Detecting Deregulated Genes

September 30, 2015

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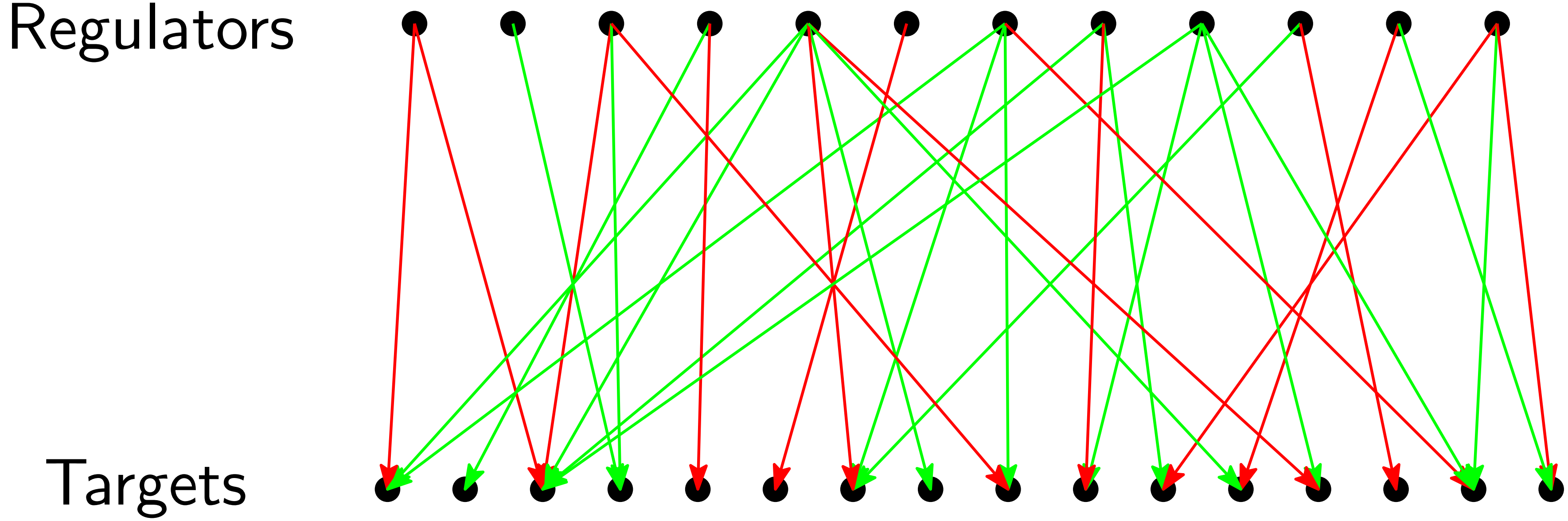
Thomas Picchetti

Problem



Input :

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- a set of expression profiles (e.g. RNA microarrays)

Question: In each profile, which target genes disobey their regulators ?

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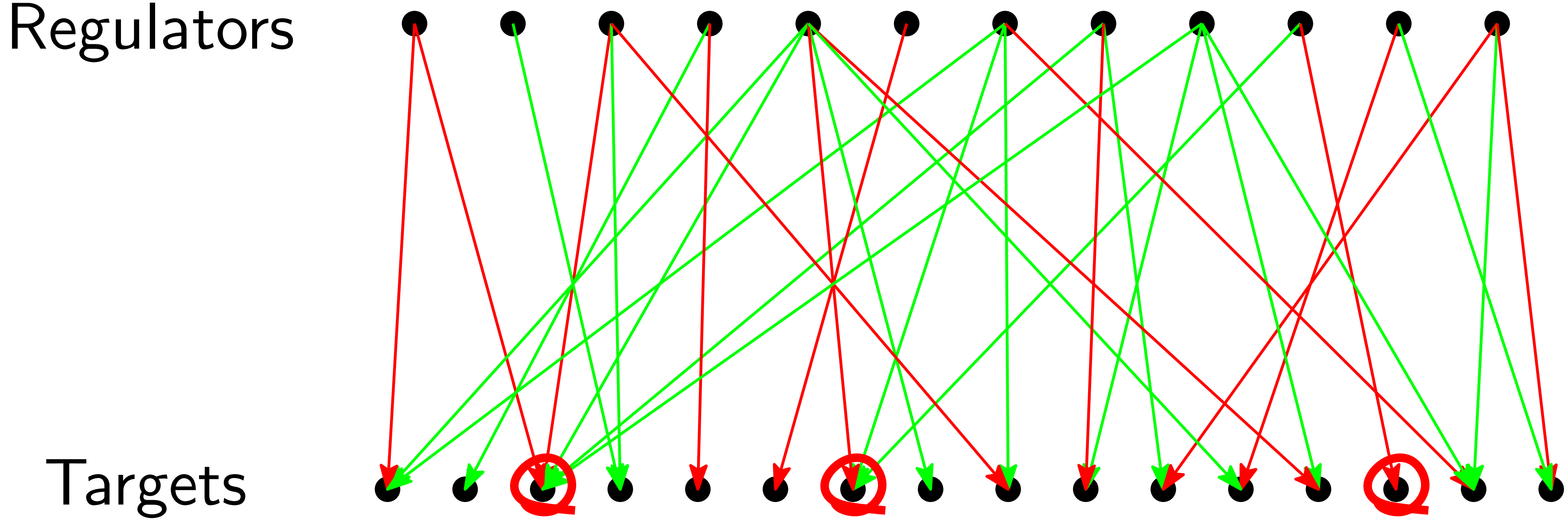

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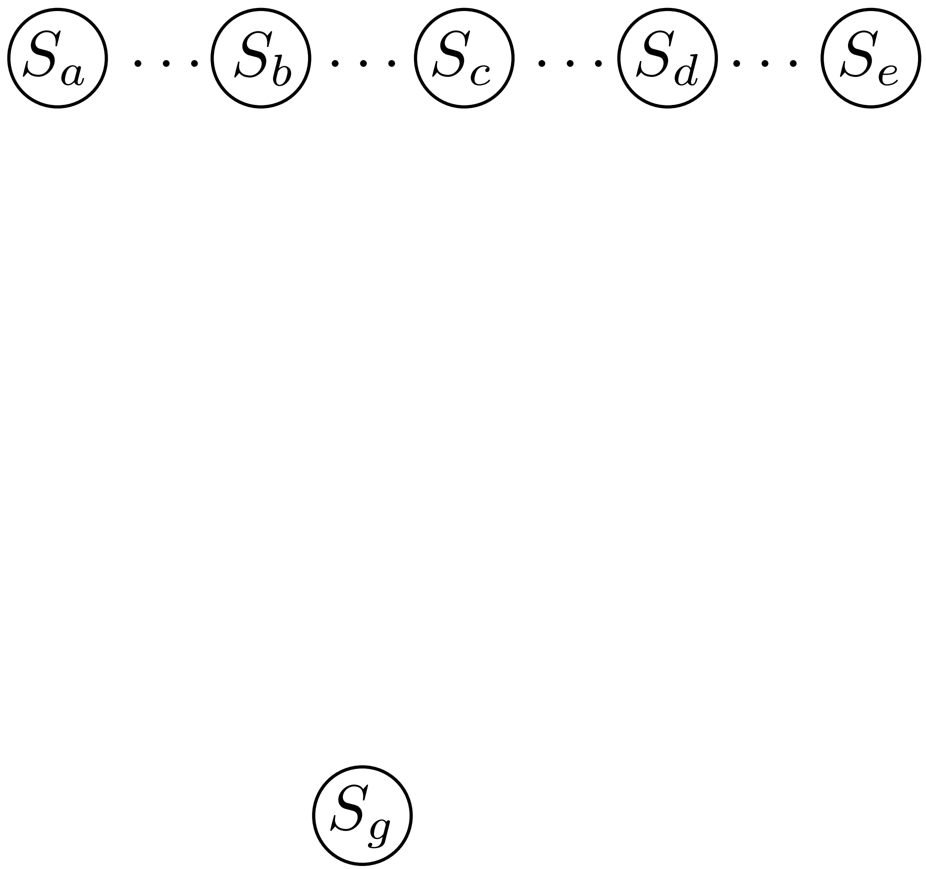

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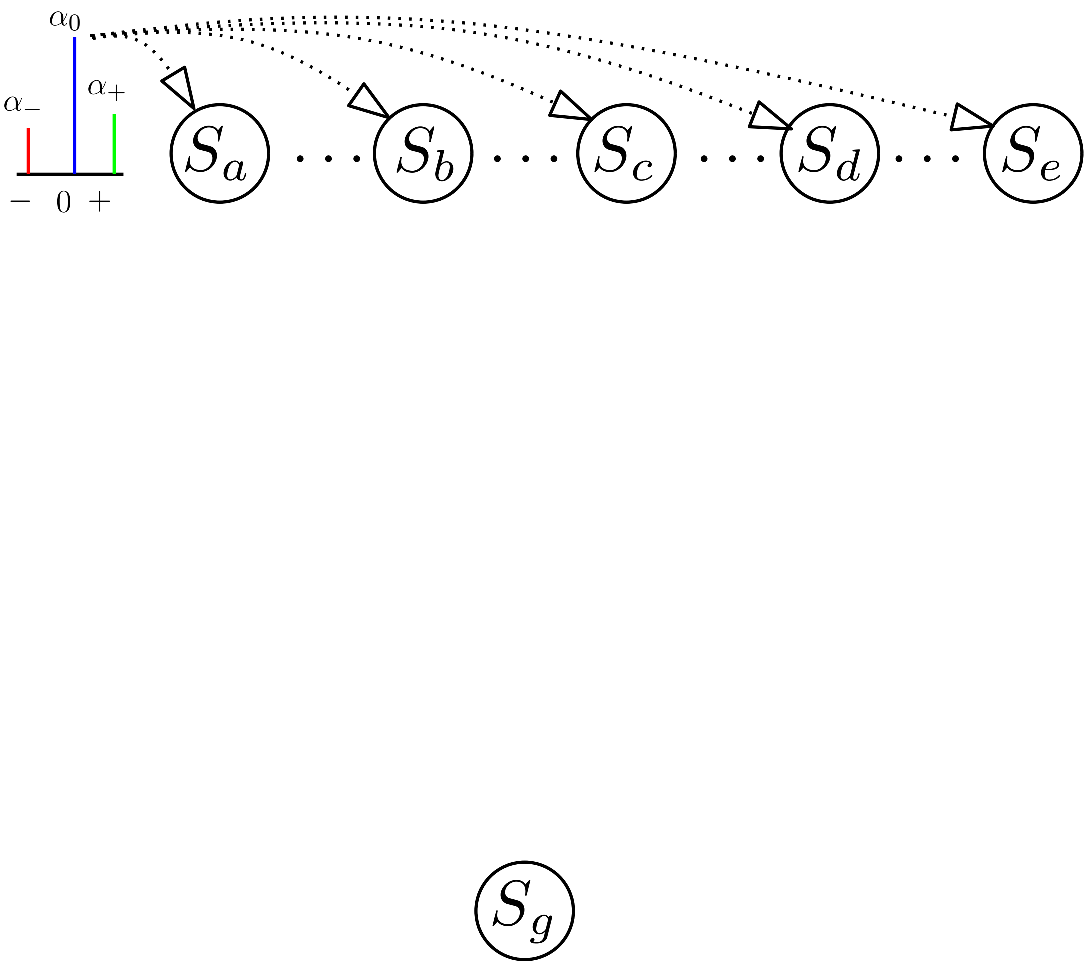

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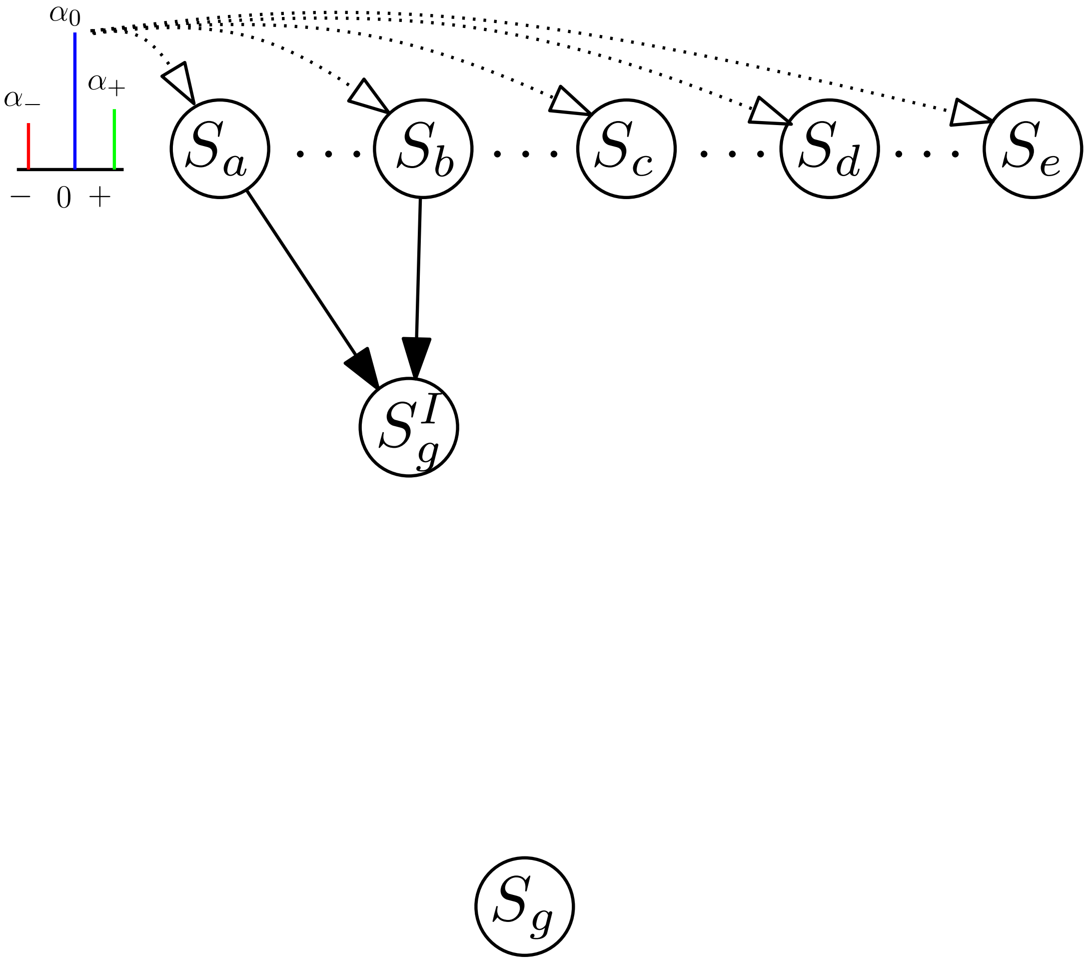

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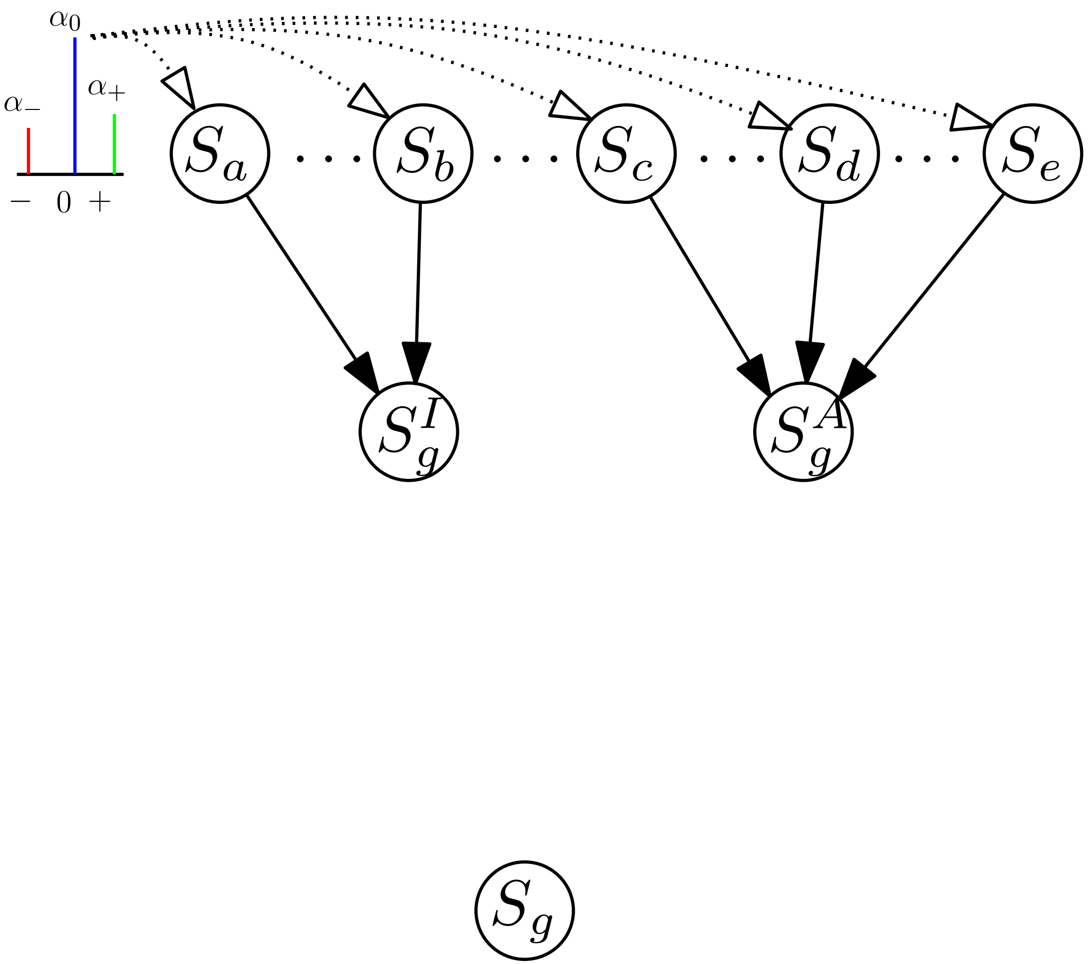

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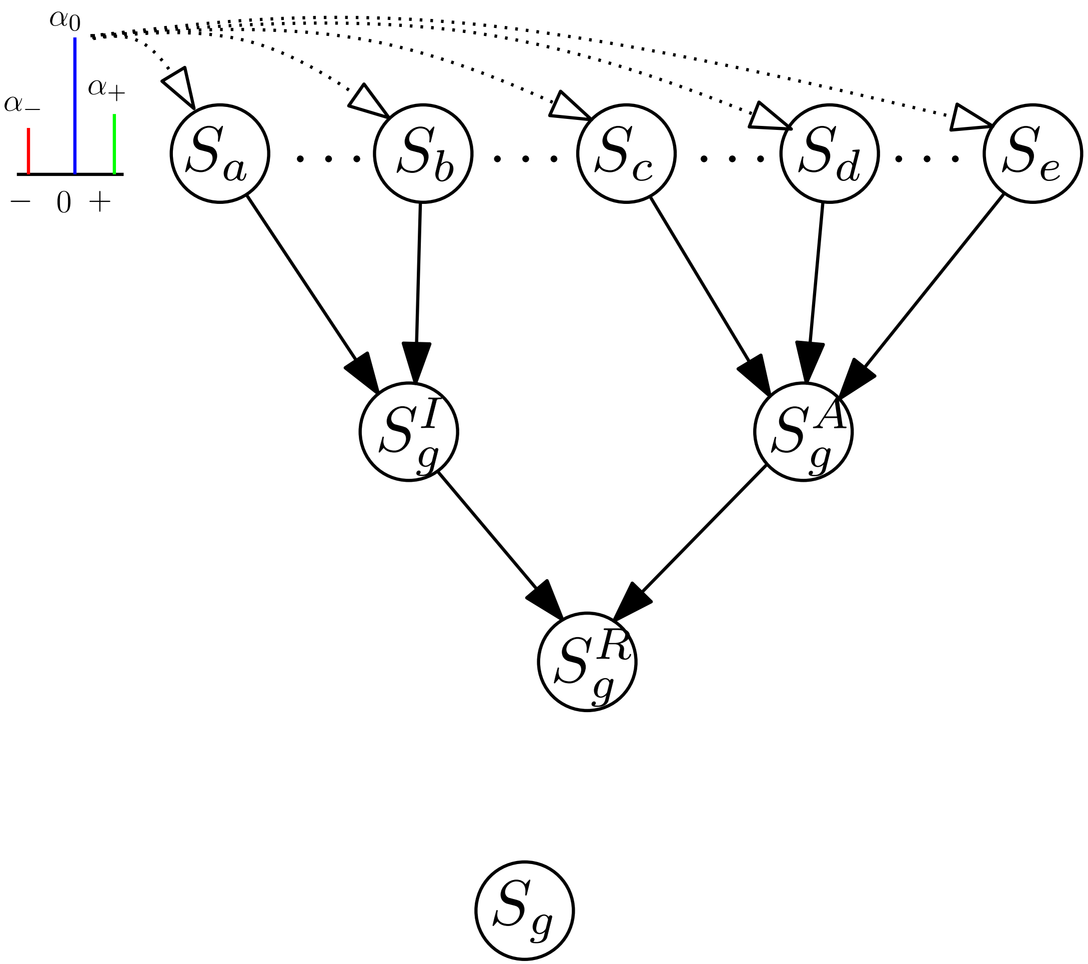

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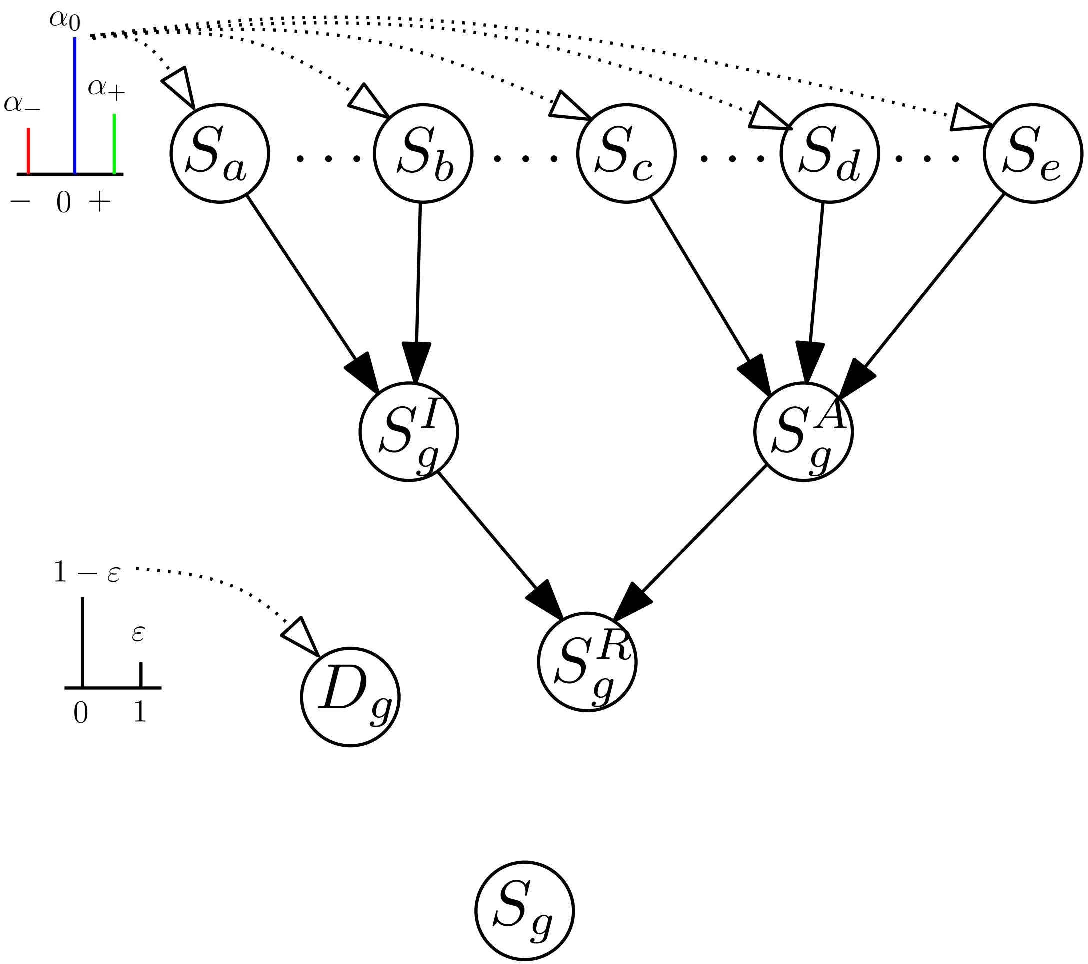

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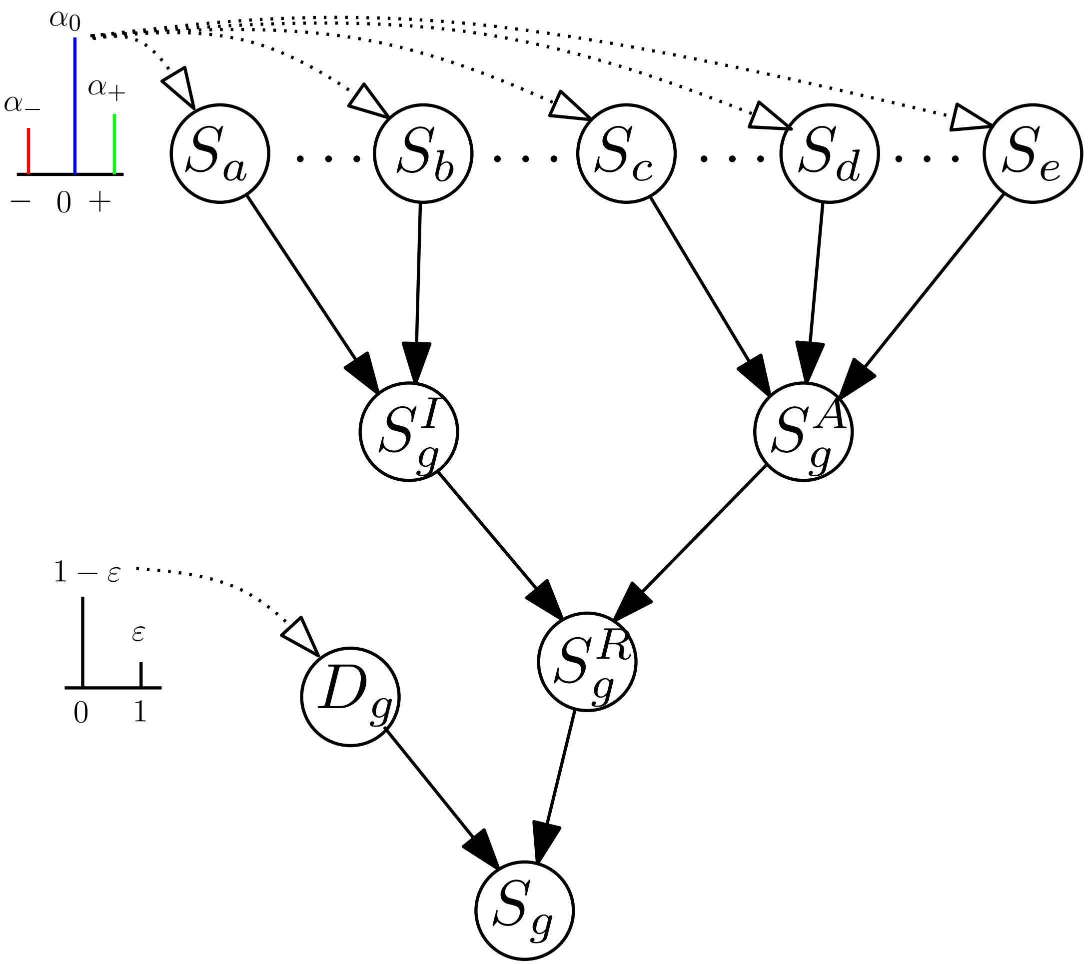

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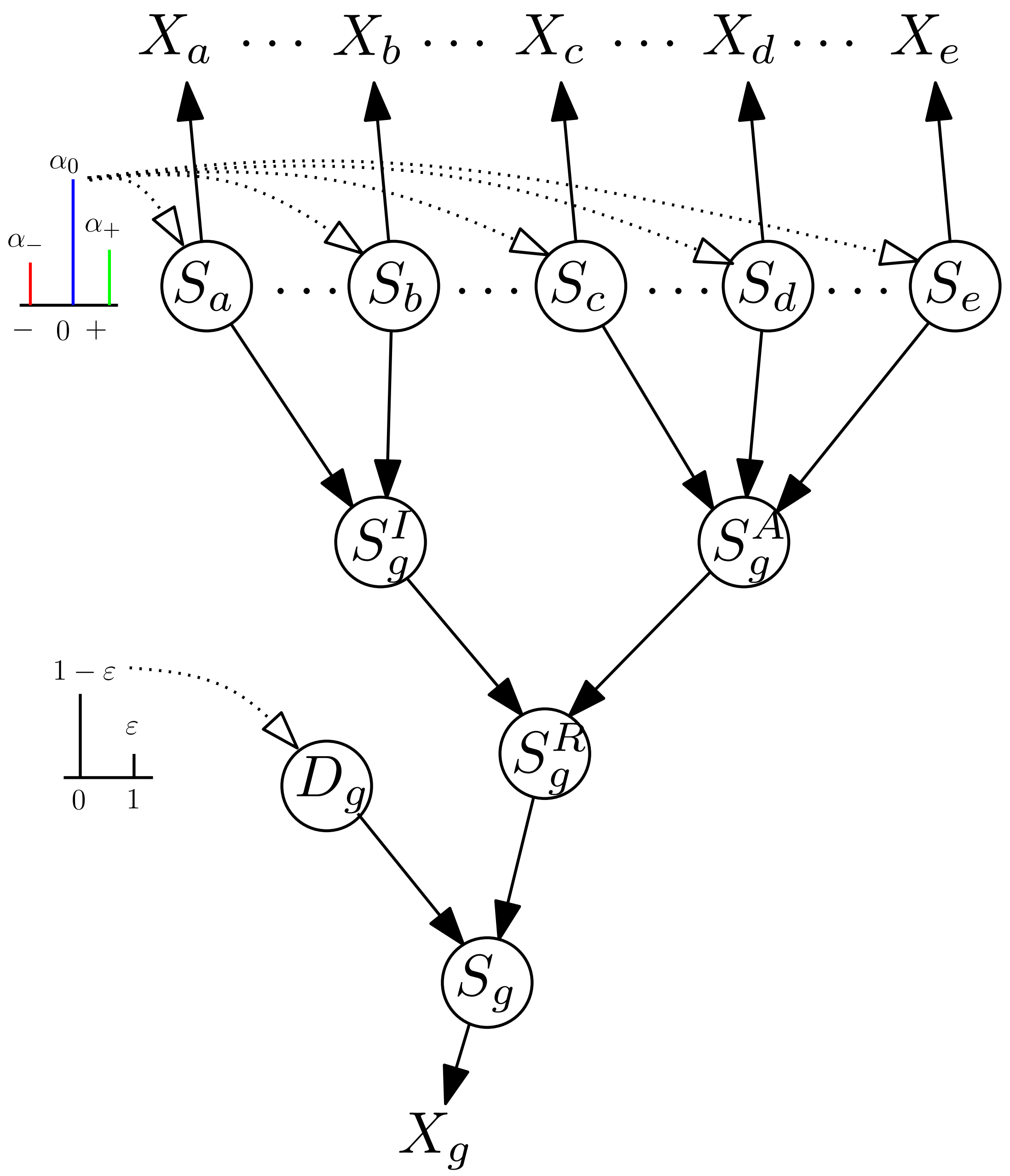

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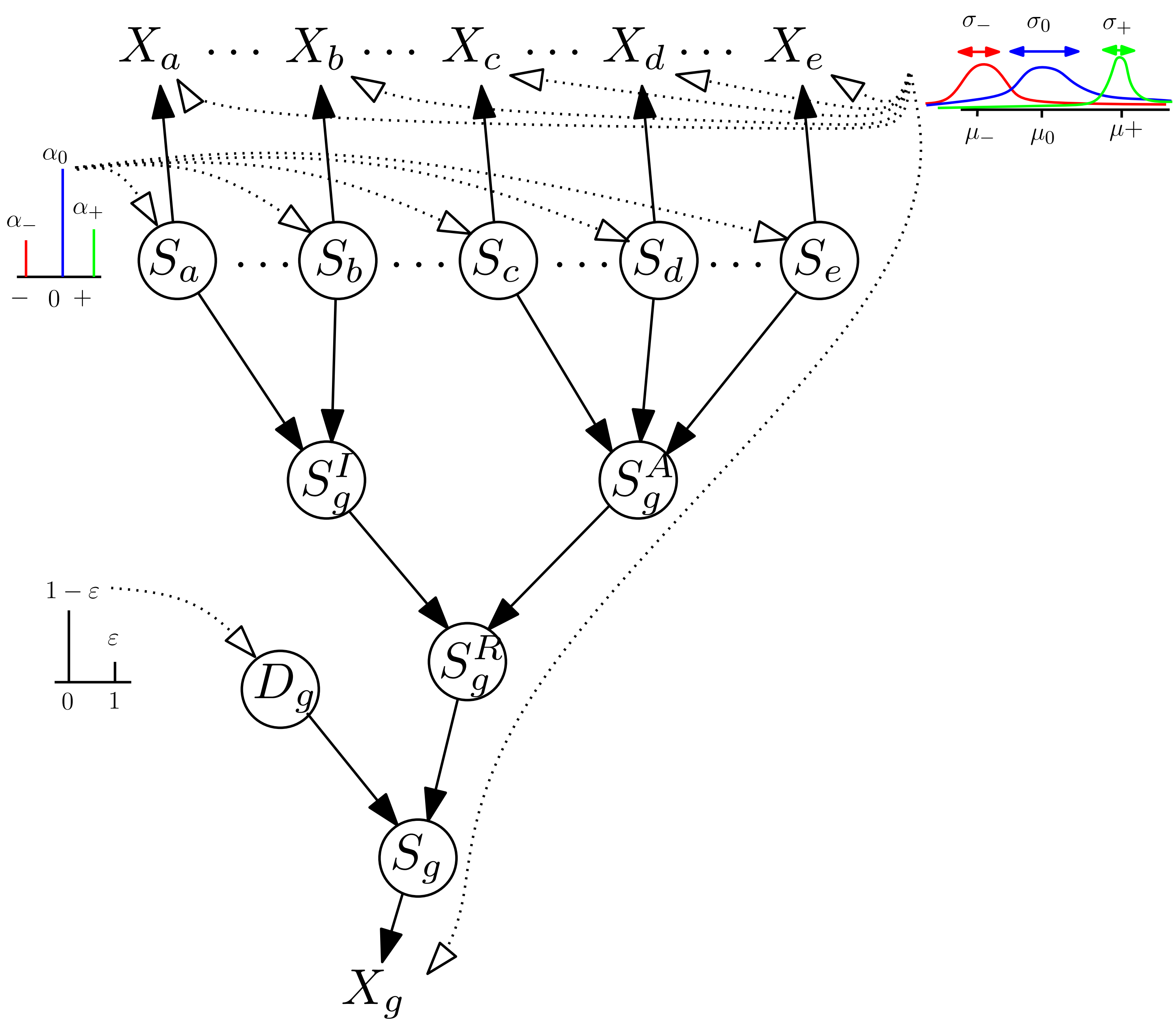

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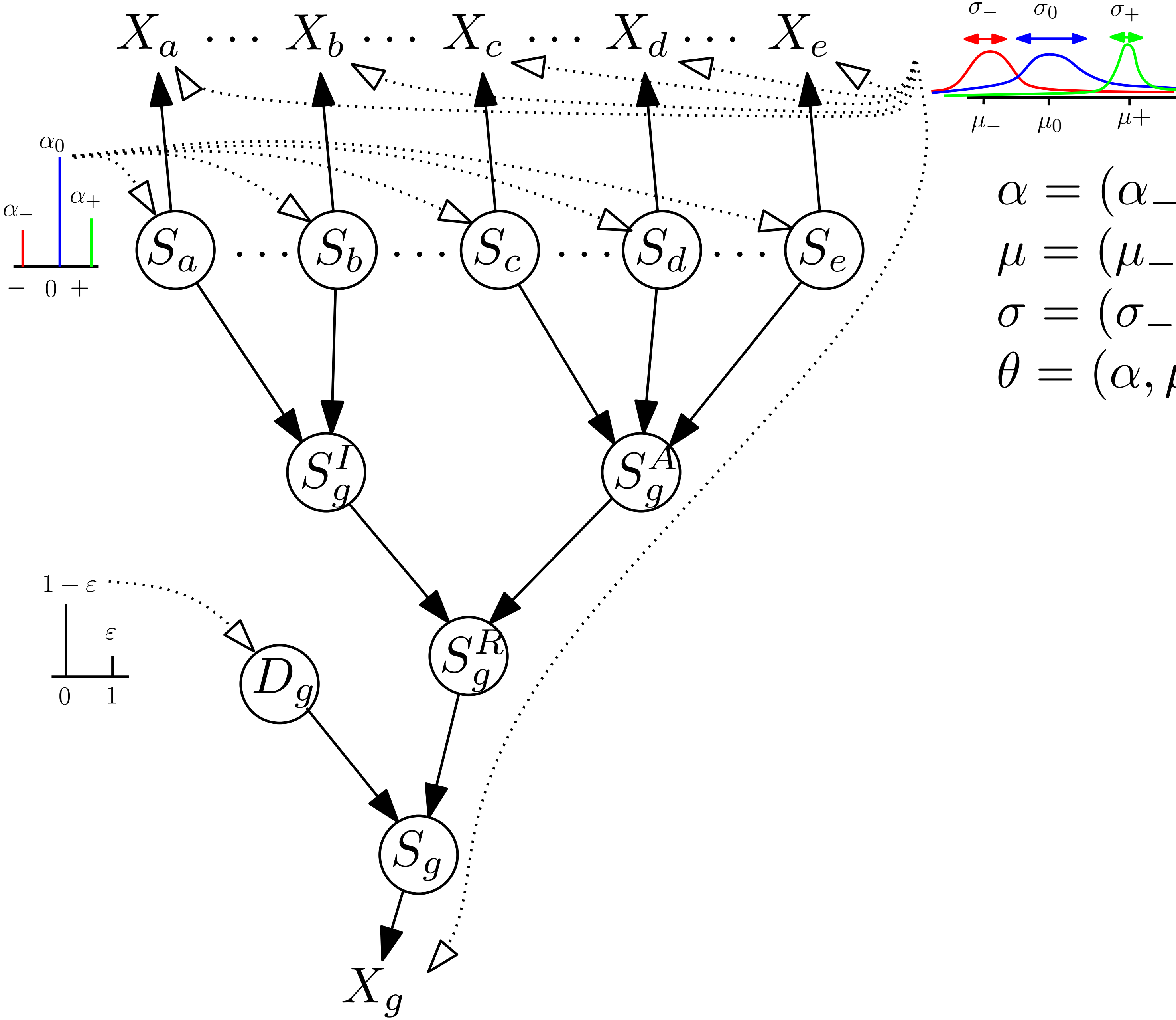

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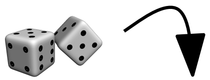
A probabilistic model



Regulator states $\in \{-, 0, +\}$

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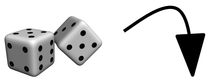

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Regulation

Target states $\in \{-, 0, +\}$

A probabilistic model

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Regulation   Deregulation

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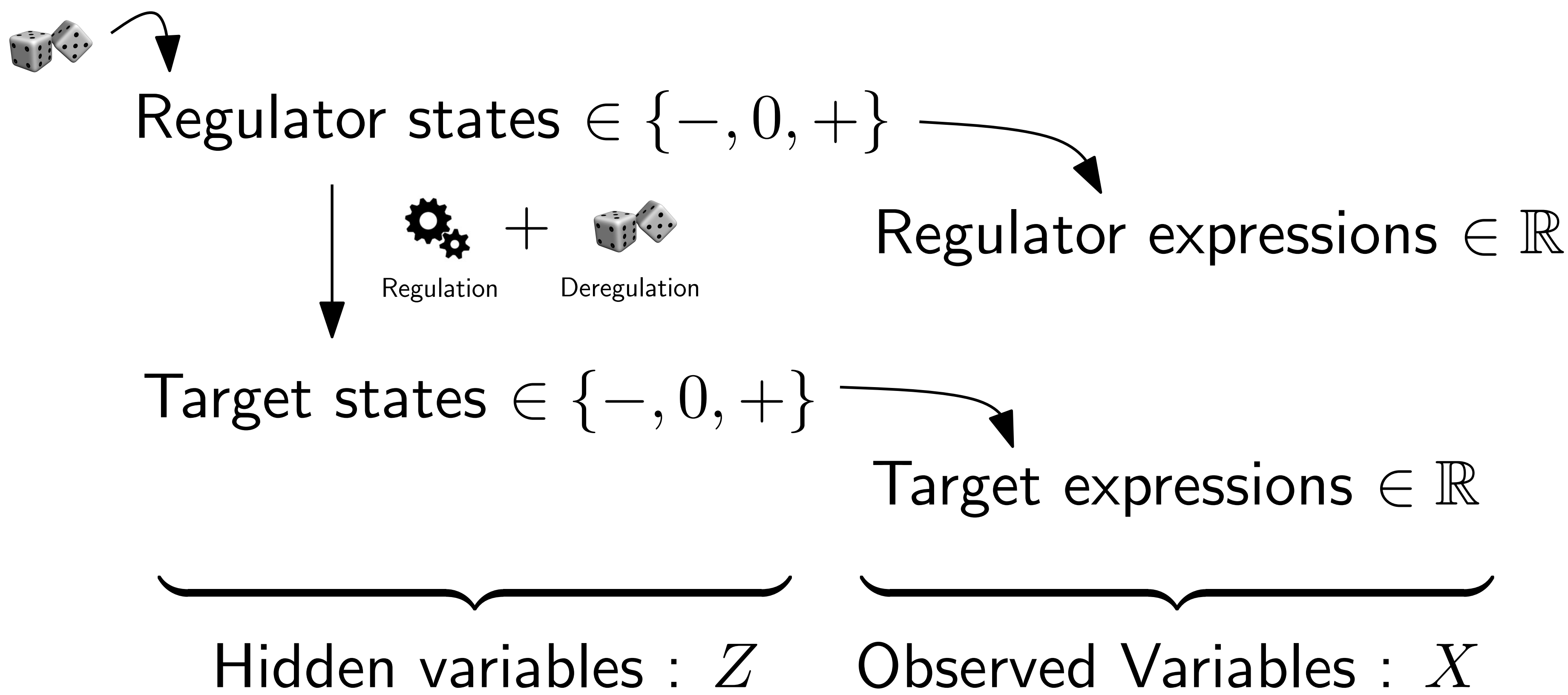

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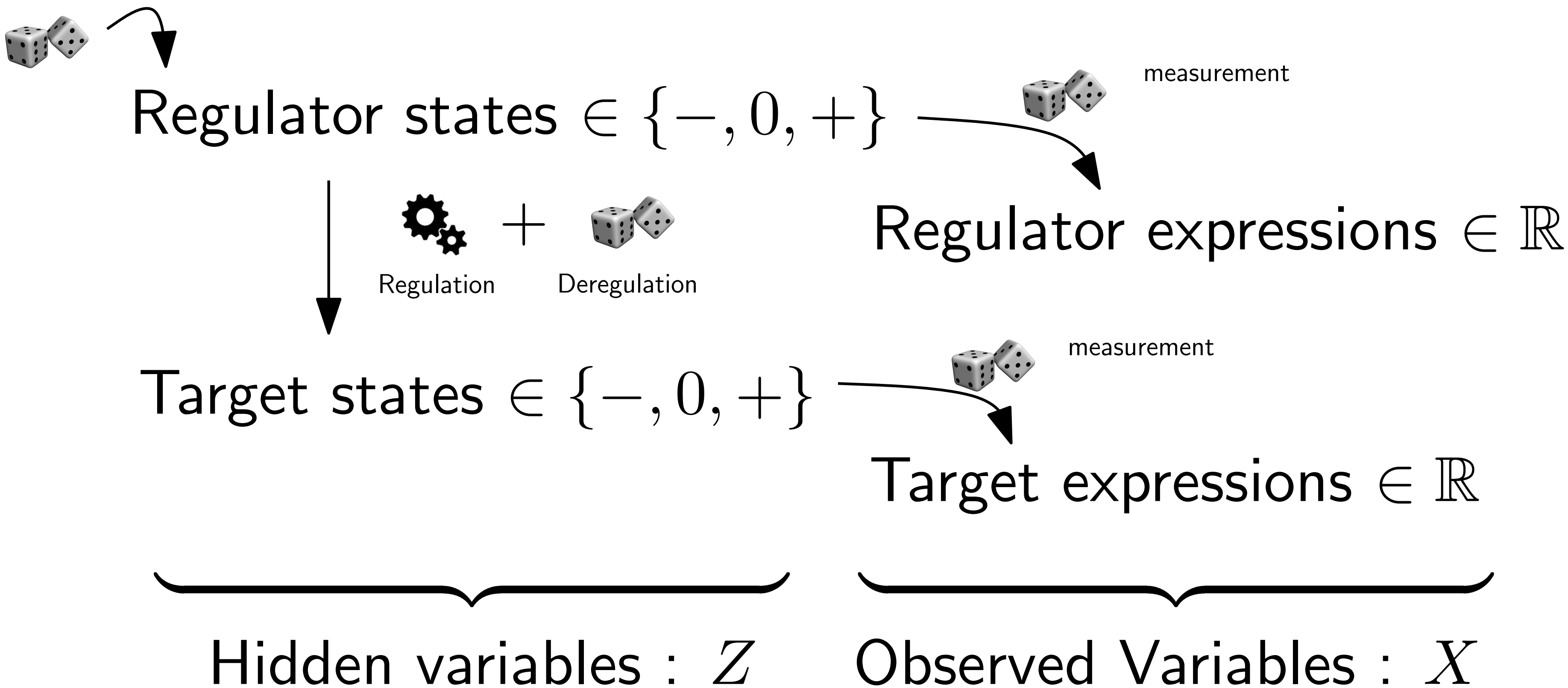

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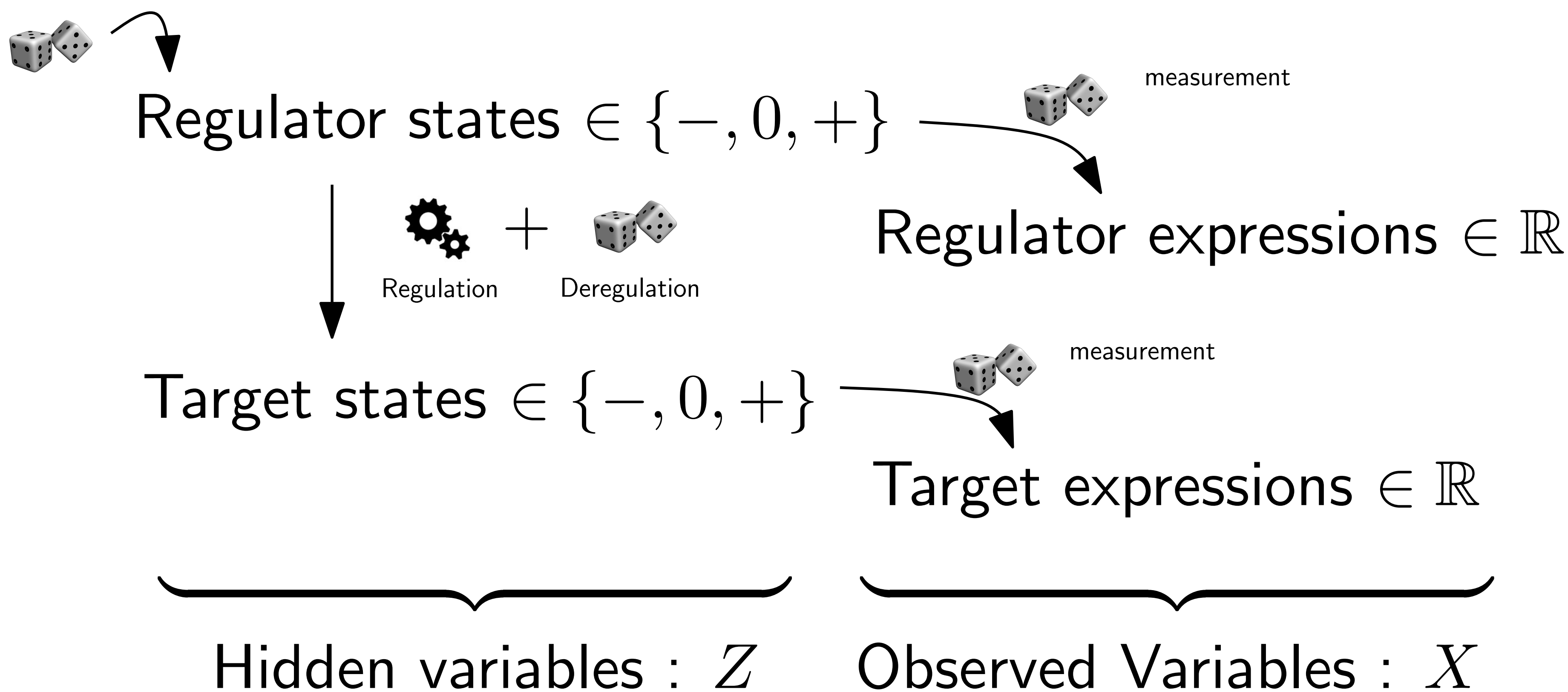
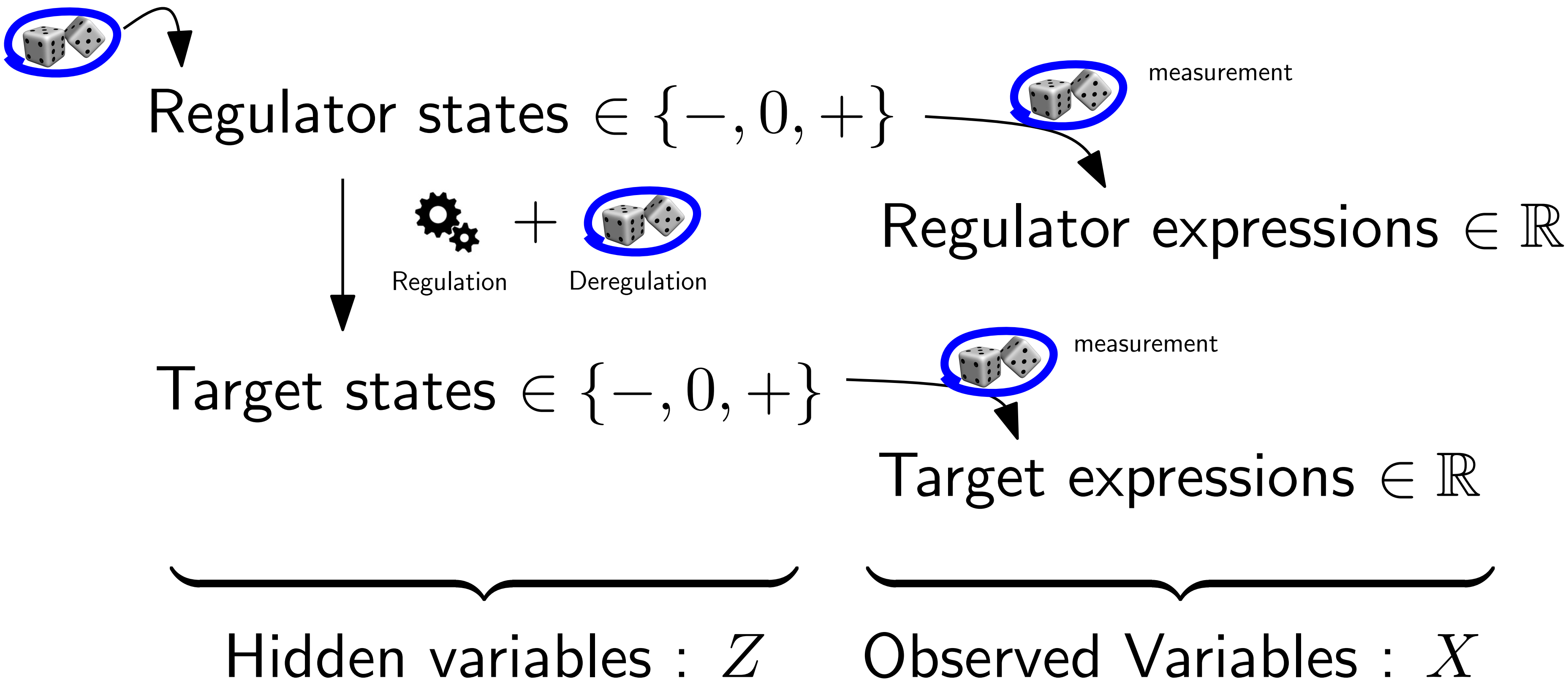


Use $P(X, Z)$ to compute $P(Z|X)$ and even $P(\text{gene } \mathbf{g} \text{ deregulated}|X)$

A probabilistic model



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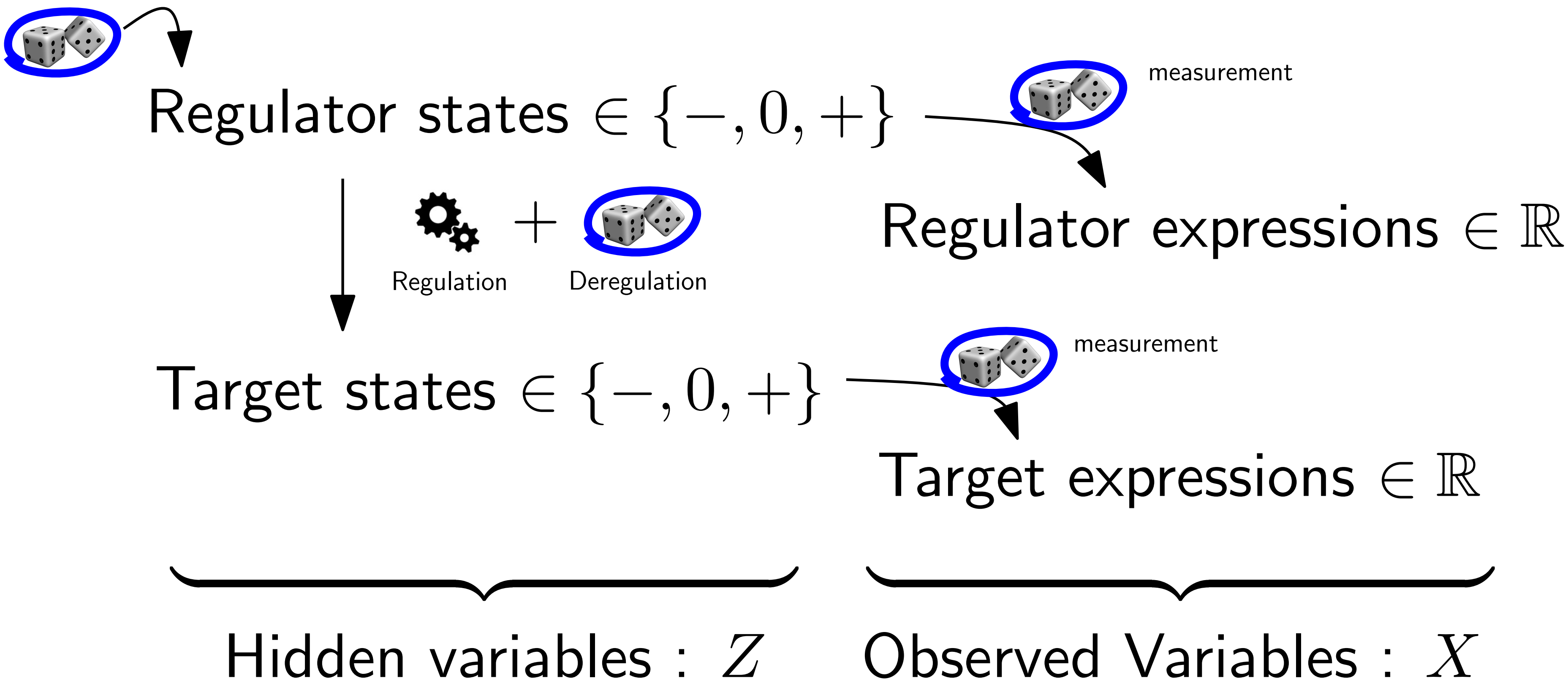

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$P(X, Z)$ depends on unknown parameters.

$\rightarrow$ To be inferred from the data.

EM...

We want parameters θ to maximize the likelihood $\mathcal{L} = P(X|\theta)$
Given θ_0, two steps provide a better θ_1:

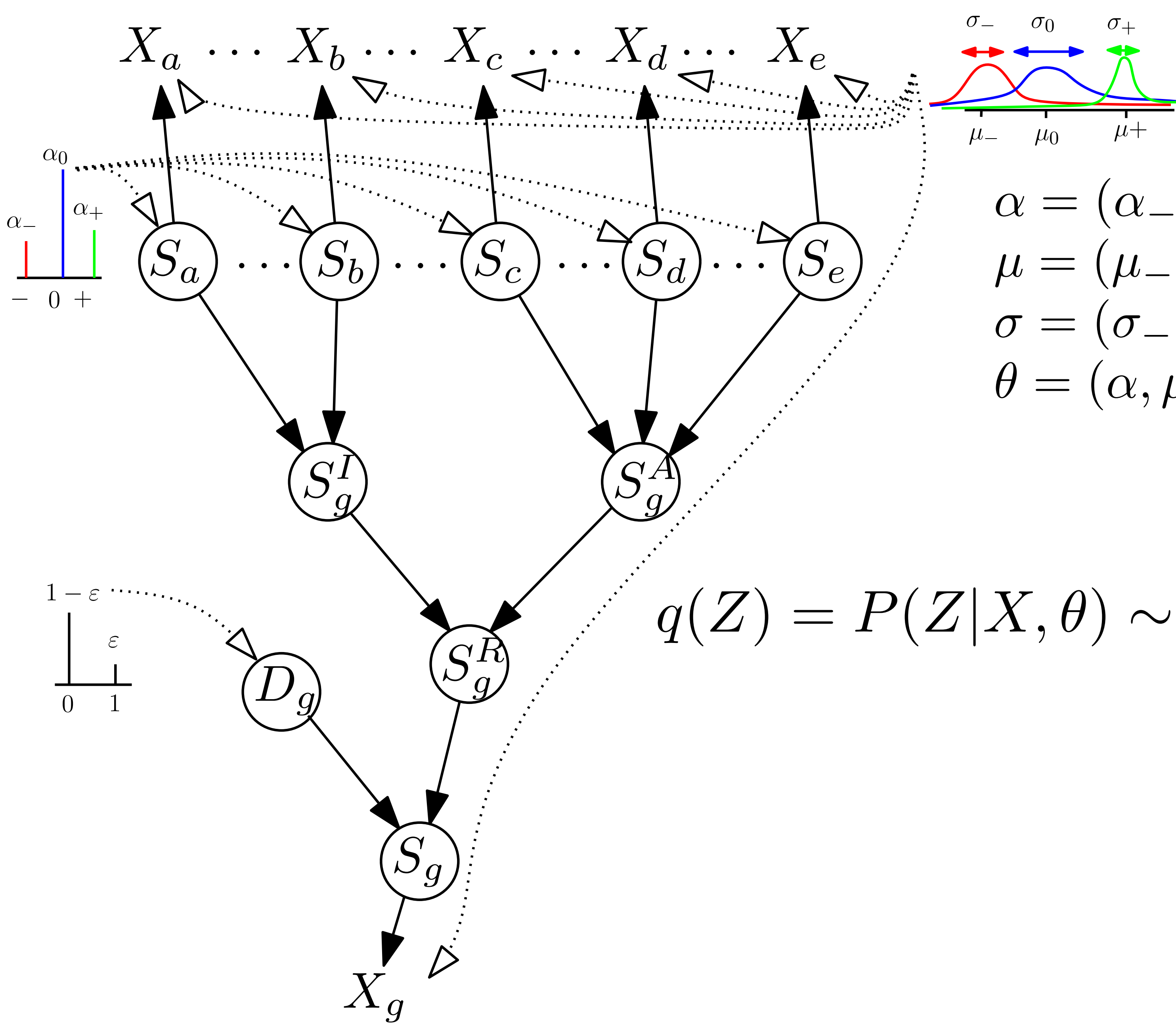
- Step E: compute $q(Z) = P(Z|X, \theta_0)$, the posterior distribution of hidden variables
- Step M: q fixed, the expectation (under q) of $\log P(X, Z|\theta)$ is a function of θ:

$$f(\theta) = \sum_Z q(Z) \log P(X, Z|\theta)$$

$\theta_1 = \operatorname{argmax} f$ is a better parameter set.

In our model, Step M is easy, Step E uses Belief Propagation (detailed later)

Detailed model : A Factor Graph



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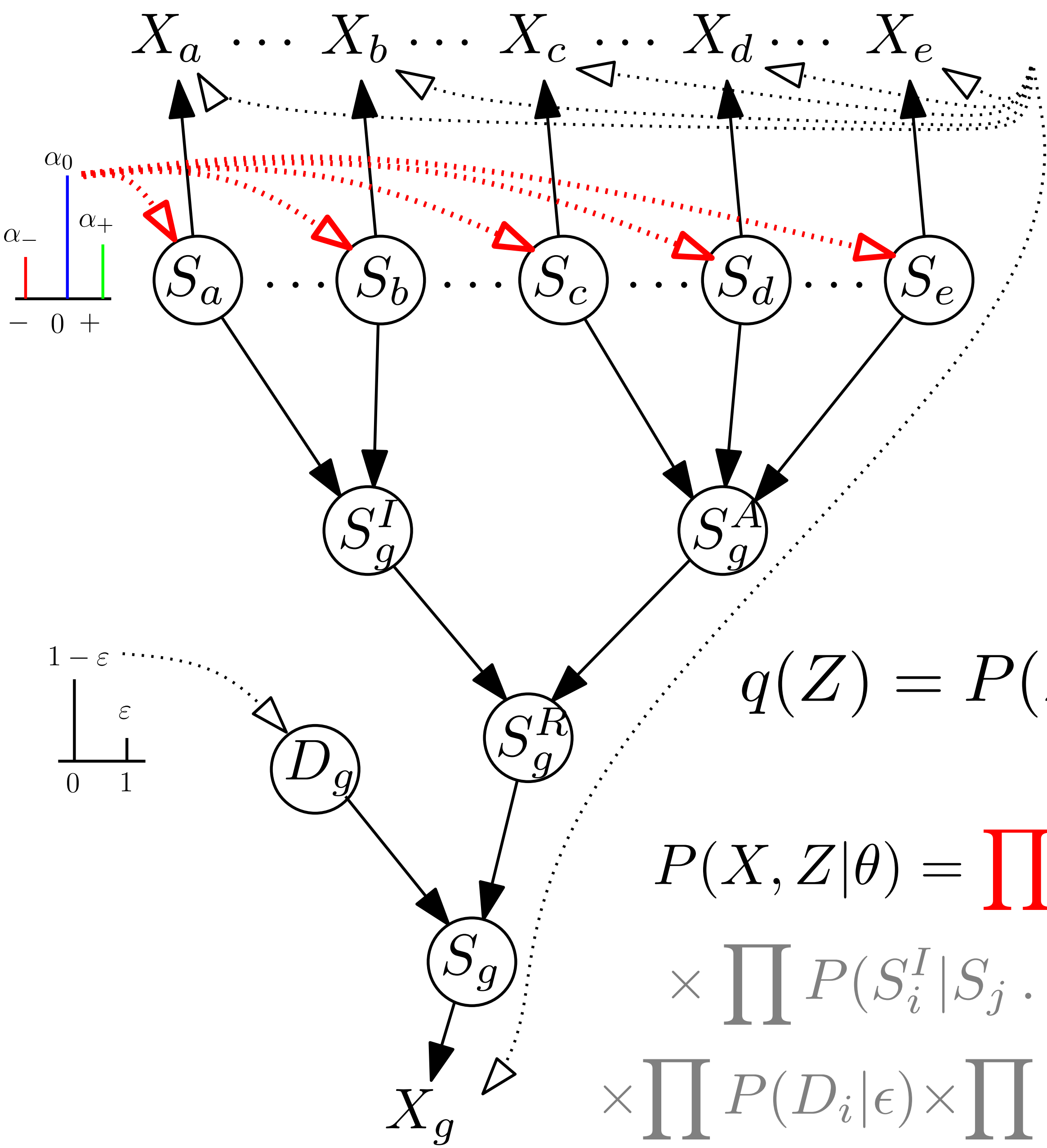

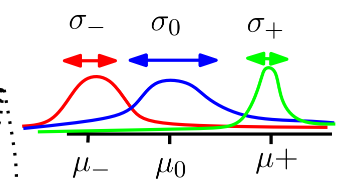

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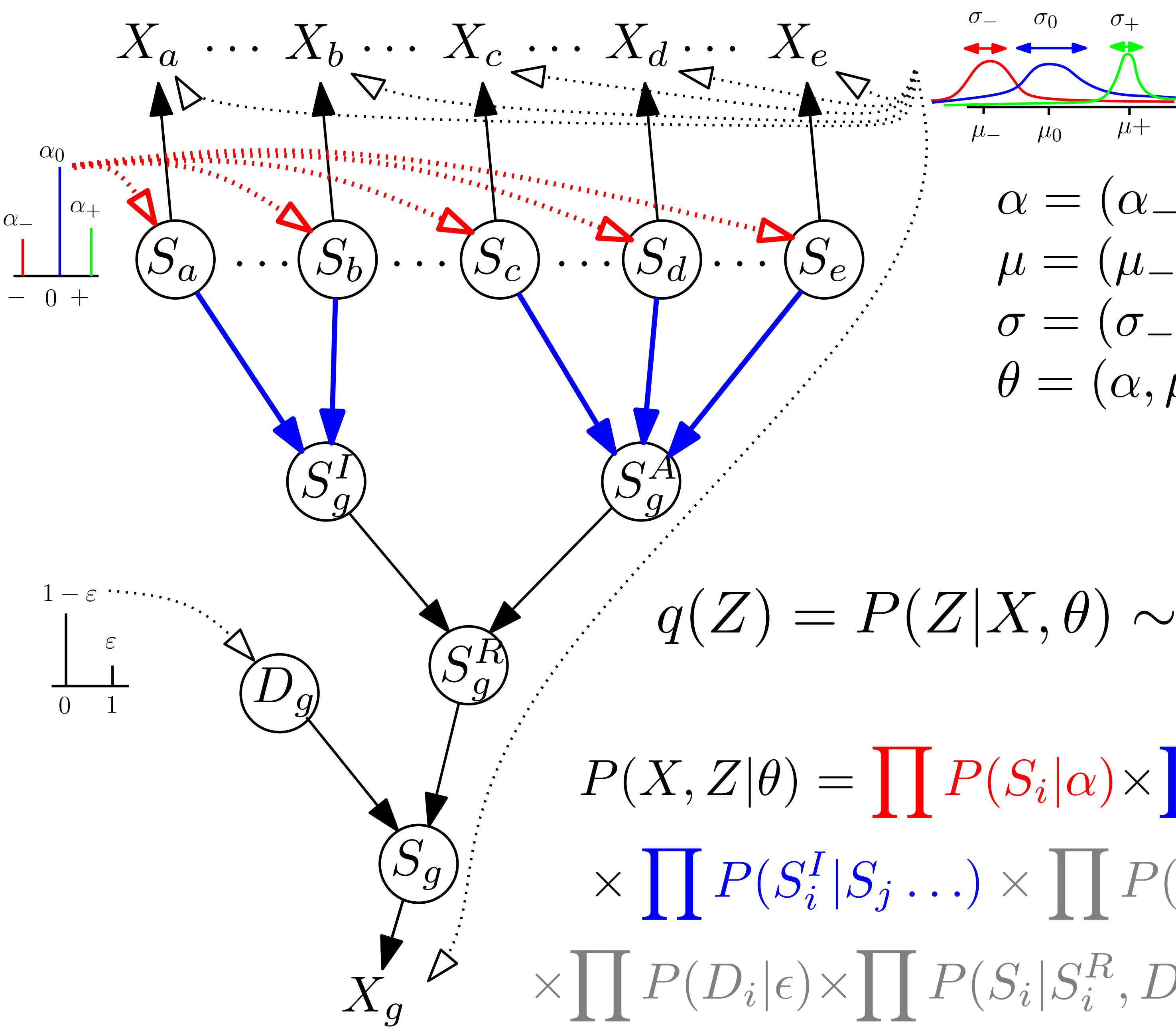

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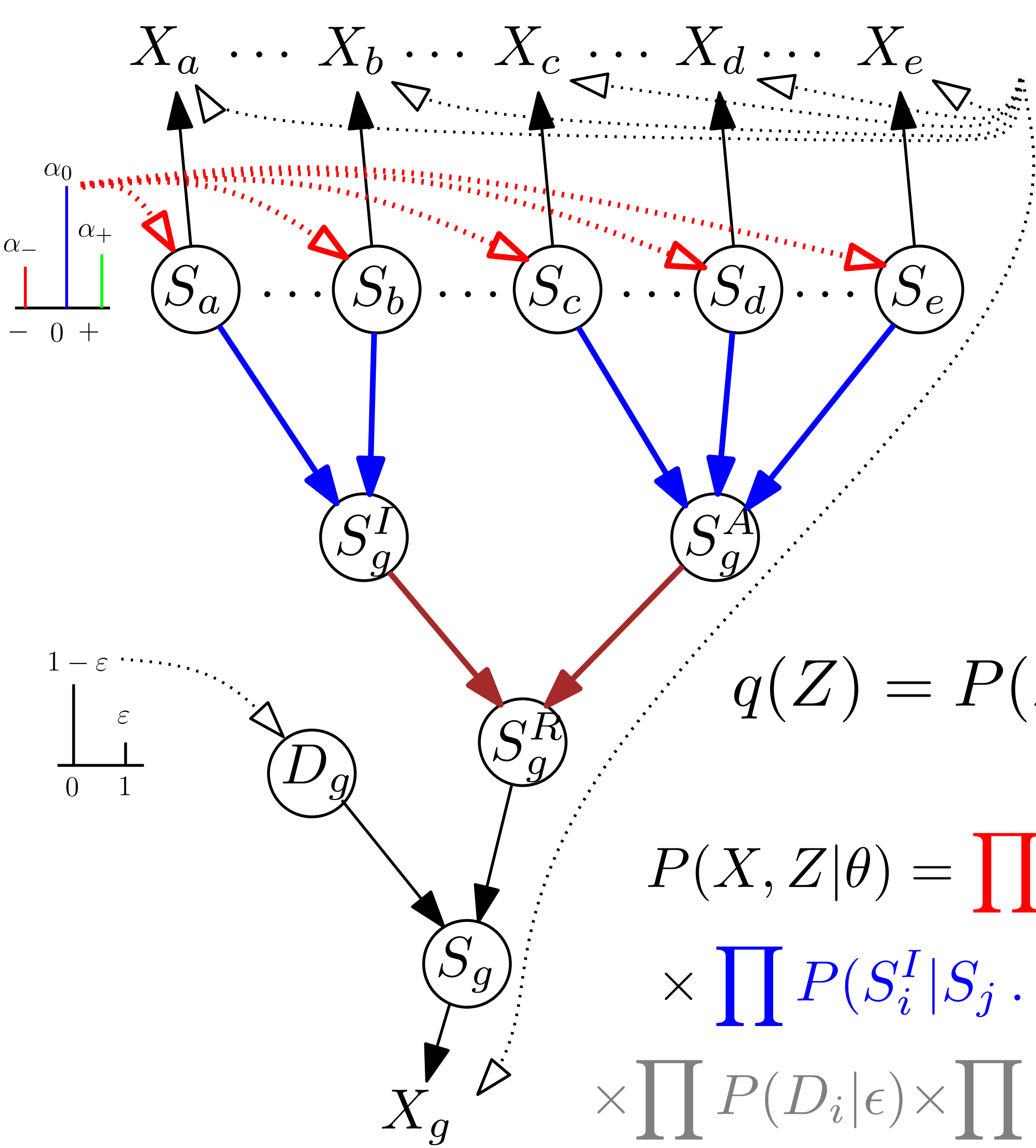

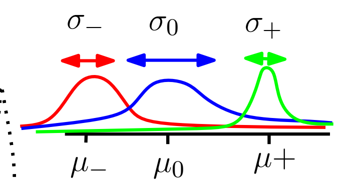

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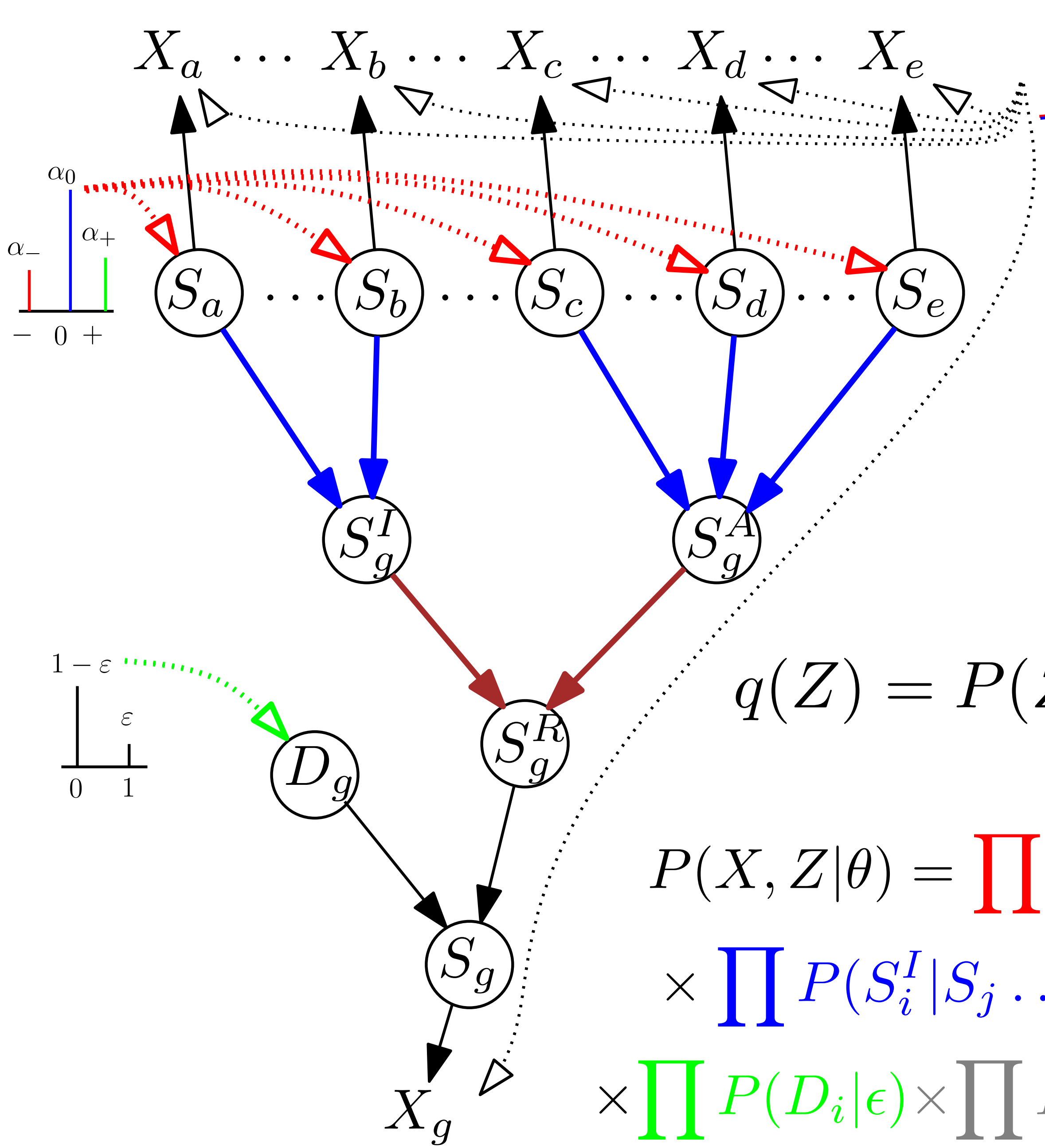

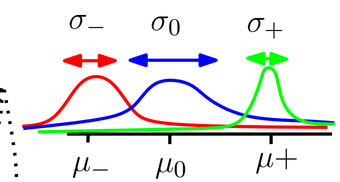

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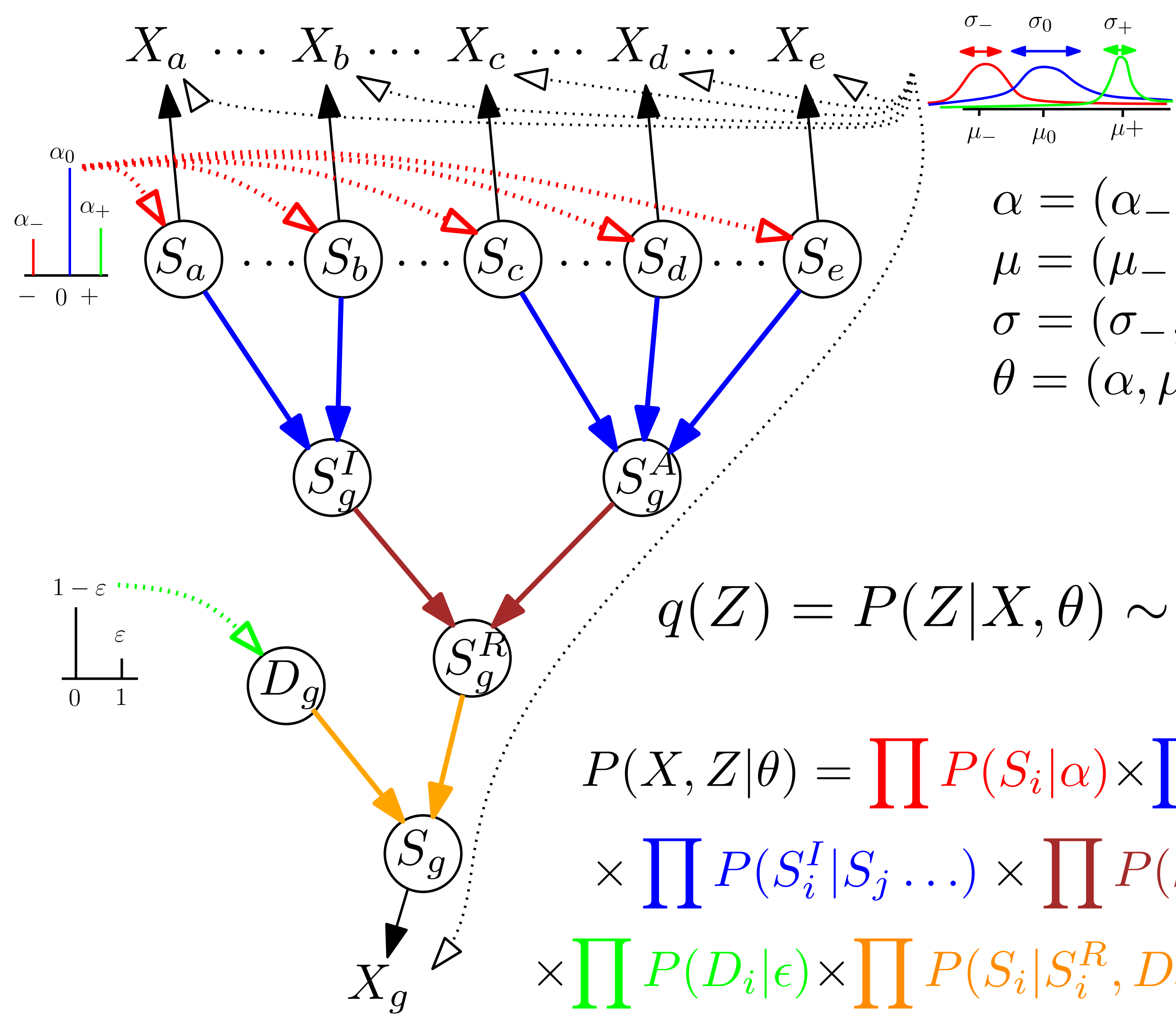

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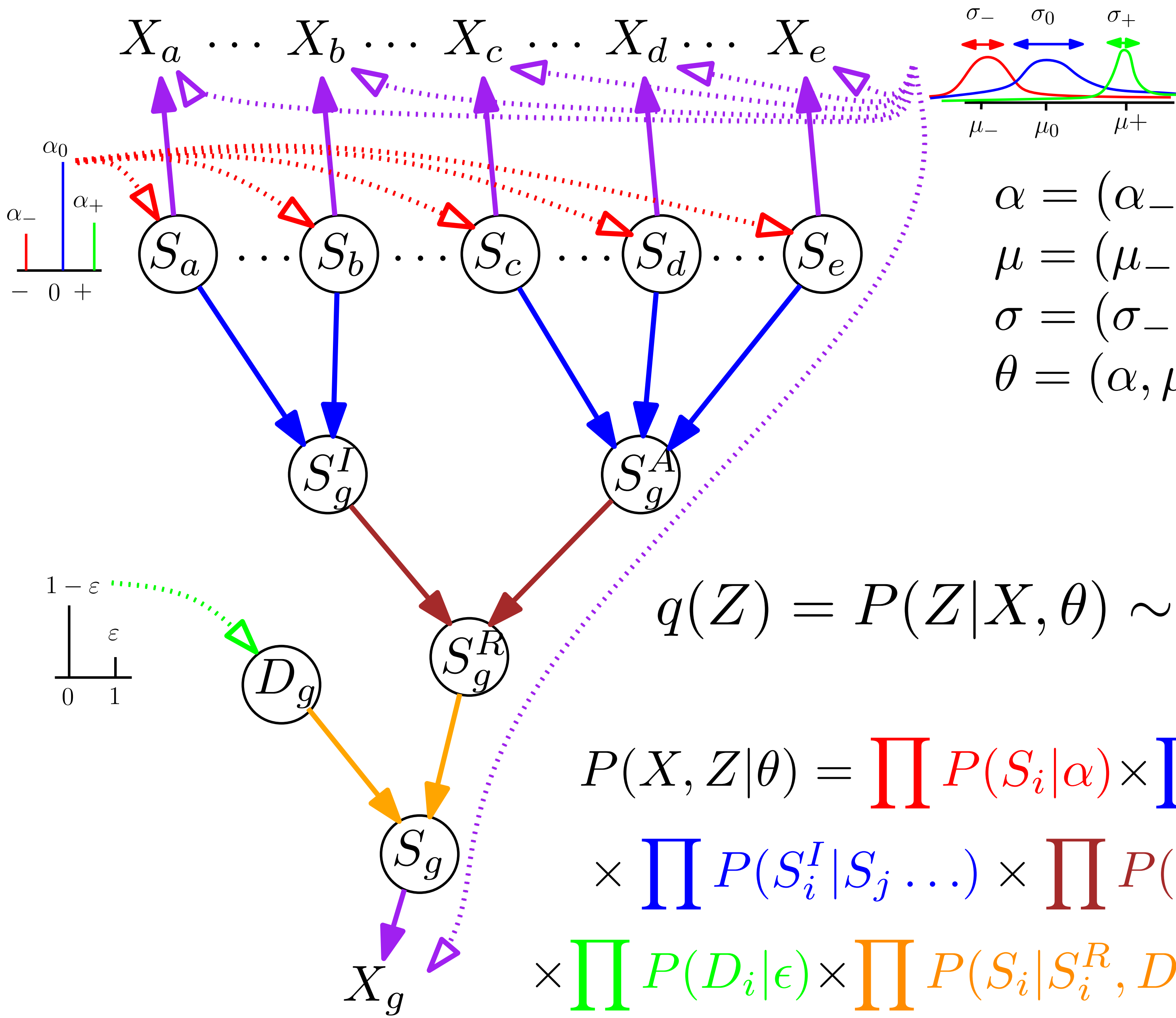

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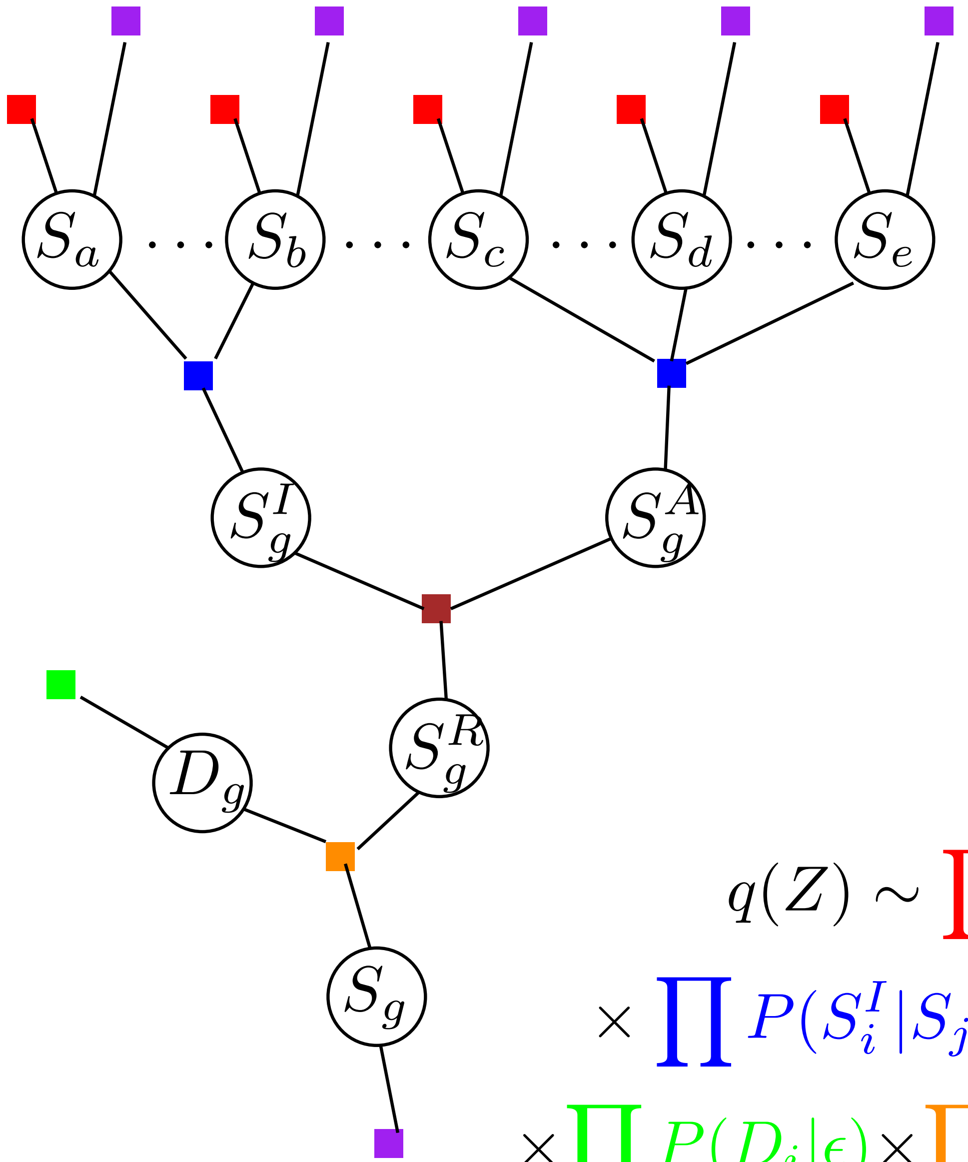

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Solving Factor graphs: Belief Propagation

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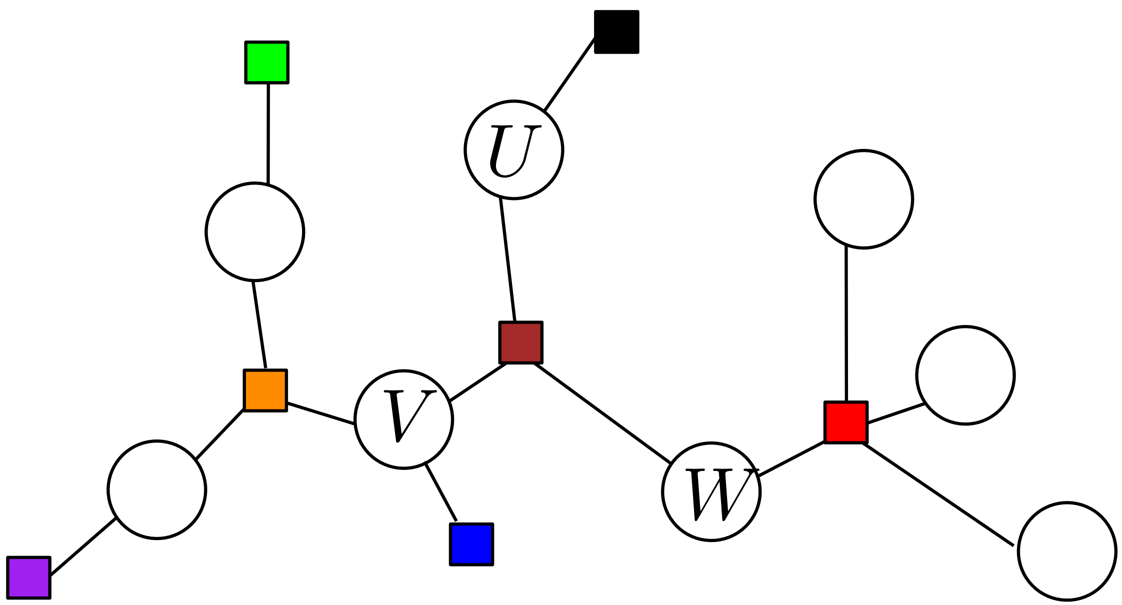

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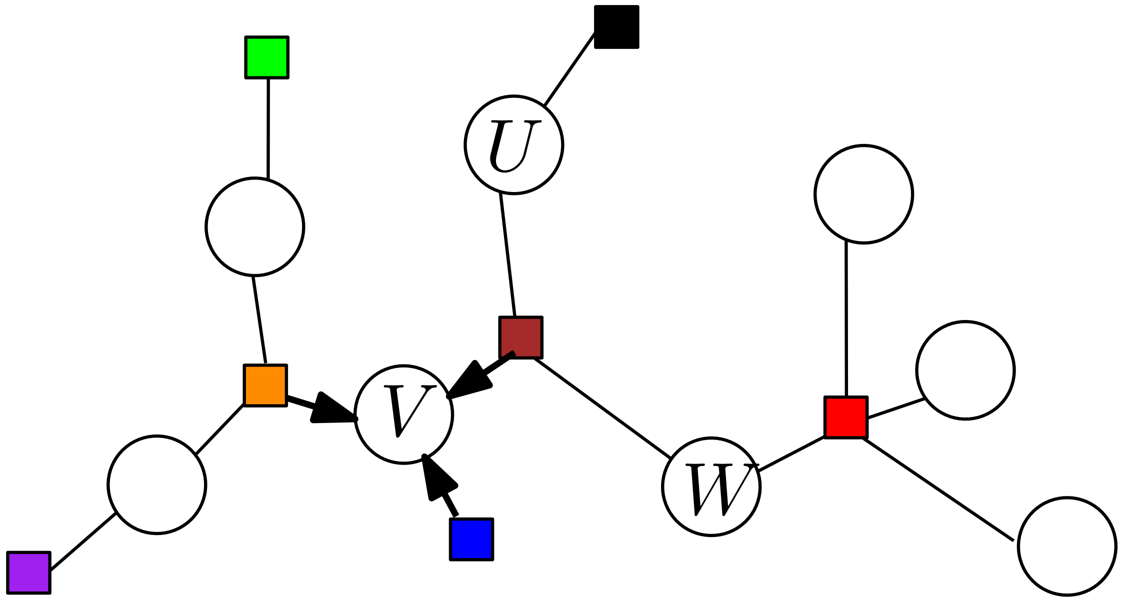
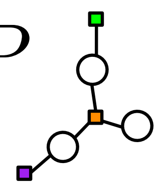
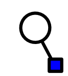
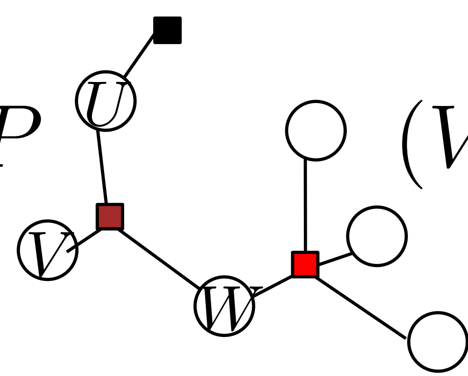


$P_G(V = v) = P$  $(V = v) \times P$  $(V = v)$

$\times P$ 

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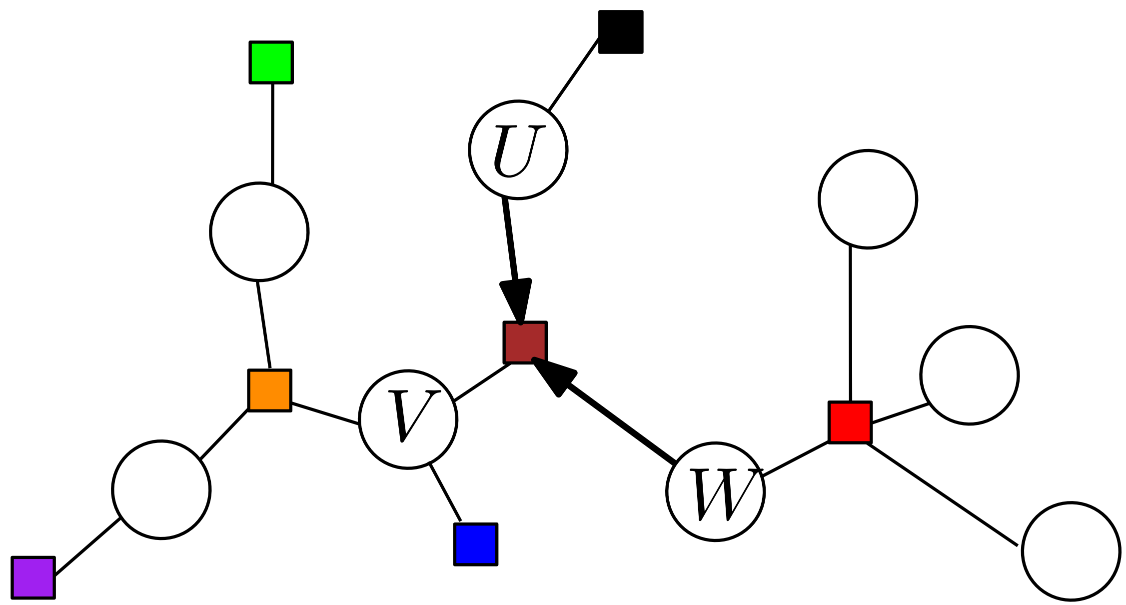
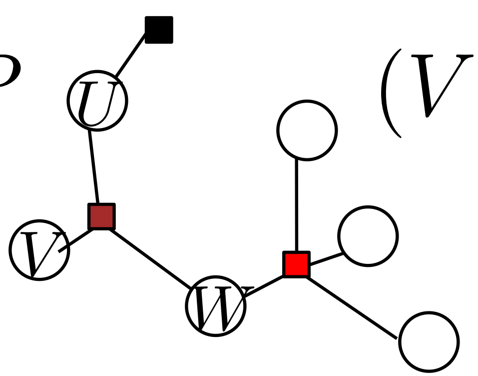
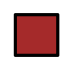
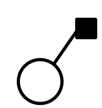
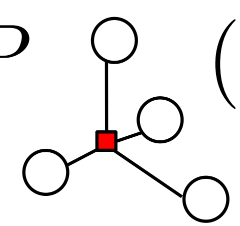
G= 

P 

$(V = v) = \sum_{u,w}$  (u, v, w)

$\times P$  $(U = u)$

$\times P$  $(W = w)$

Solving Factor graphs: Belief Propagation

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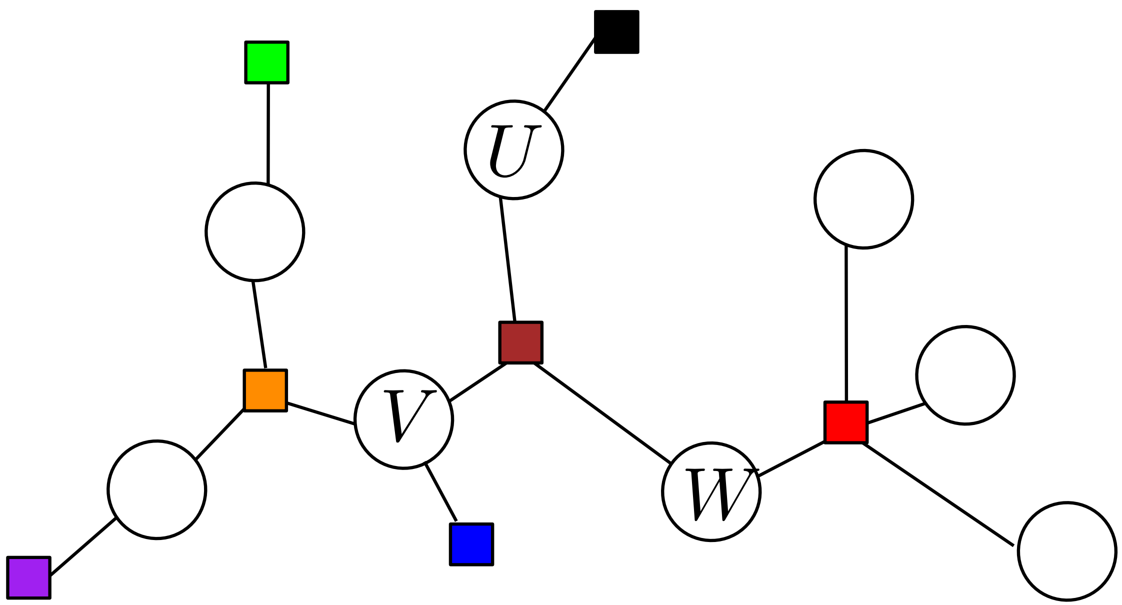


- Belief Propagation computes the exact marginals in one linear pass when the factor graph is a tree
- If it has bounded tree-width, the exact marginals can be obtained working on a tree decomposition
- Otherwise, the propagation process must be iterated
- Theory shows it can go wrong, but experience shows it often converges towards the correct marginals.

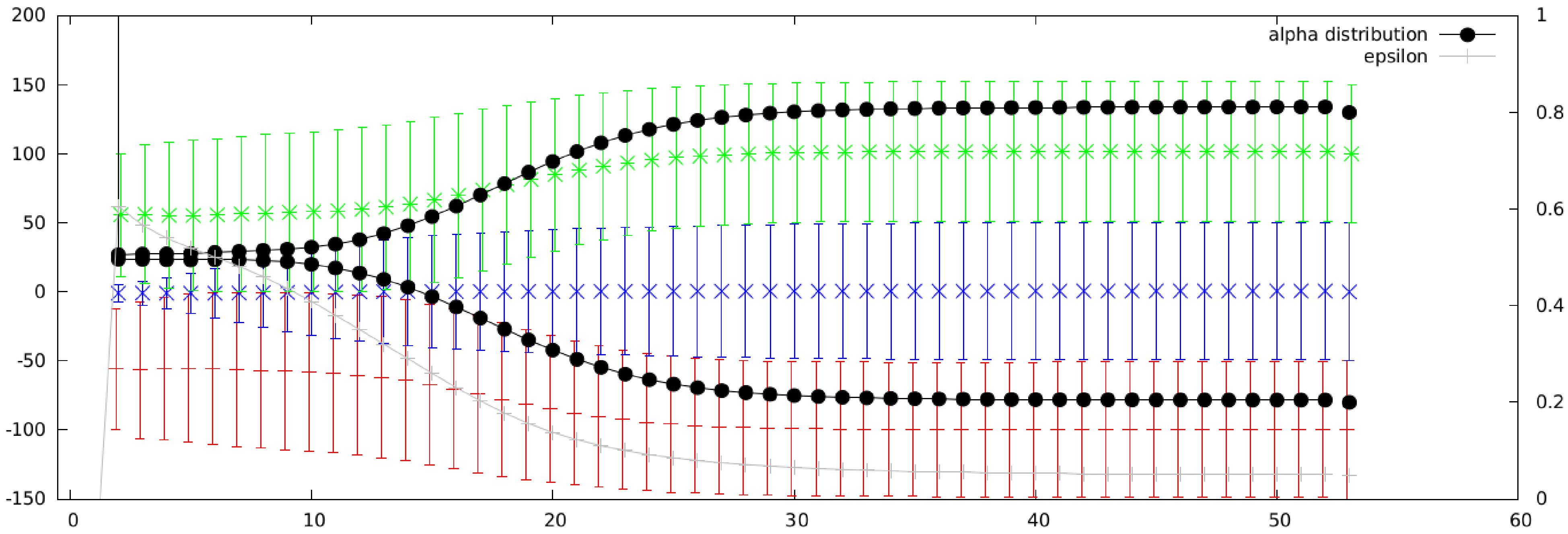
Summing up

- Using Belief Propagation, we obtain an approximation of q
- The EM algorithm uses this as an approximated step E
- The system parameters are inferred
- We obtain the posterior probability for each gene to be deregulated.

Validation ?

- No way to know the deregulation status in a real data set
- The method is tested on simulated data
- It is run on real data, and results are compared with other perturbations (Copy-Number Alterations)
- Further analyses of the results should give information about the tumors (cause, subtypes...)

EM progress



Small sensitivity to initial parameter set θ_0. (here $\mu_0 = (-1, 0, 1)$ and $\sigma_0 = (1, 1, 1)$)
First iteration usually finds good estimates of μ, σ, then α and ε are slowly refined.

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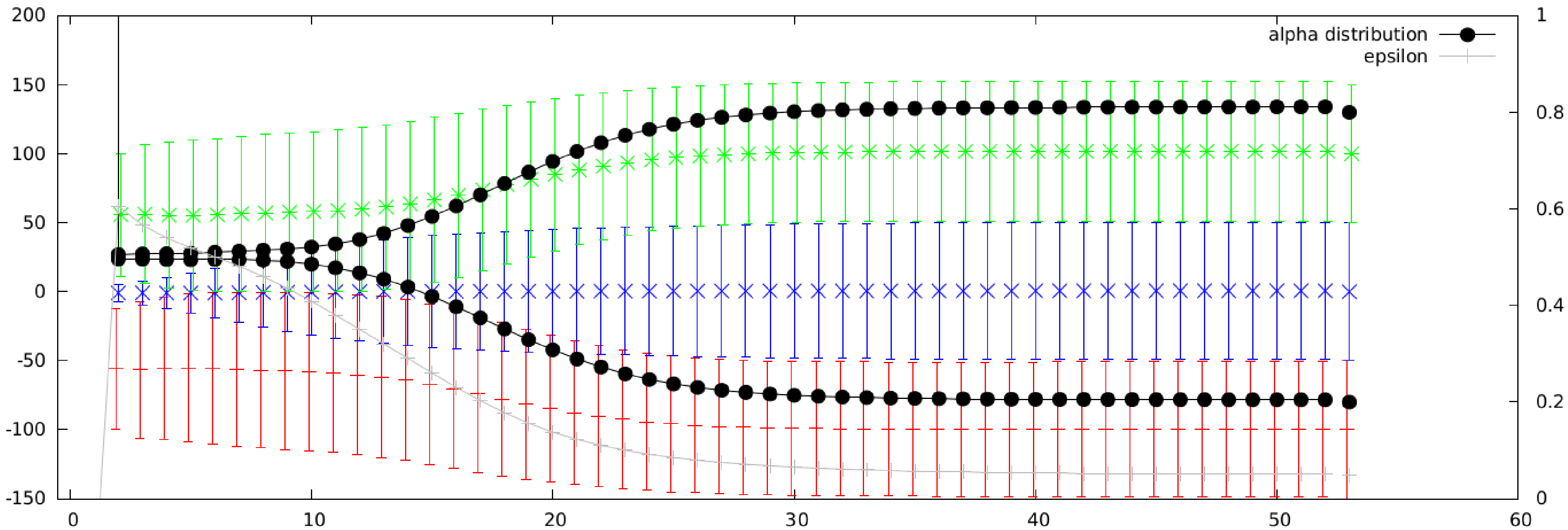

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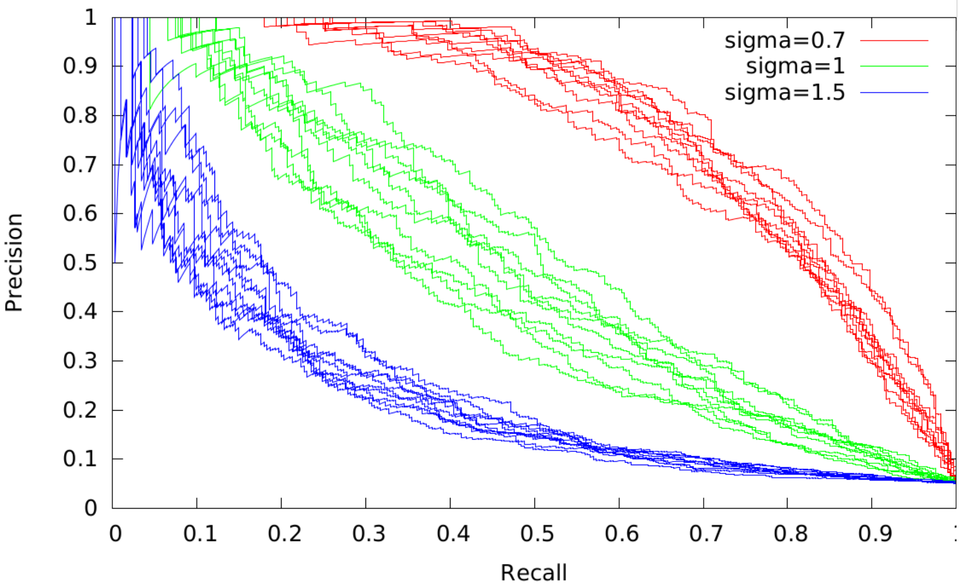
What about deregulated genes ?

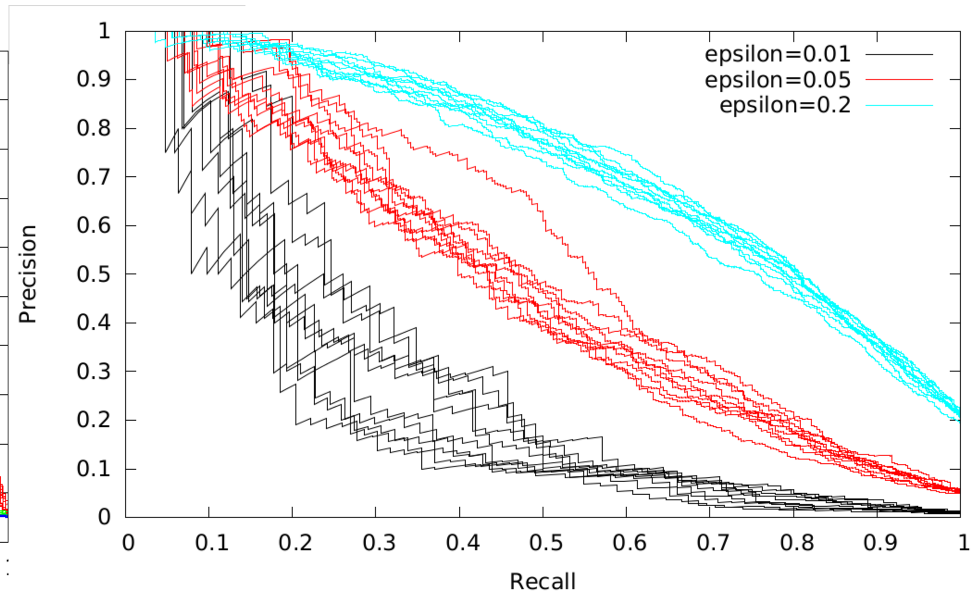
Precision-Recall (PR) curves

Default parameter set :

- $\mu = (-1, 0, 1)$
- $\sigma = (1, 1, 1)$
- $\alpha = (0.1, 0.8, 0.1)$
- $\epsilon = 0.1$

Then, various parameters are individually varied.





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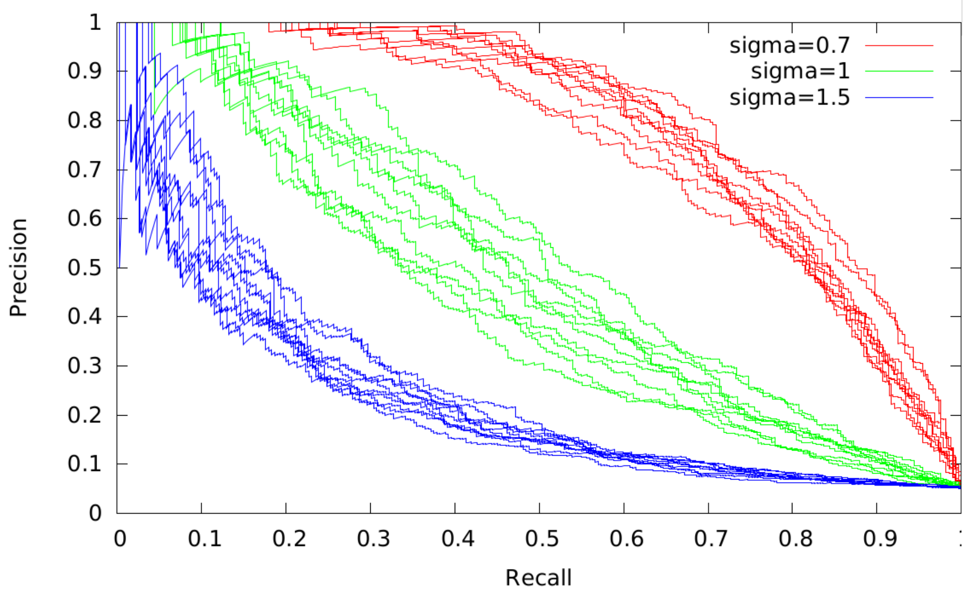

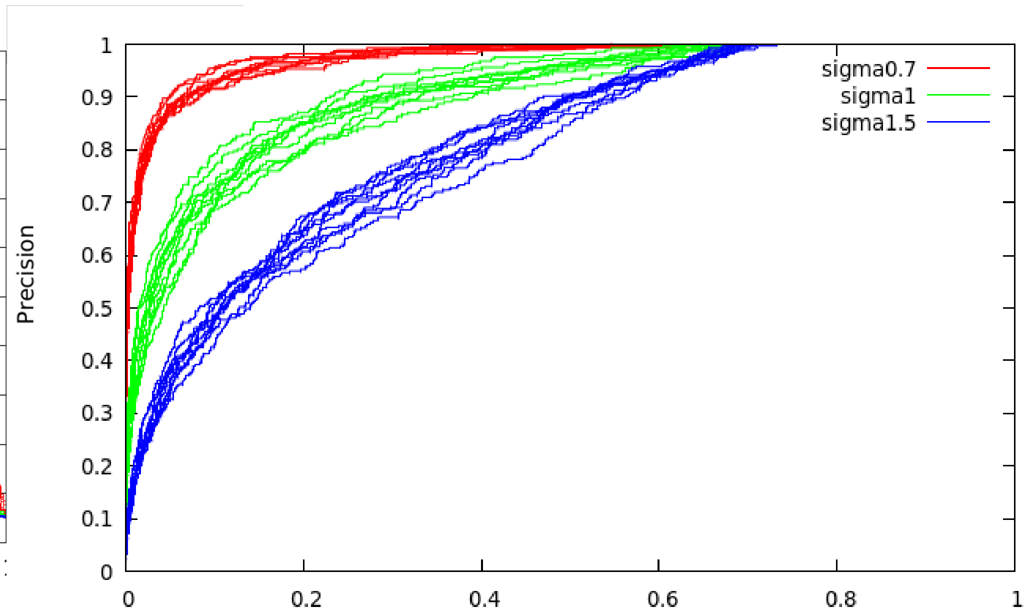

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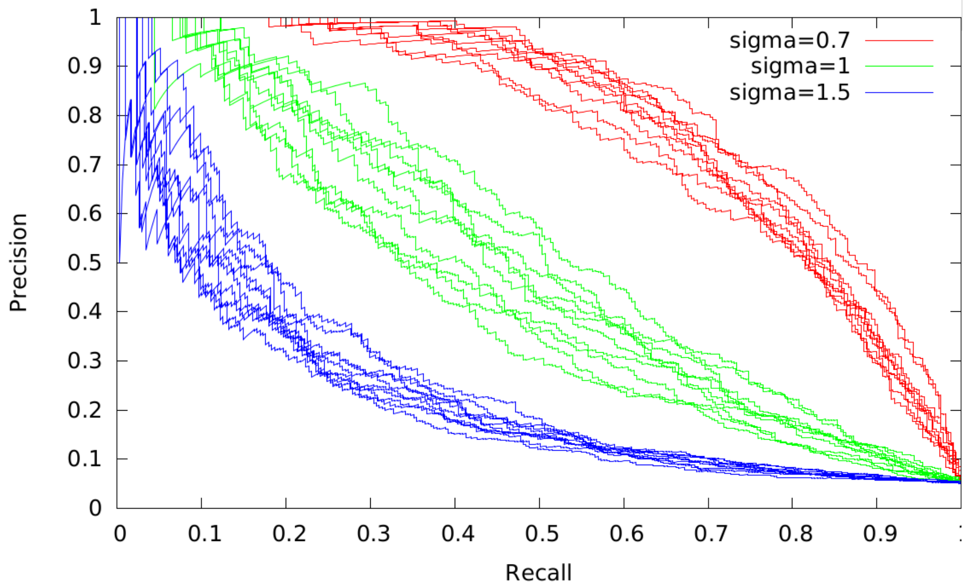
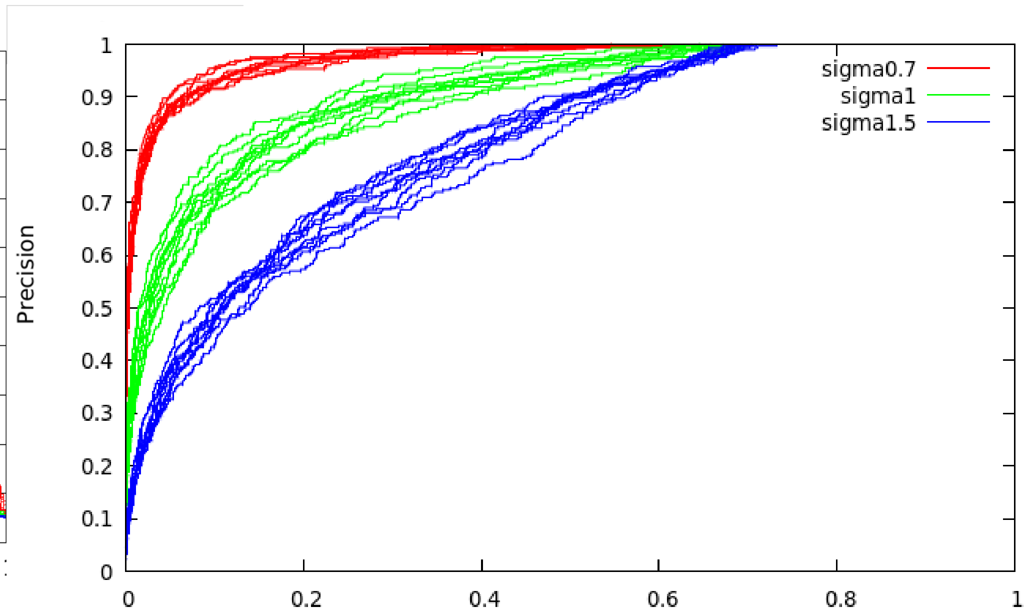
- $\epsilon = 0.1$

Then, various parameters are individually varied.





Thank you