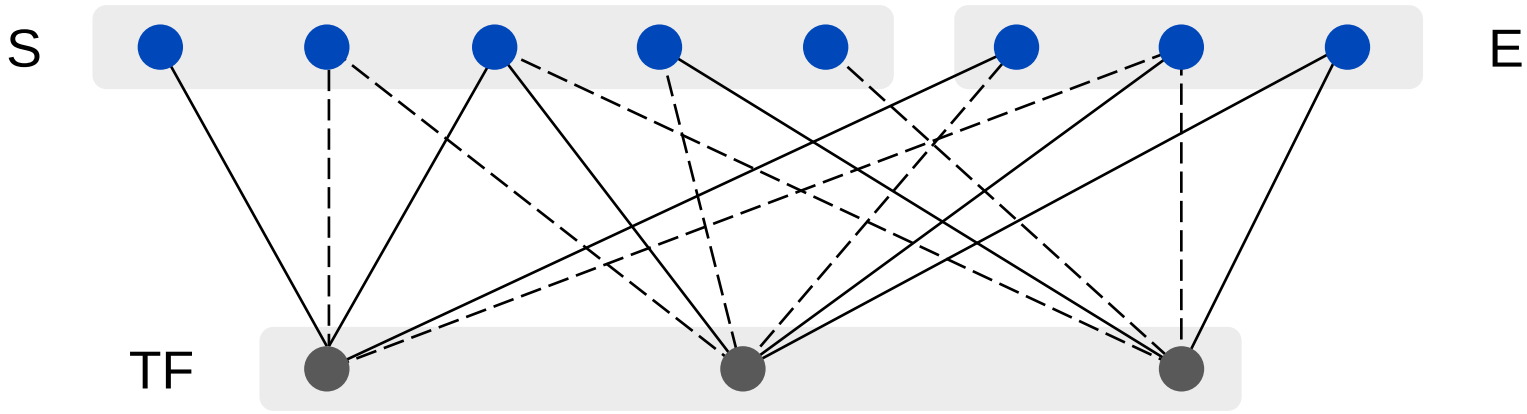
… we define S and E as **visible Layer** …

Modeling Regulation as RBM



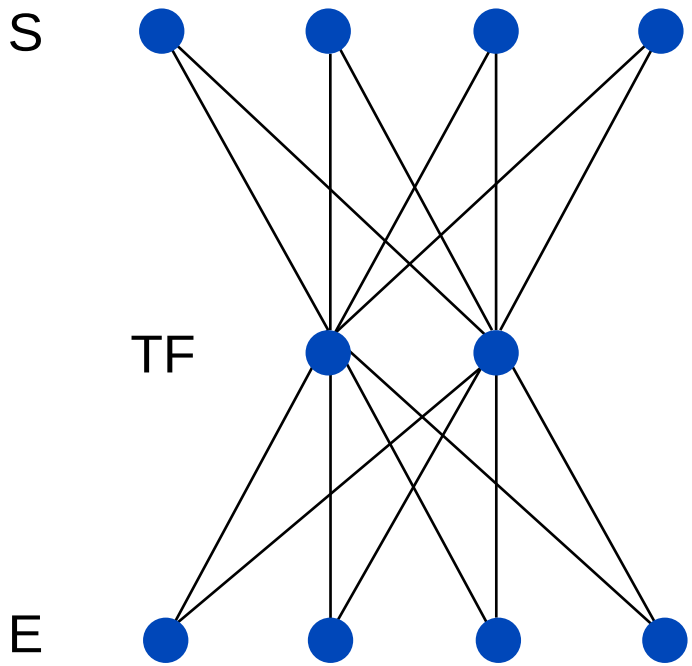
… we define S and E as **visible Layer** …

Modeling Regulation as RBM



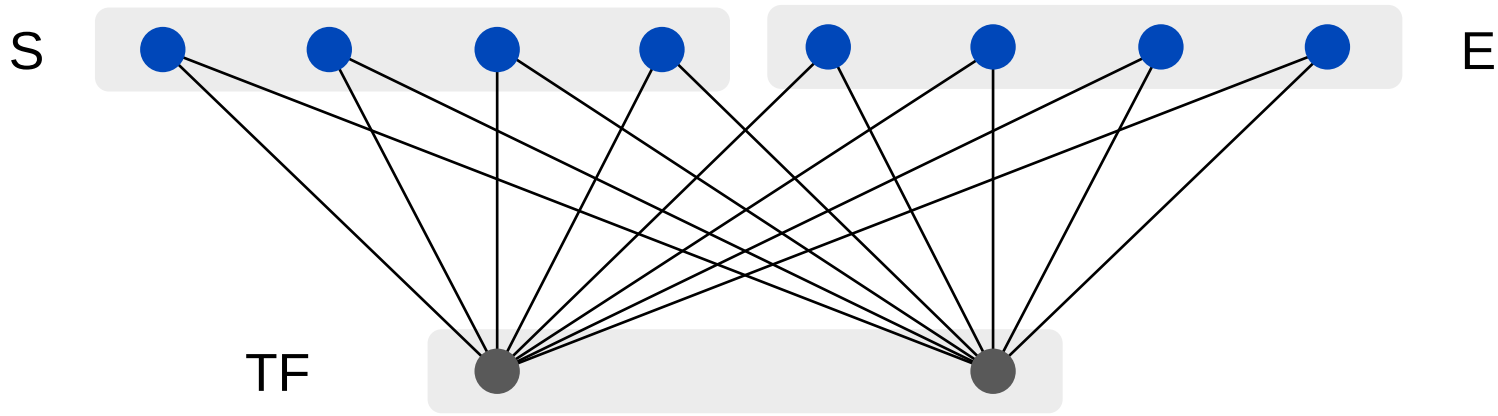
… and TF as **hidden Layer**

Example



Let‘s try it as simple as possible

Example

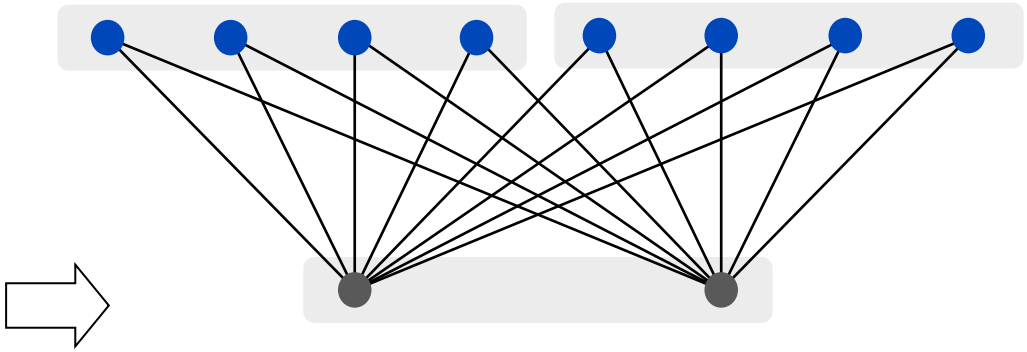


… so we get 8 visible and 2 hidden units, fully connected

Example

Learning samples

S	E
1,0,0,1	1,0,0,0
1,0,0,1	1,1,0,0
1,0,0,1	1,0,1,0
1,0,0,1	1,0,0,1
1,0,1,1	0,0,0,0
1,0,1,1	0,1,0,0
1,0,1,1	0,0,1,0
1,0,1,1	0,0,0,1

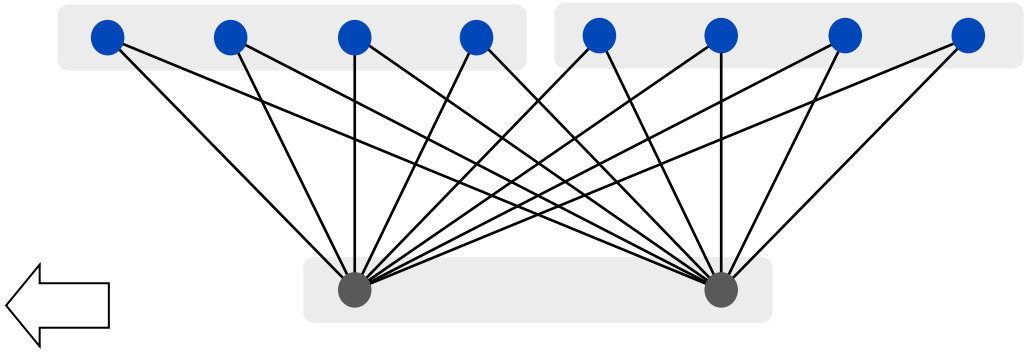


Let‘s feed the machine with **learning samples** …

Example

Weight matrix

	TF_1	TF_2
S_1	0,3	0,8
S_2	0,5	0,6
S_3	0,9	0,1
S_4	0,3	0,8
E_1	1,0	0,0
E_2	0,1	0,0
E_3	0,1	0,0
E_4	0,2	0,0

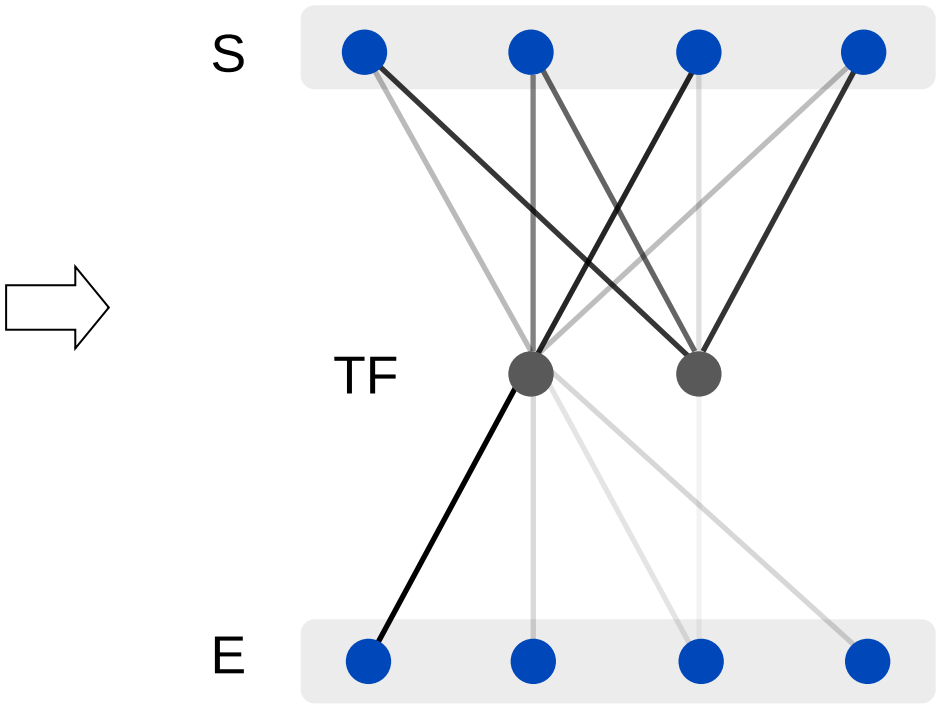


.. to get the calculated **weight matrix**

Example

Weight matrix

	TF_1	TF_2
S_1	0,3	0,8
S_2	0,5	0,6
S_3	0,9	0,1
S_4	0,3	0,8
E_1	1,0	0,0
E_2	0,1	0,0
E_3	0,1	0,0
E_4	0,2	0,0

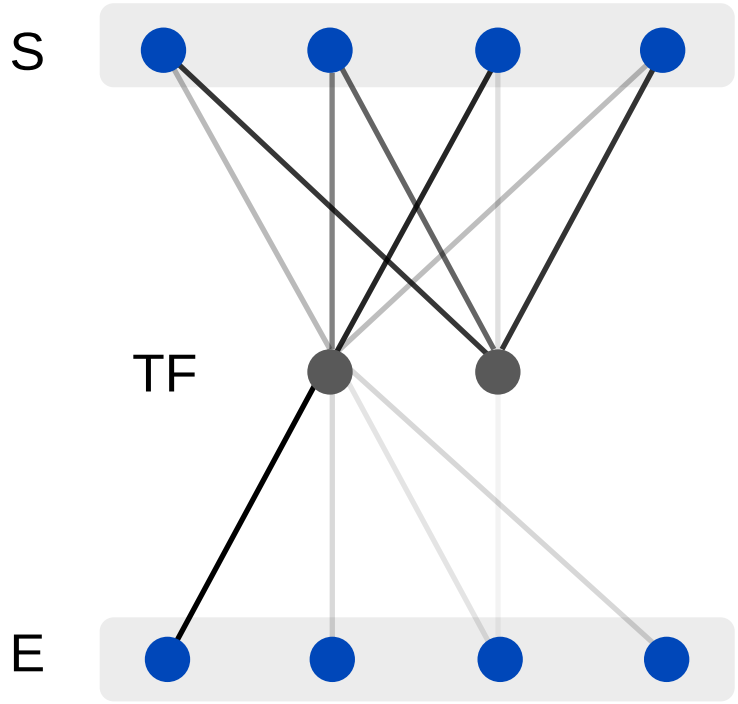


The weights are visualized by the **intensity** of the edges

Example

Learning samples

S	E
1,0,0,1	1,0,0,0
1,0,0,1	1,1,0,0
1,0,0,1	1,0,1,0
1,0,0,1	1,0,0,1
1,0,1,1	0,0,0,0
1,0,1,1	0,1,0,0
1,0,1,1	0,0,1,0
1,0,1,1	0,0,0,1

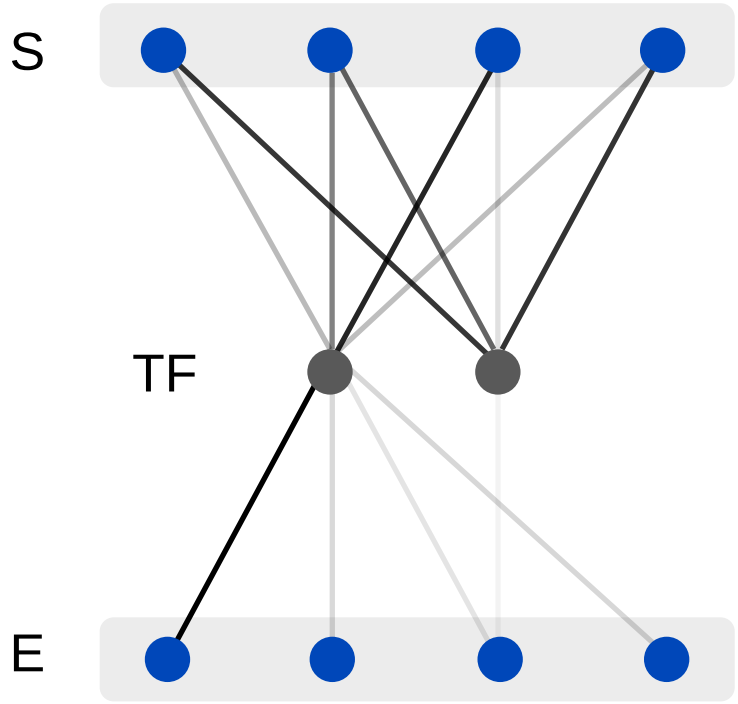


Now we can compare the results with the samples

Example

Learning samples

S	E
1,0,**0**,1	**1**,0,0,0
1,0,**0**,1	**1**,1,0,0
1,0,**0**,1	**1**,0,1,0
1,0,**0**,1	**1**,0,0,1
1,0,**1**,1	**0**,0,0,0
1,0,**1**,1	**0**,1,0,0
1,0,**1**,1	**0**,0,1,0
1,0,**1**,1	**0**,0,0,1

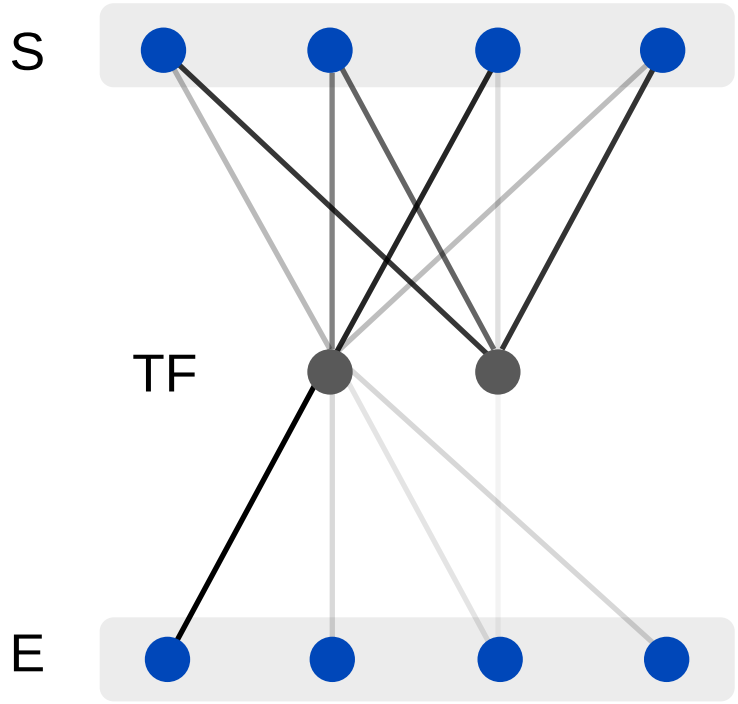


There‘s a strong dependency between S_3 an E_1

Example

Learning samples

S	E
1,**0**,0,**1**	1,0,0,0
1,**0**,0,**1**	1,1,0,0
1,**0**,0,**1**	1,0,1,0
1,**0**,0,**1**	1,0,0,1
1,**0**,1,**1**	0,0,0,0
1,**0**,1,**1**	0,1,0,0
1,**0**,1,**1**	0,0,1,0
1,**0**,1,**1**	0,0,0,1



S_1, S_2 and S_4 do almost not affect the metabolism

Further Objectives

Since 2006 RBMs have successfully be used to train (pre-train) Multi-Layer ANNs (Hinton, Osindero, 2006)

This new branch in machine learning („deep learning“) already has a wide area of applications, incuding:

- Face recognition / Voice recognition
- Unsupervised detection of features
- Imagetransformation

It has to be asumed that deep learning strategies also provide further capabilities in regulatory analysis