Boosted Categorical Restricted Boltzmann Machine for Computational Prediction of Splice Junctions

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ICML Lille
International Conference on Machine Learning

Outline

- Motivation
- Preliminary
- Boosted contrastive divergence
- Categorical restricted Boltzmann machine
- Experiment results
- Conclusion

Motivation

- Deep Neural Networks (DNN) show human level performance on many recognition tasks.
- We focus on **class-imbalanced prediction**.
    - Insufficient samples to represent the true distribution of a class.

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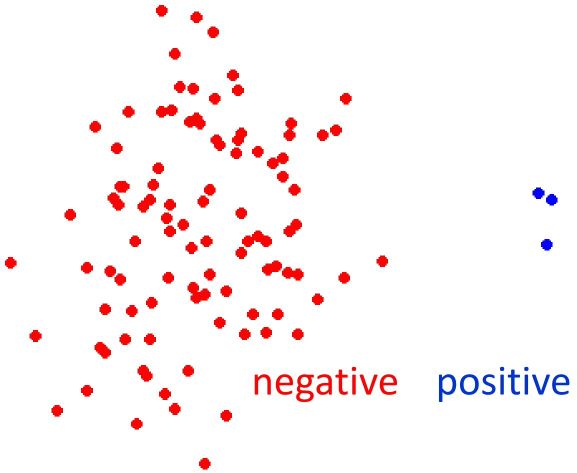

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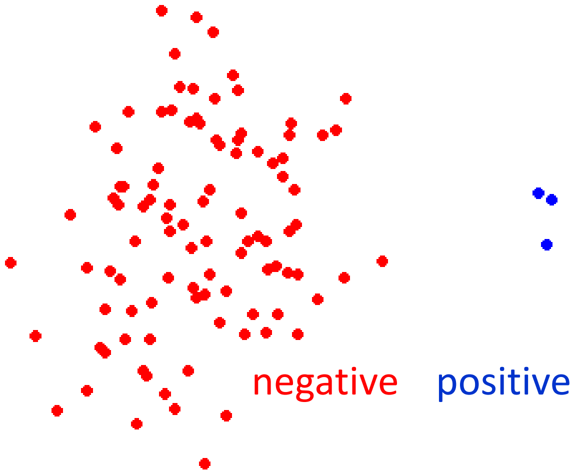

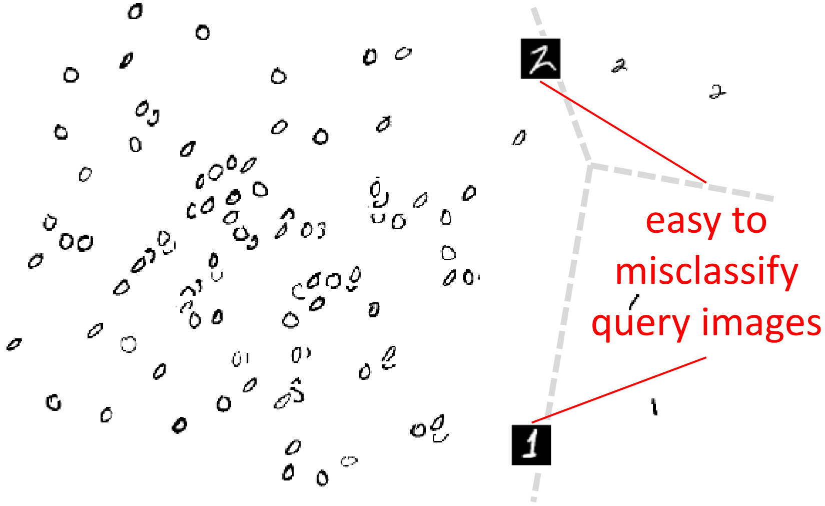
easy to misclassify query images

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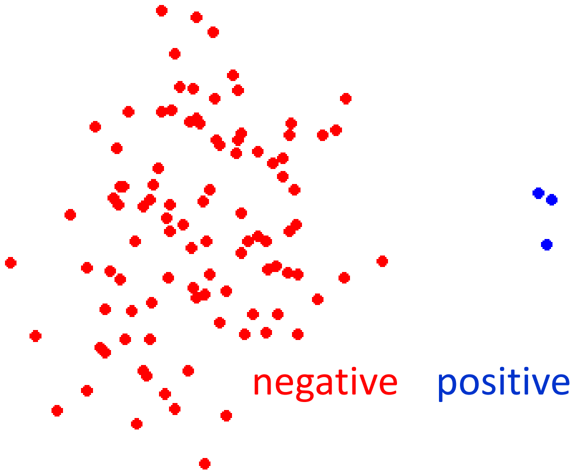

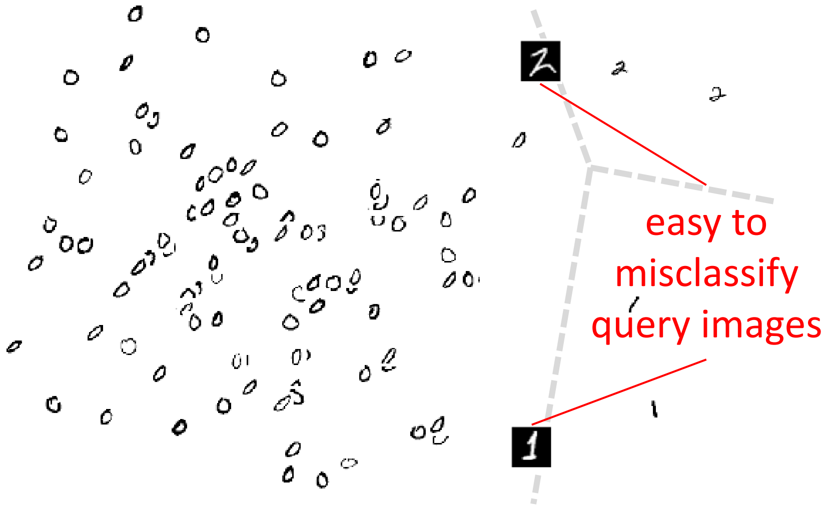

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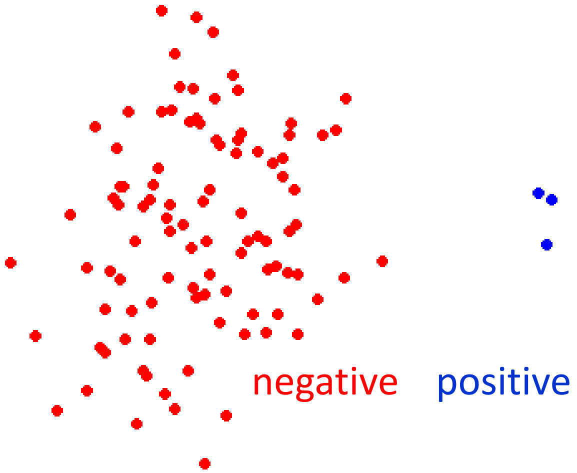

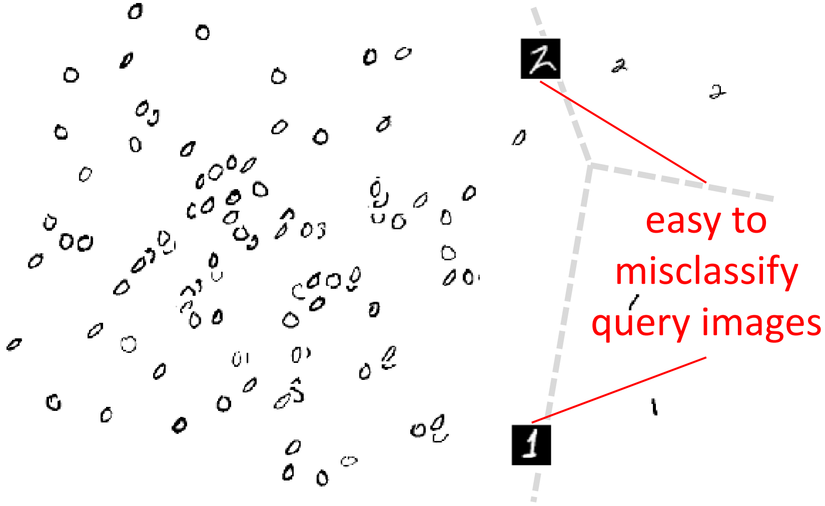

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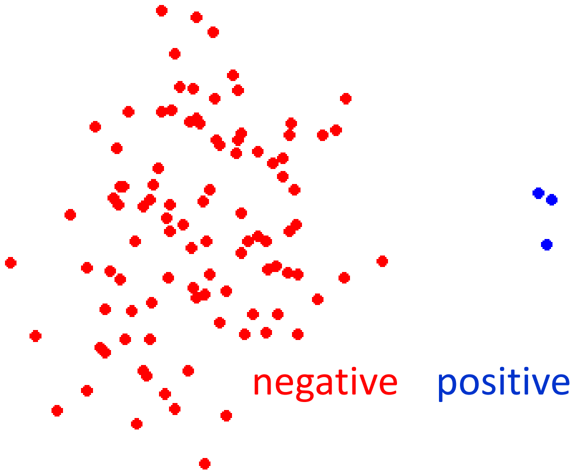

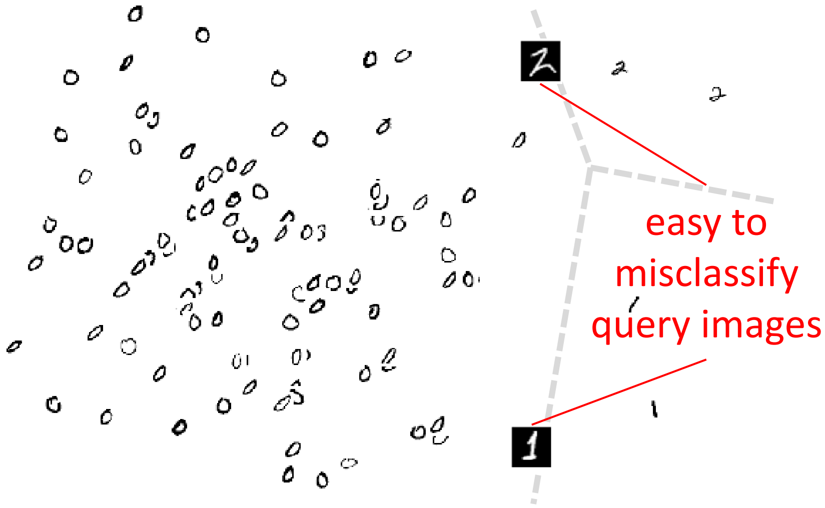

- Q. How can we learn **minor but important features** using neural networks?
    - We propose a **new RBM training method** called ***boosted CD***.
    - We also devise a **regularization term** for sparsity of DNA sequences.

(Splice) Junction Prediction: Extremely Class-Imbalanced Problem

- Genetic information flows through the **gene expression** process.
- **DNA: a sequence** of four types of nucleotides (A, G, T, C).
- **Gene: a segment of DNA** (the basic unit of heredity).

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DNA

RNA

protein

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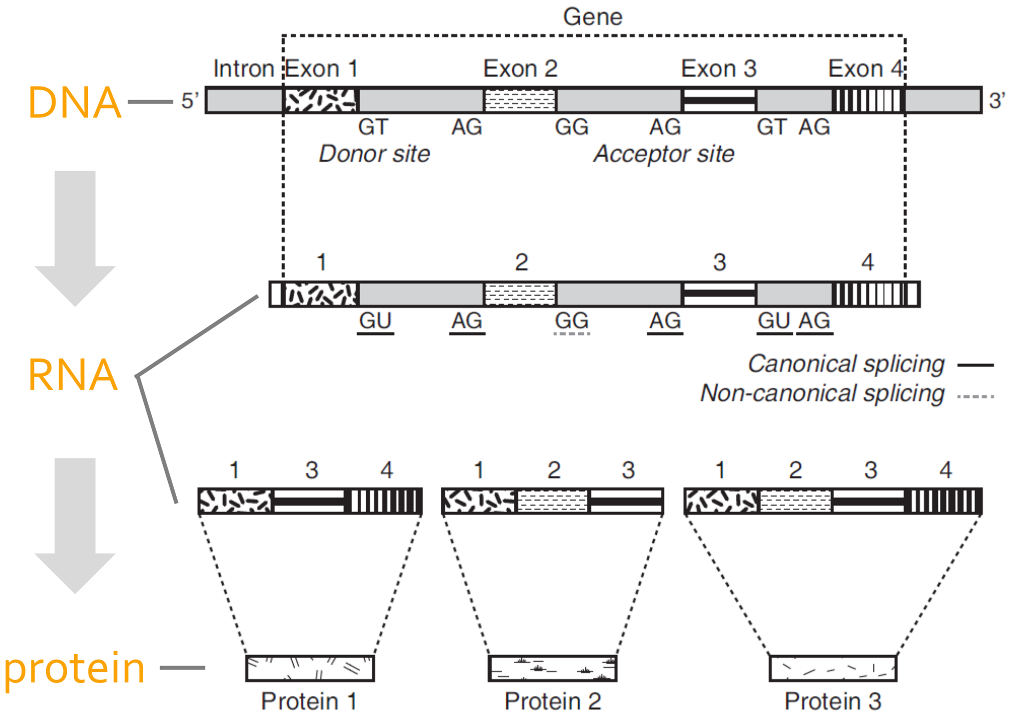

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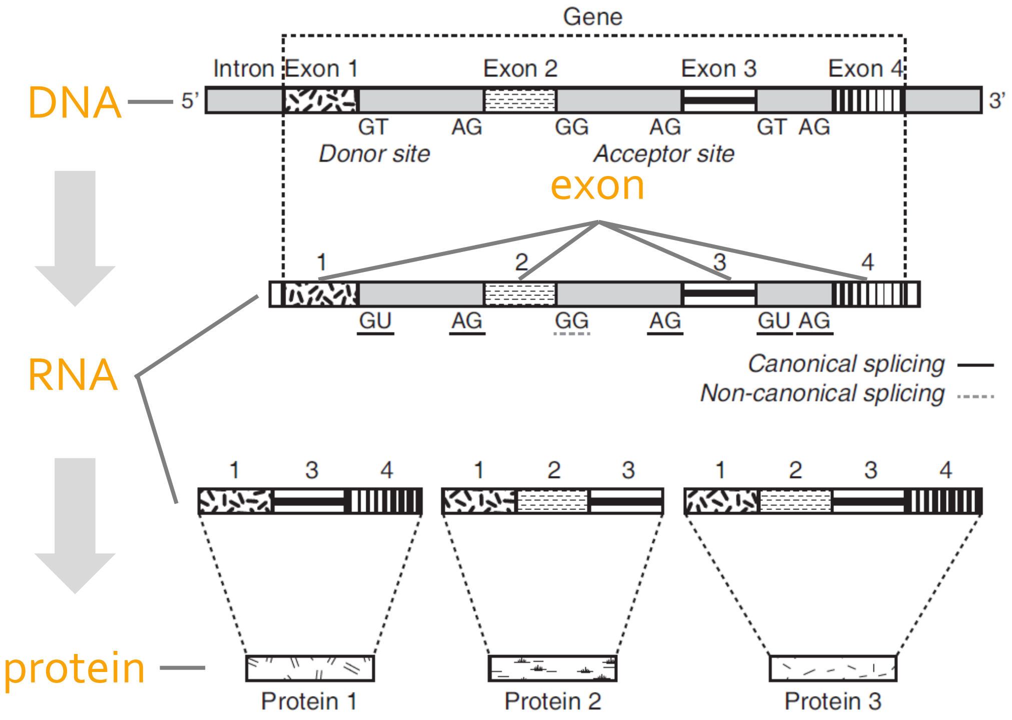

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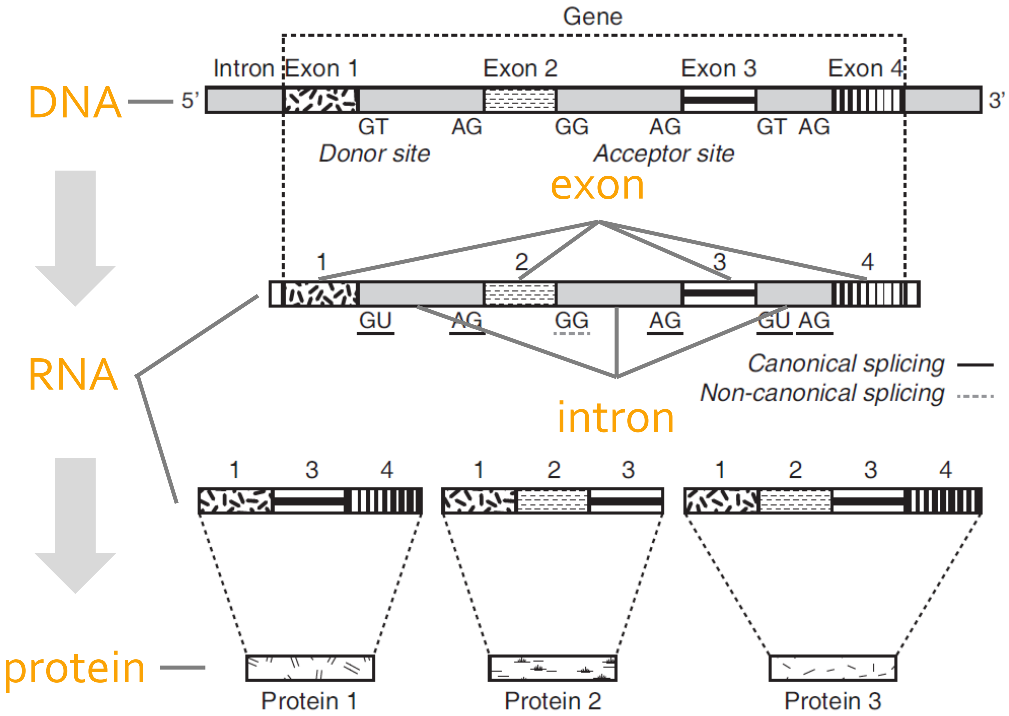

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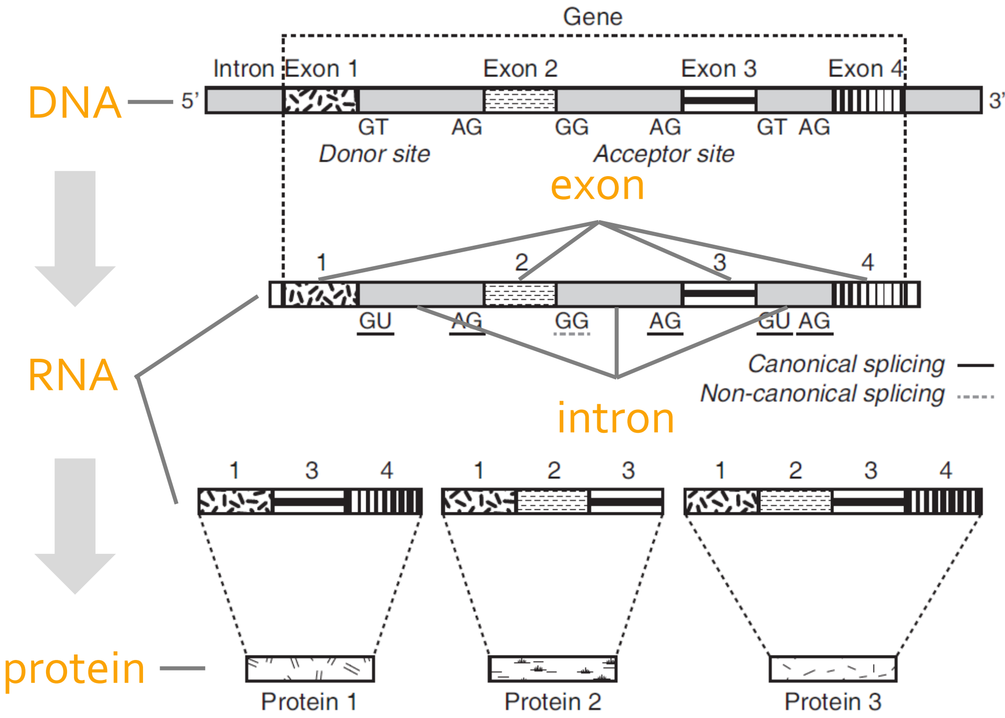

gene expression

exon

ACGTCGACTGCTACGTAGCAGCGA
TACGTACCGATCATCACTATCATC
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GT: false boundary

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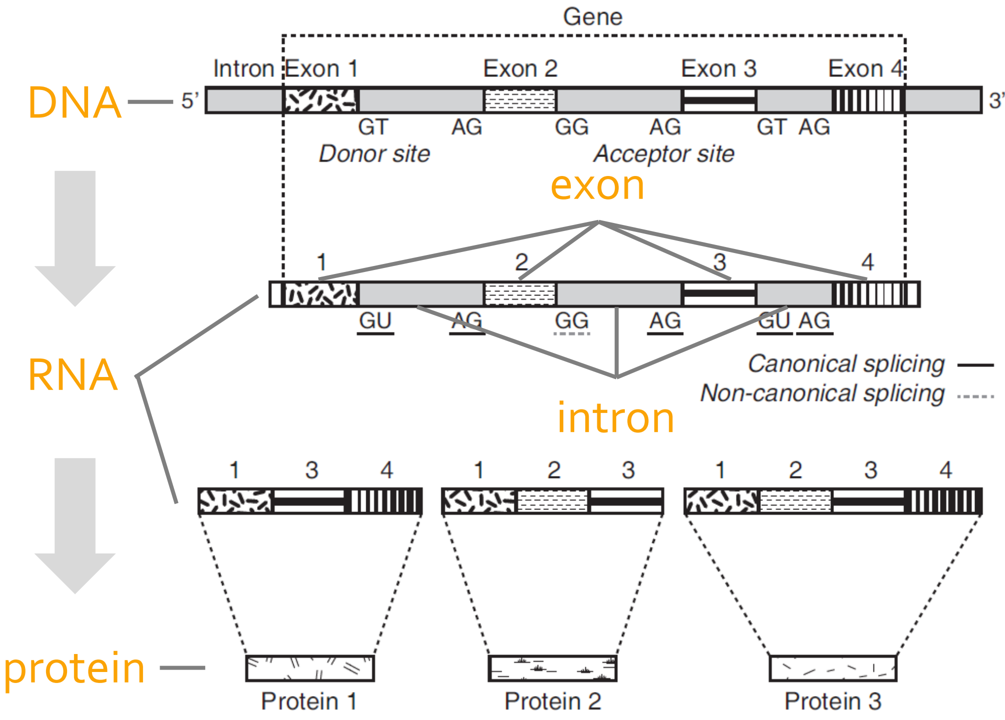

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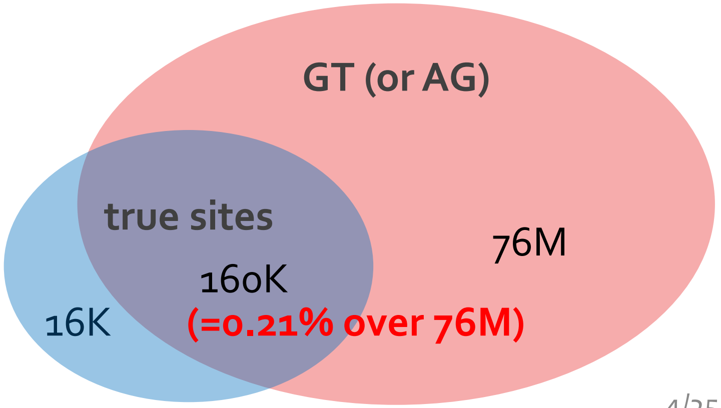

Previous Work on Junction Prediction

- Two approaches:

1. Machine learning-based:
   - ANN (Stormo et al., 1982; Noordewier et al., 1990; Brunak et al., 1991),
   - SVM (Degroeve et al., 2005; Huang et al., 2006; Sonnenburg et al., 2007),
   - HMM (Reese et al., 1997; Pertea et al., 2001; Baten et al., 2006).
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We want to construct a **learning model** [1] which can boost prediction performance in a **complementary** way to **alignment-based** [2] method.

We propose a **learning model** based on (multilayer) RBMs and its **training scheme**.

Related Methodologies

- Training methods of RBM

	Description	Training cost	Noise handling	Class-imbalance handling
CD (Hinton, Neural Comp. 2002)	Standard and widely used	-	-	-
Persistent CD (Tieleman, ICML 2008)	Use of a single Markov chain	-	☺	-
Parallel tempering (Cho et al., IJCNN 2010)	Simultaneous Markov chains generation	☹	☺	☺

- RBM for categorical values
  - Softmax input units (Salakhutdinov et al., ICML 2007).

- Class-imbalance problems
  - Refer to a review by Galar et al. (IEEE T SMC 2012).

Main Contributions

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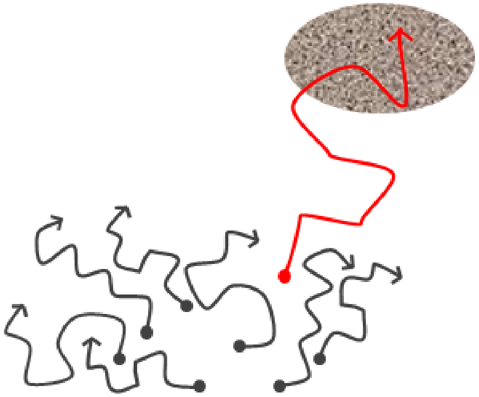

New RBM training methods called *boosted CD*

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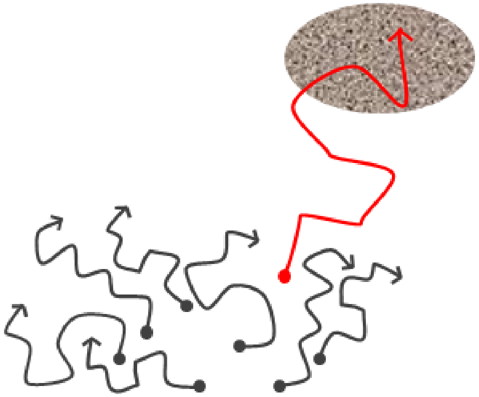

$$\phi(\mathbf{v}) = \frac{1}{2}\sum_{i=1}^{m}(\sum_{j=1}^{n_c} v^{(k)}_{n_c(i-1)+j} - 1)^2$$

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New penalty term to handle sparsity of DNA sequences

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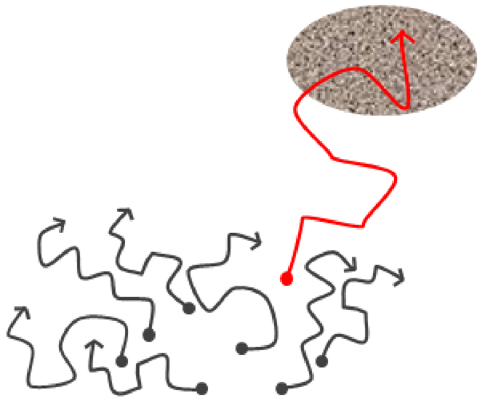

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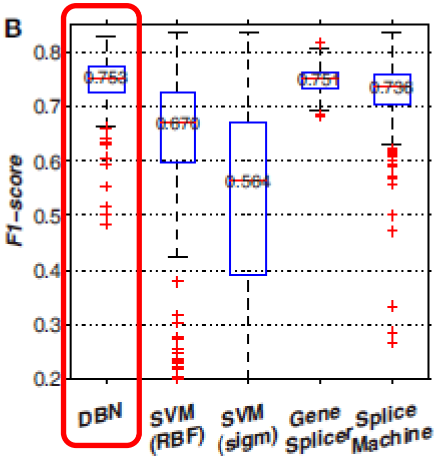

Significant boosts in splicing prediction performance

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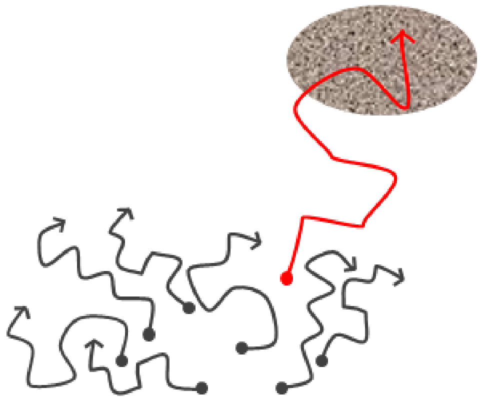

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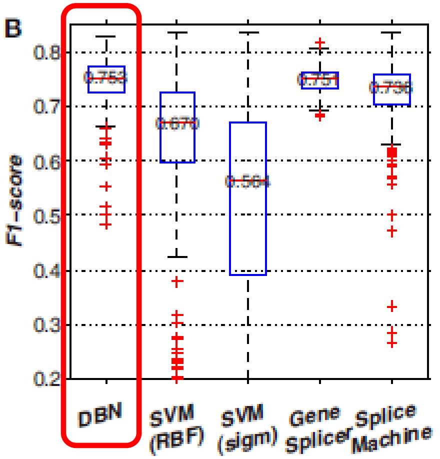

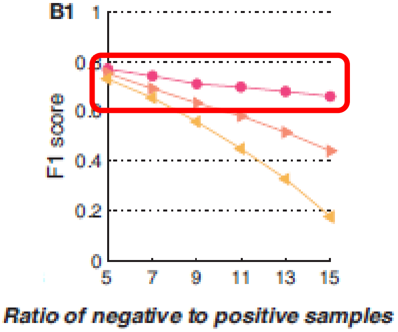

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Robustness to high-dimensional class-imbalanced data

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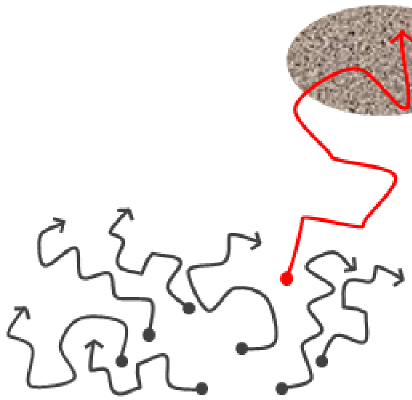

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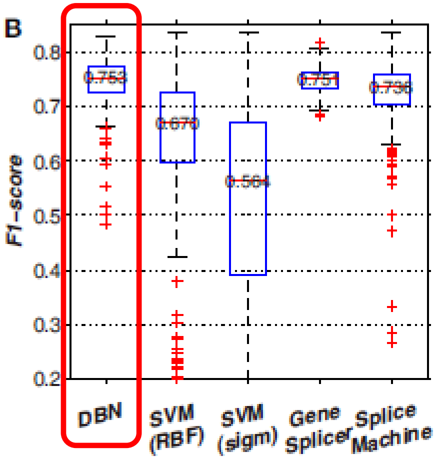

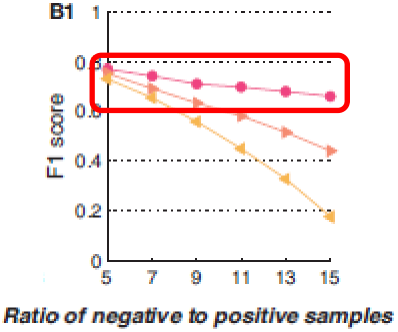

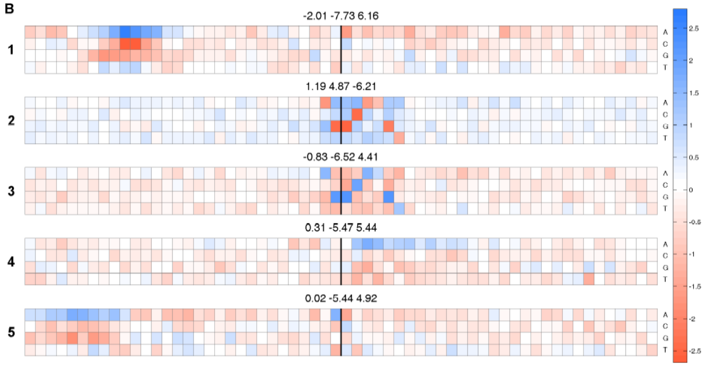

Significant boosts in splicing prediction performance

Robustness to high-dimensional class-imbalanced data

The ability to detect subtle non-canonical splicing signals

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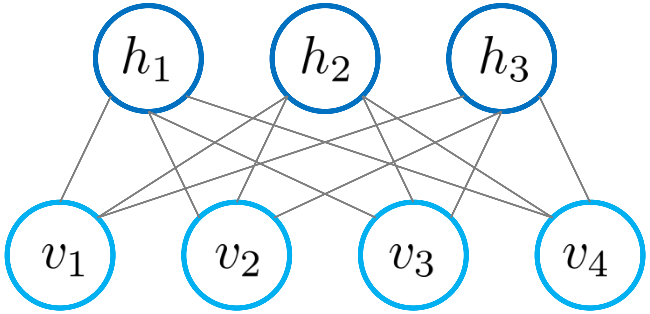
Restricted Boltzmann Machines

- RBM is a type of logistic belief network whose structure is a bipartite graph.
  - Nodes:
    - Input layer: $\mathbf{v} = \{v_1, ..., v_{n_v}\}$
    - Hidden layer: $\mathbf{h} = \{h_1, ..., h_{n_h}\}$



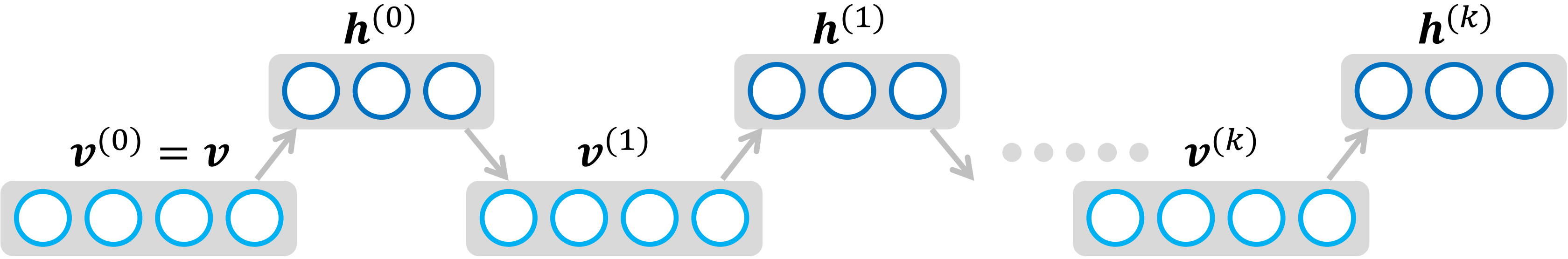
  - Probability of a configuration $(\mathbf{v}, \mathbf{h})$:
    - $P(\mathbf{v}, \mathbf{h}) = \frac{1}{Z} e^{-E(\mathbf{v},\mathbf{h})} \quad Z = \sum_{\mathbf{v},\mathbf{h}} e^{-E(\mathbf{v},\mathbf{h})}$
    - $$E(\mathbf{v}, \mathbf{h}) = -\sum_{i=1}^{n_v} \sum_{j=1}^{n_h} v_i w_{ij} h_j - \sum_{i=1}^{n_v} b_i v_i - \sum_{j=1}^{n_h} c_j h_j.$$
  - Each node is a stochastic binary unit:
    - $P(v_i = 1 | \mathbf{h}) = \mathrm{sigm}(b_i + \sum_{j=1}^{n_h} w_{ij} h_j)$
    - $P(h_j = 1 | \mathbf{v}) = \mathrm{sigm}(c_j + \sum_{i=1}^{n_v} v_i w_{ij})$ can be used as a feature.

Contrastive Divergence (CD) for Training RBMs

- Training weights to minimize **negative log-likelihood** of data.

$$W^*, \mathbf{b}^*, \mathbf{c}^* = \arg\min_{W,\mathbf{b},\mathbf{c}} \underbrace{\mathbf{E}[-\sum_{n=1}^{N} \log P(\mathbf{v}_n)]}_{L(W,\mathbf{b},\mathbf{c};\mathbf{v}_1,\dots,\mathbf{v}_N)} .$$

  - Run the MCMC chain $\boldsymbol{v}^{(0)}, \boldsymbol{v}^{(1)}, \dots, \boldsymbol{v}^{(k)}$ for k steps.



  - The **CD-k updates** after seeing example $\boldsymbol{v}$:

$$\frac{\partial L}{\partial w_{ij}} = \frac{\partial}{\partial w_{ij}} \mathbf{E}\left[-\log \left(\frac{\sum_{\mathbf{h}} e^{-E(\mathbf{v}_n,\mathbf{h})}}{\sum_{\mathbf{v},\mathbf{h}} e^{-E(\mathbf{v},\mathbf{h})}} \right) \right]$$
$$= \mathbf{E}_{data}[v_i h_j] - \mathbf{E}_{model}[v_i h_j].$$

$$\frac{\partial L}{\partial W} \approx \frac{1}{N} \sum_{n=1}^{N} \left(\mathbf{v}_n^{(0)} \mathbf{h}_n^{(0)^T} - \mathbf{v}_n^{(k)} \mathbf{h}_n^{(k)^T} \right), \qquad (2)$$

$$\frac{\partial L}{\partial \mathbf{b}} \approx \frac{1}{N} \sum_{n=1}^{N} \left(\mathbf{v}_n^{(0)} - \mathbf{v}_n^{(k)} \right),$$

$$\frac{\partial L}{\partial \mathbf{c}} \approx \frac{1}{N} \sum_{n=1}^{N} \left(\mathbf{h}_n^{(0)} - \mathbf{h}_n^{(k)} \right).$$

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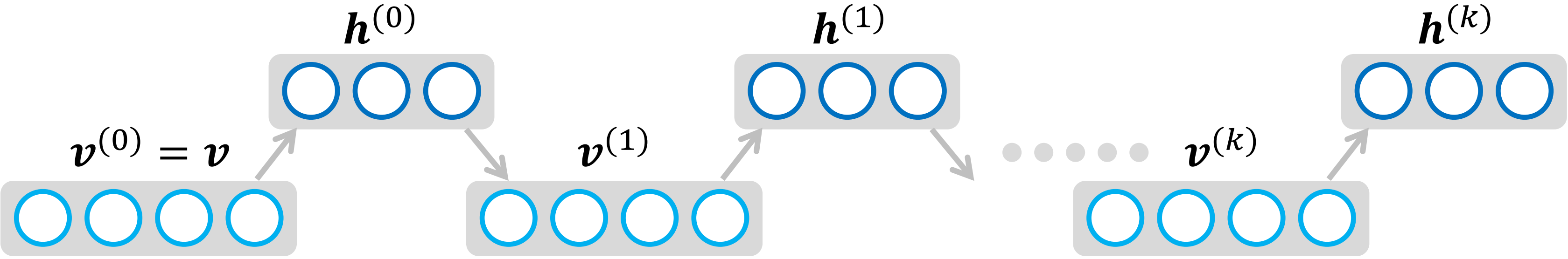

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approximated by
k-step Markov chain

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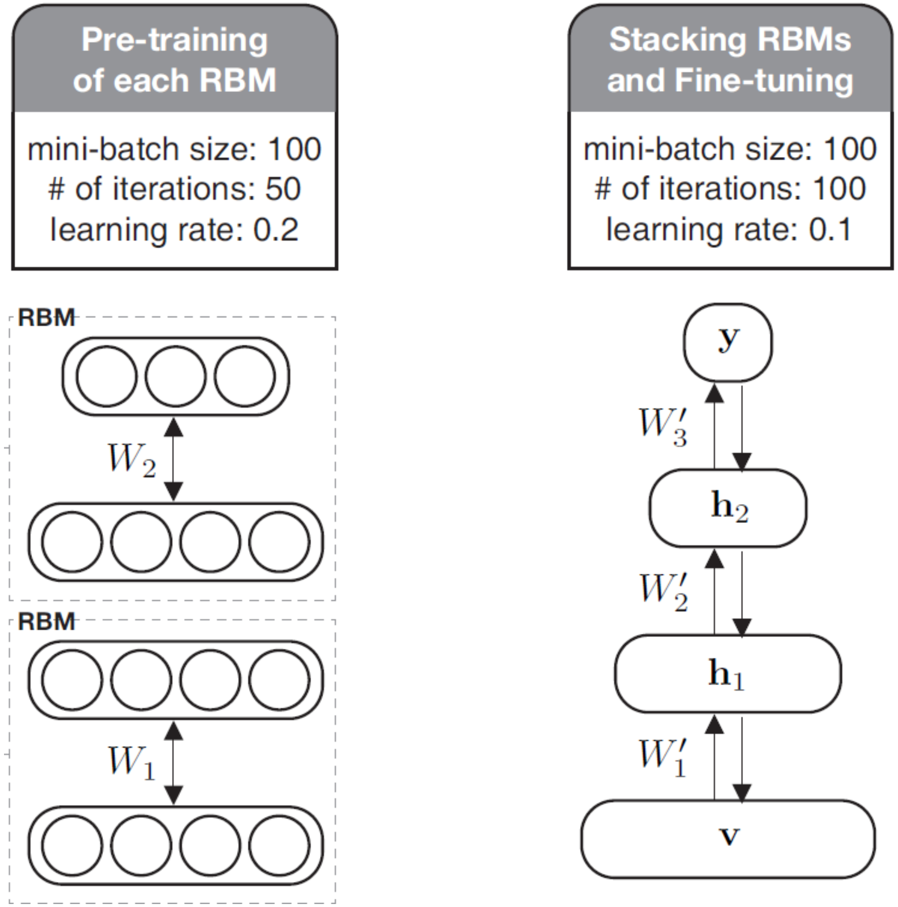

Pre-training of each RBM

mini-batch size: 100
# of iterations: 50
learning rate: 0.2

Stacking RBMs and Fine-tuning

mini-batch size: 100
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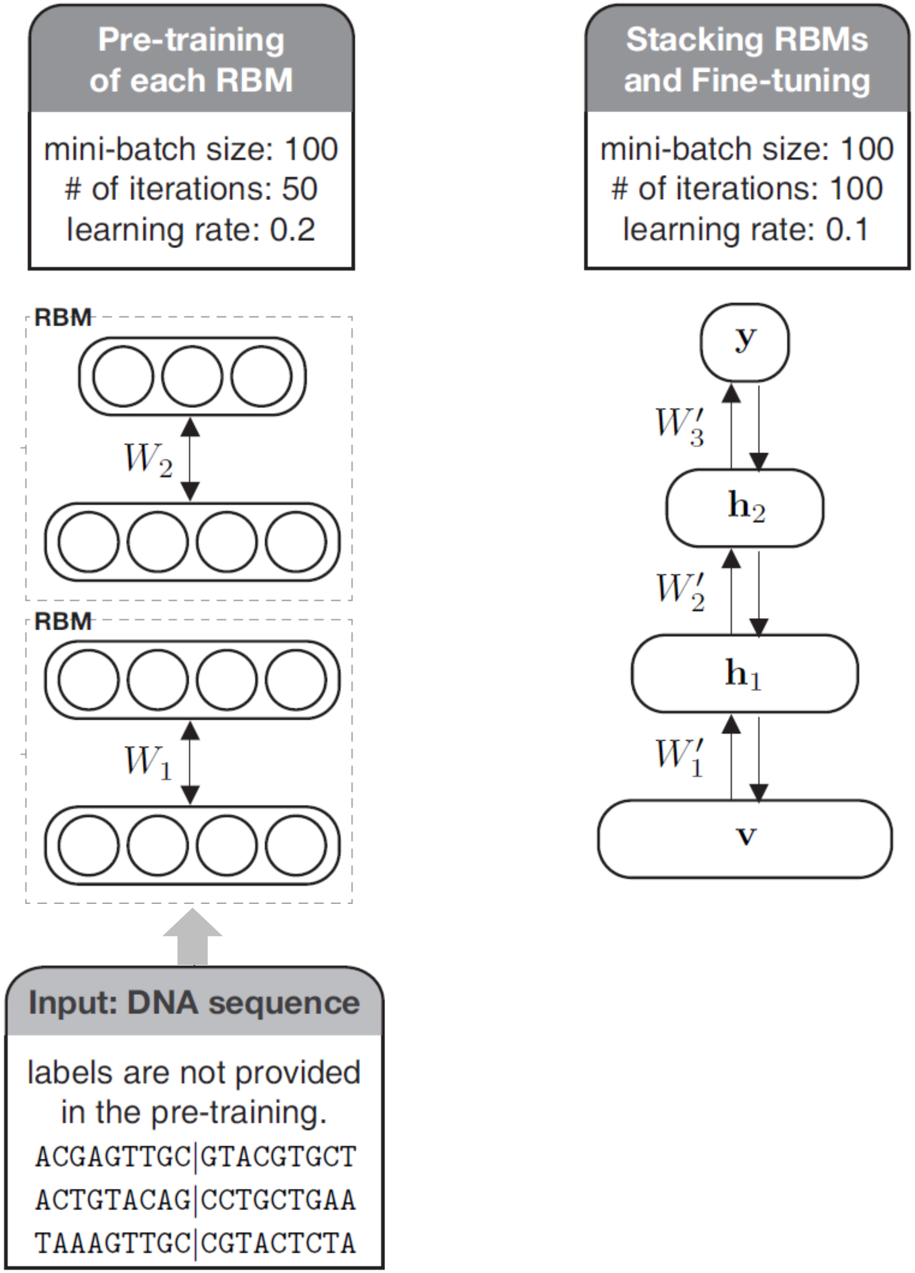

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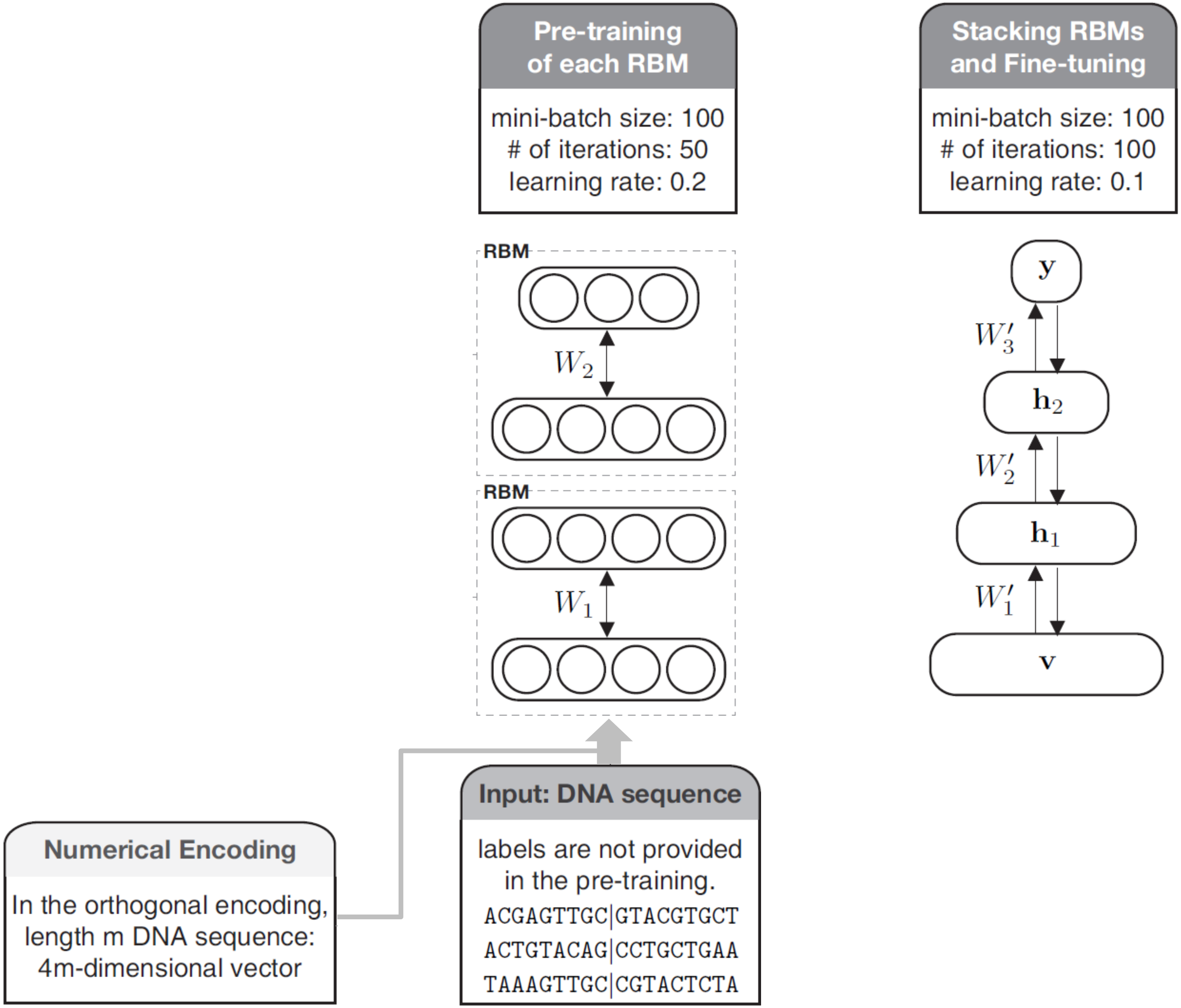

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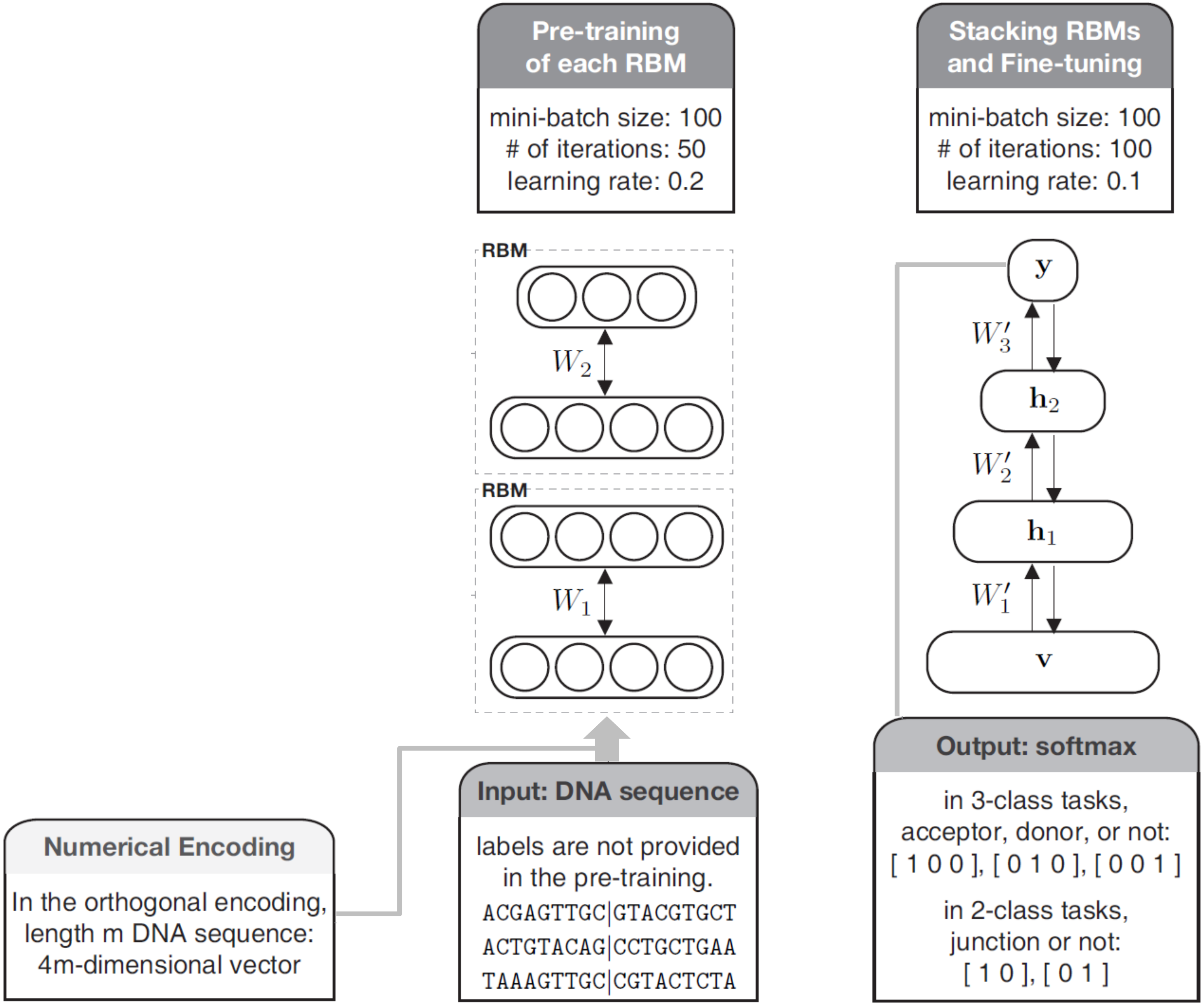

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Output: softmax

in 3-class tasks, acceptor, donor, or not:
[1 0 0], [0 1 0], [0 0 1]

in 2-class tasks, junction or not:
[1 0], [0 1]

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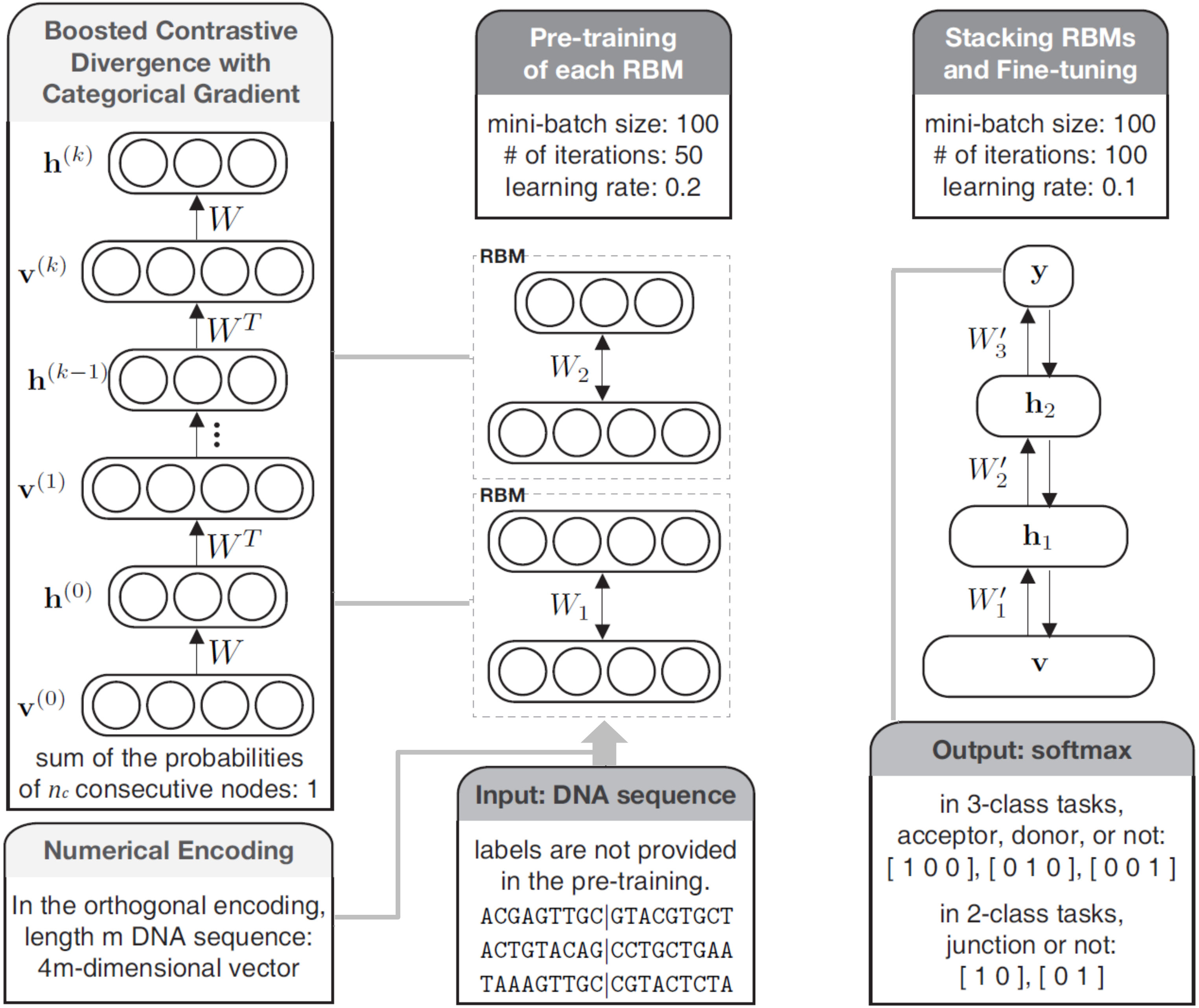

Boosted Contrastive Divergence with Categorical Gradient

sum of the probabilities of n_c consecutive nodes: 1

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# of iterations: 100
learning rate: 0.1

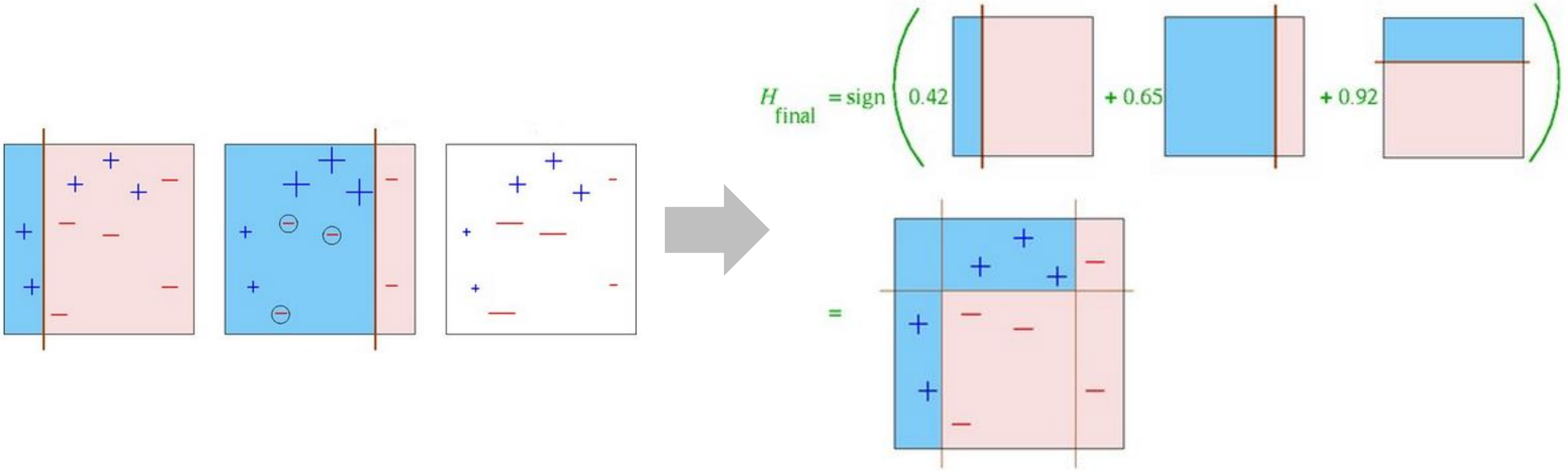
Output: softmax

in 3-class tasks, acceptor, donor, or not: [1 0 0], [0 1 0], [0 0 1]

in 2-class tasks, junction or not: [1 0], [0 1]

What Boosting Is

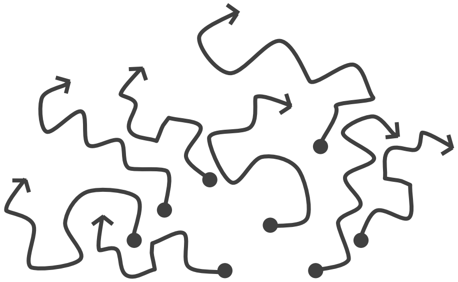
- Boosting is a meta-algorithm which converts weak learners to strong ones.
- Most boosting algorithms consist of **iteratively learning weak classifiers** with respect to a distribution and adding them to a final strong classifier.
- The main variation between many boosting algorithms:
  - The method of **weighting training data points** and hypotheses.
  - AdaBoost, LPBoost, TotalBoost, …



from lecture notes @ UCIrvine CS 271 Fall 2007

Boosted Contrastive Divergence (1/2)

- Contrastive divergence training is looped over all mini-batches and known to be stable.



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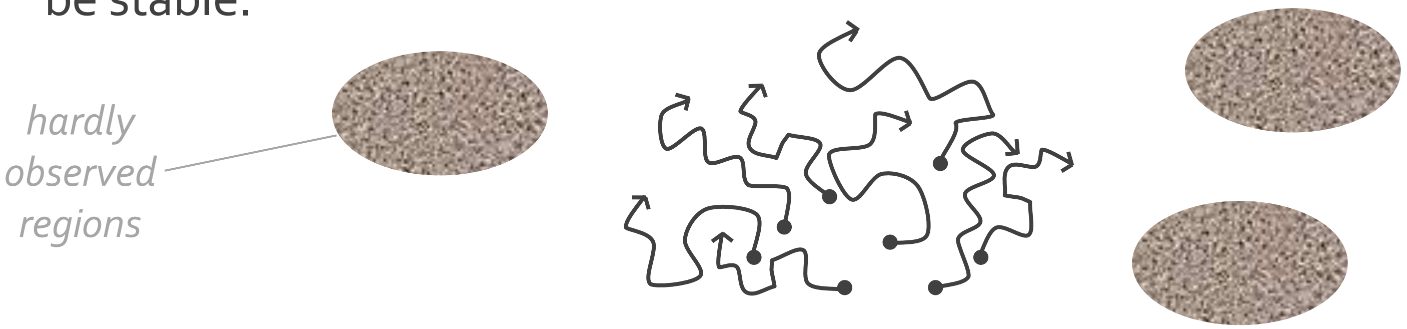

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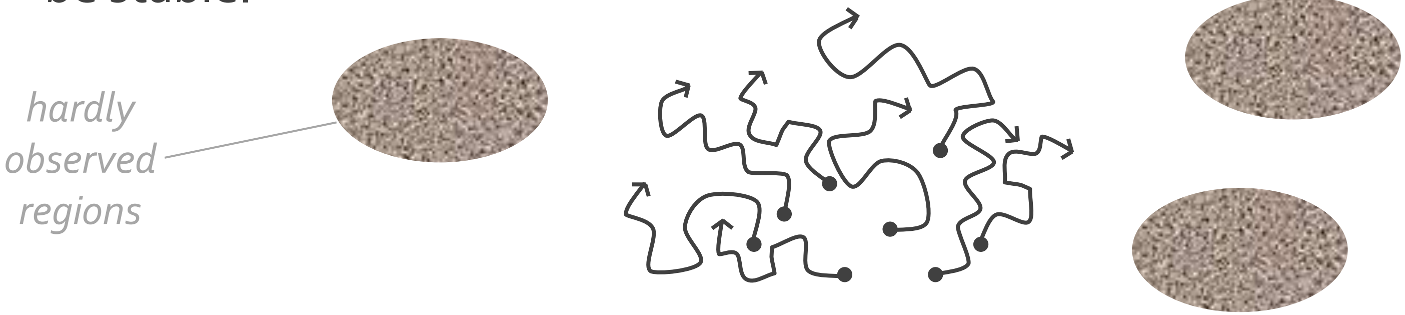

- However, for a class-imbalance distribution, we need to **assign higher weights to rare samples** in order to **jump to unseen examples** by Gibbs chains.

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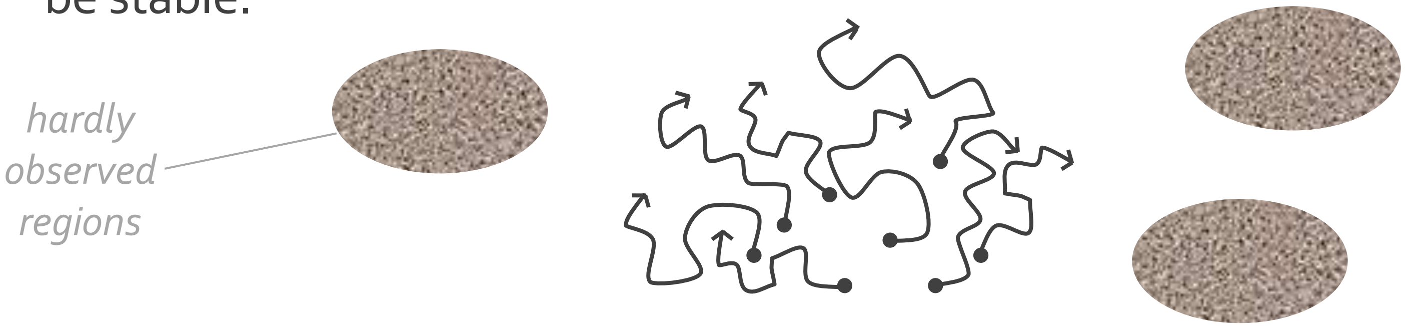

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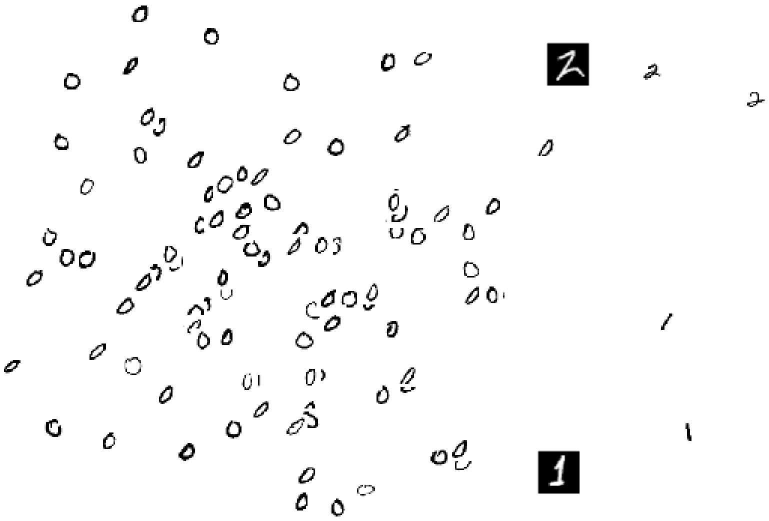

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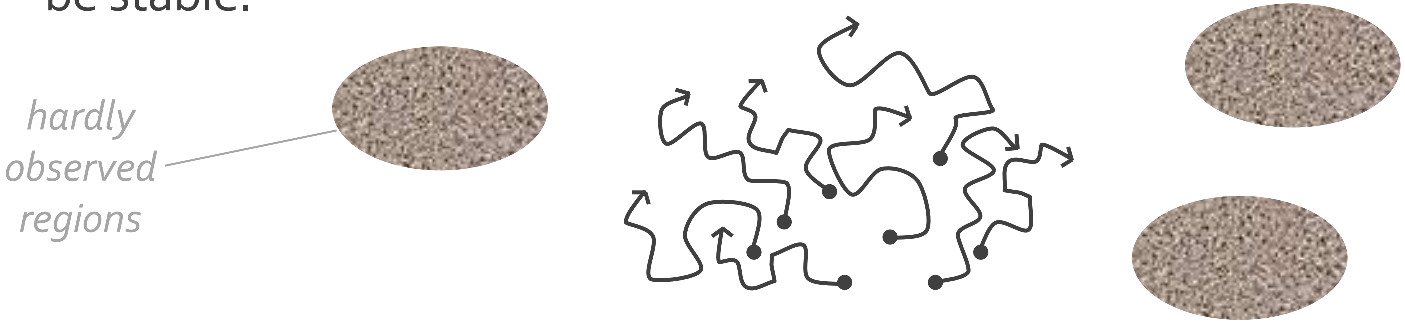

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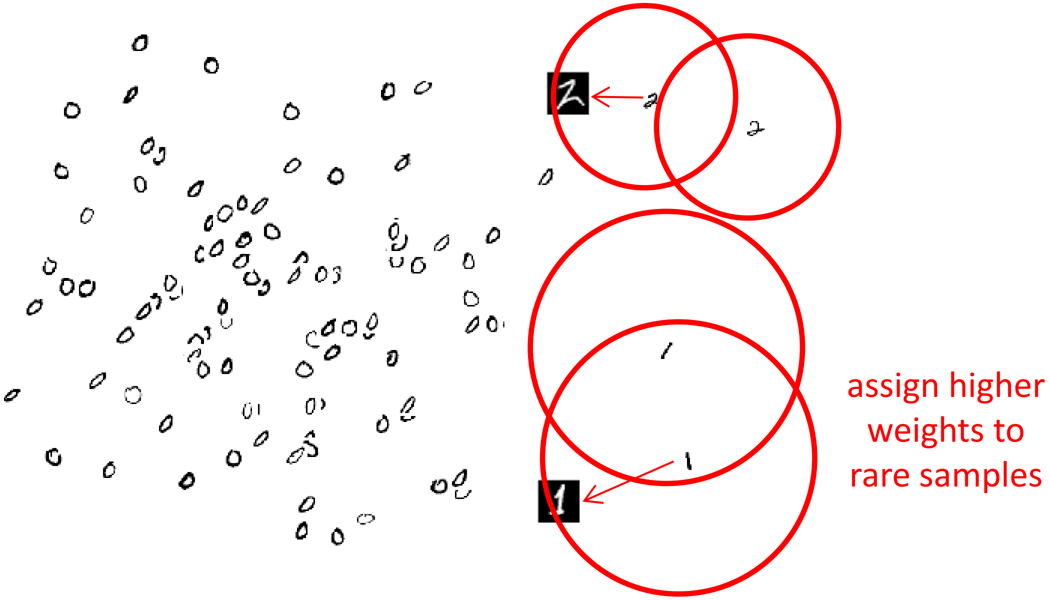

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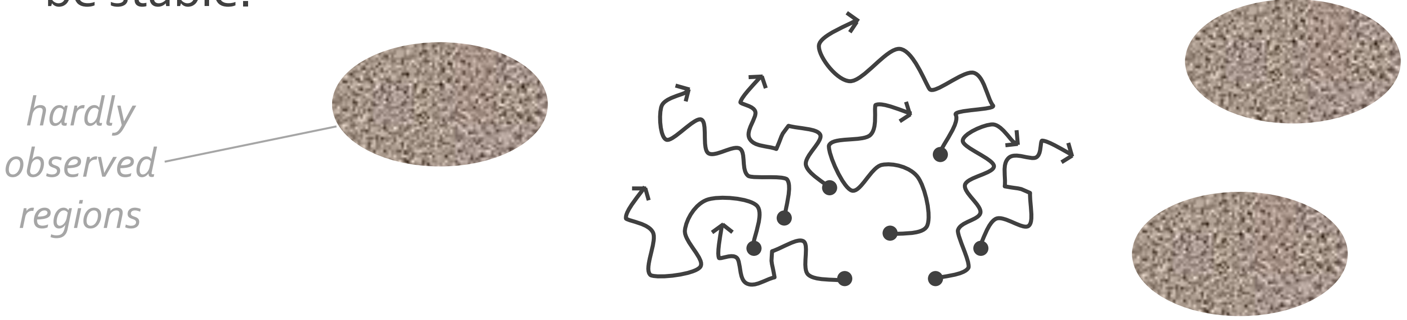

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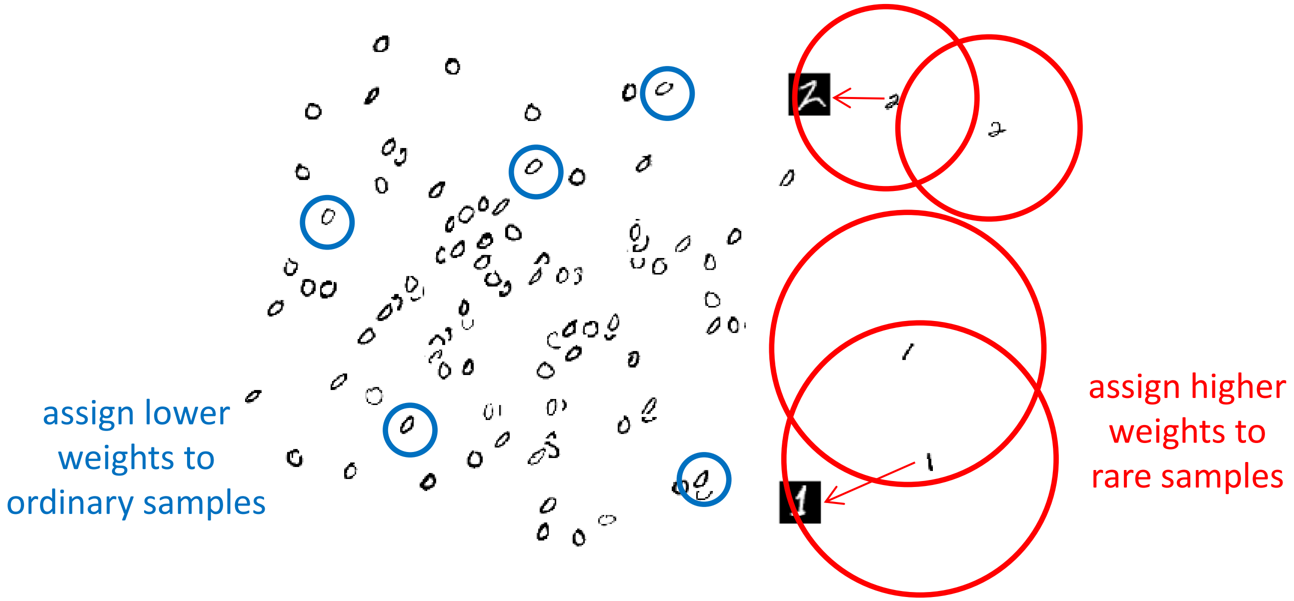
assign lower weights to ordinary samples
assign higher weights to rare samples

Boosted Contrastive Divergence (2/2)

- If we assign the same weight to all the data, the performance of Gibbs sampling would degrade in the regions that are hardly observed.
- Whenever sampling, we therefore **re-weight each observation by the energy** of its reconstruction $E(\boldsymbol{v}_n{}^{(k)}, \boldsymbol{h}_n{}^{(k)})$.

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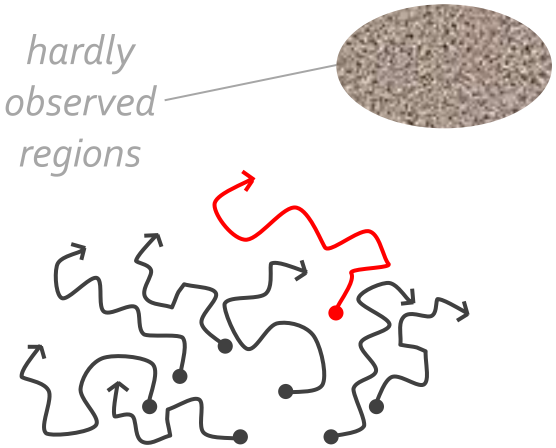

Relative locations of samples and corresponding Markov chains by CD

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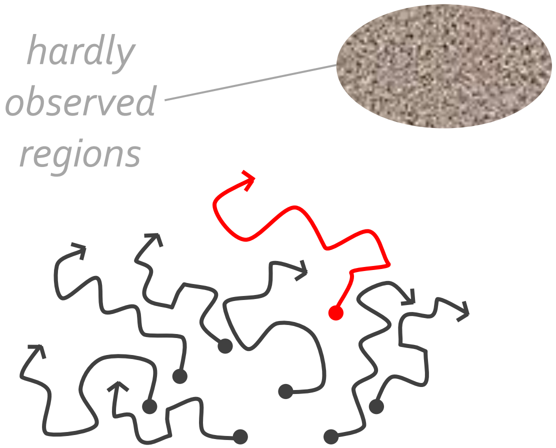

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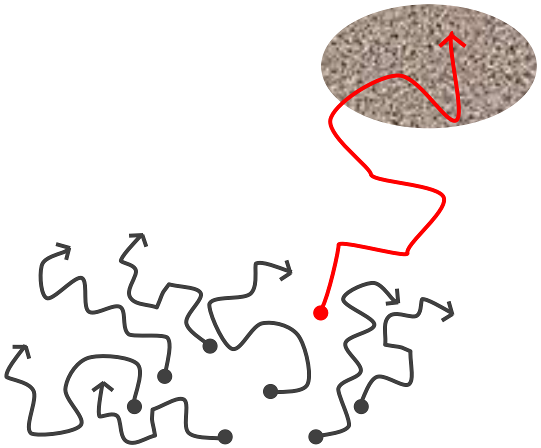

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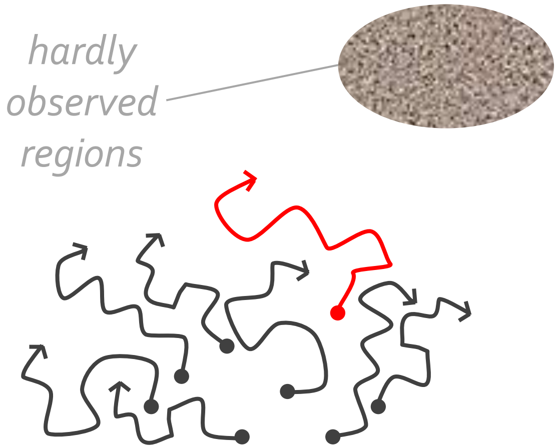

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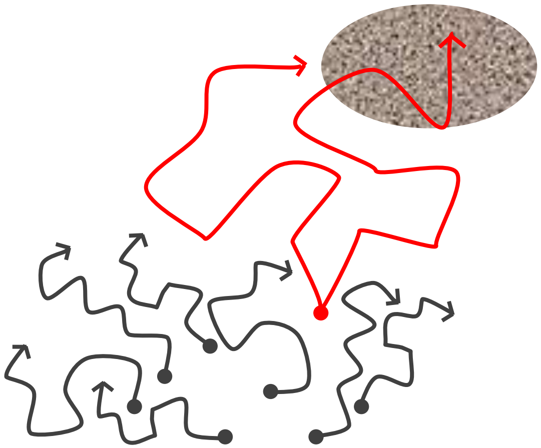
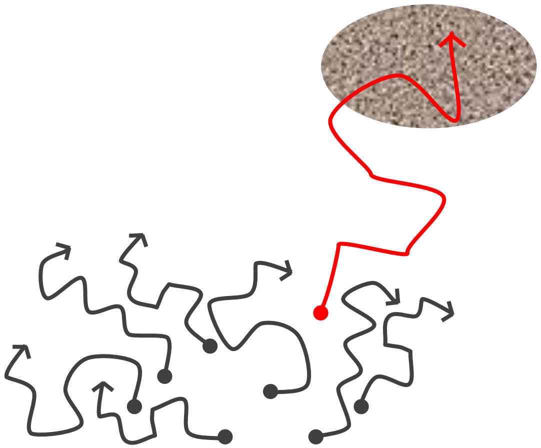


Relative locations of samples and corresponding Markov chains by PT



Relative locations of samples and corresponding Markov chains by the proposed

Categorical Gradient

- For biological sequences, 1-hot encoding is widely used (Baldi & Brunak, 2001).
    - A, C, G, and T are encoded by 1000, 0100, 0010, and 0001, respectively.
    - In encoded binary vectors, 75% of the elements are zero.

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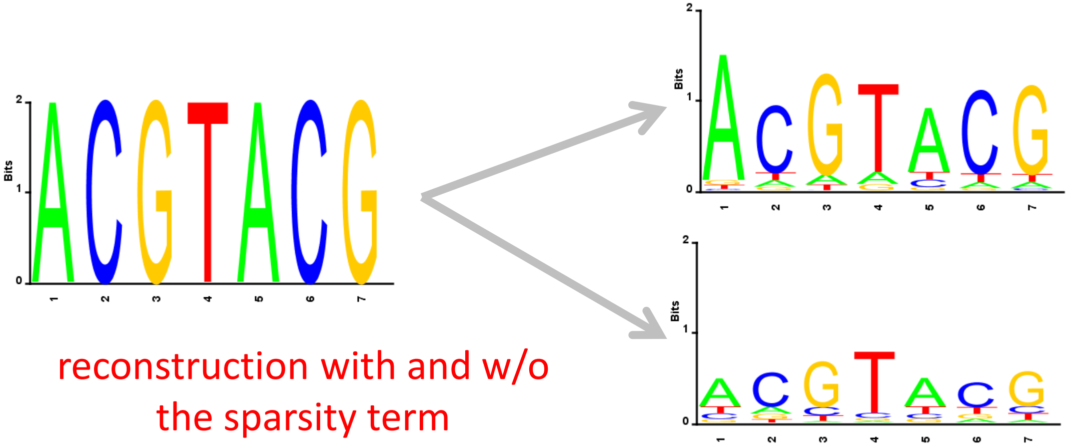
$$\min_{W,\mathbf{b},\mathbf{c}} \mathbf{E}\left[-\sum_{n=1}^{N} \log P(\mathbf{v}_n)\right] + \lambda_c \underbrace{\phi(\mathbf{v}_n),}_{\text{sparsity term}} \qquad \phi(\mathbf{v}) = \frac{1}{2}\sum_{i=1}^{m}\Big(\sum_{j=1}^{n_c} v^{(k)}_{n_c(i-1)+j} - 1\Big)^2$$



reconstruction with and w/o the sparsity term

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sparsity term

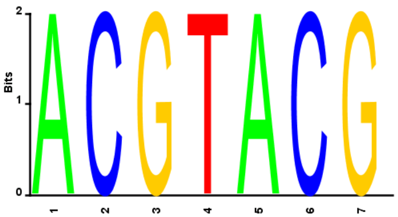
derived from the sparsity term

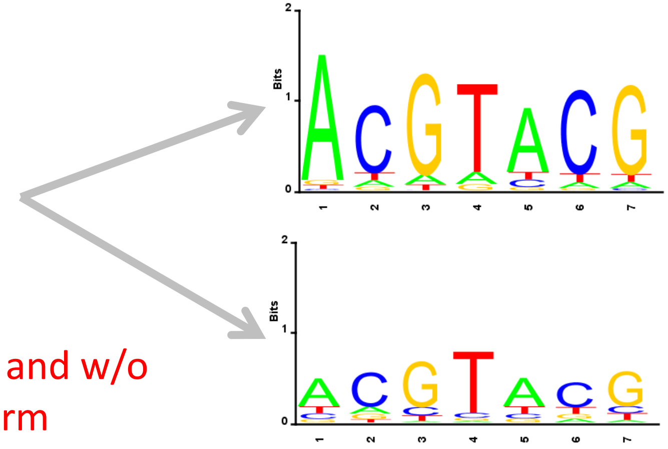
$$\frac{\partial L}{\partial W} \approx \text{Eq. } (2) + \boxed{\frac{1}{N}\sum_{n=1}^{N} f(\mathbf{v}_n^{(k)})\mathbf{h}_n^{(k-1)}} \tag{3}$$

$$\frac{\partial L}{\partial \mathbf{b}} \approx \frac{1}{N}\sum_{n=1}^{N}\left(\mathbf{v}_n^{(0)} - \mathbf{v}_n^{(k)} + \boxed{f(\mathbf{v}_n^{(k)})}\right) \tag{4}$$

$$\frac{\partial L}{\partial \mathbf{c}} \approx \frac{1}{N}\sum_{n=1}^{N}\left(\mathbf{h}_n^{(0)} - \mathbf{h}_n^{(k)}\right) \tag{5}$$

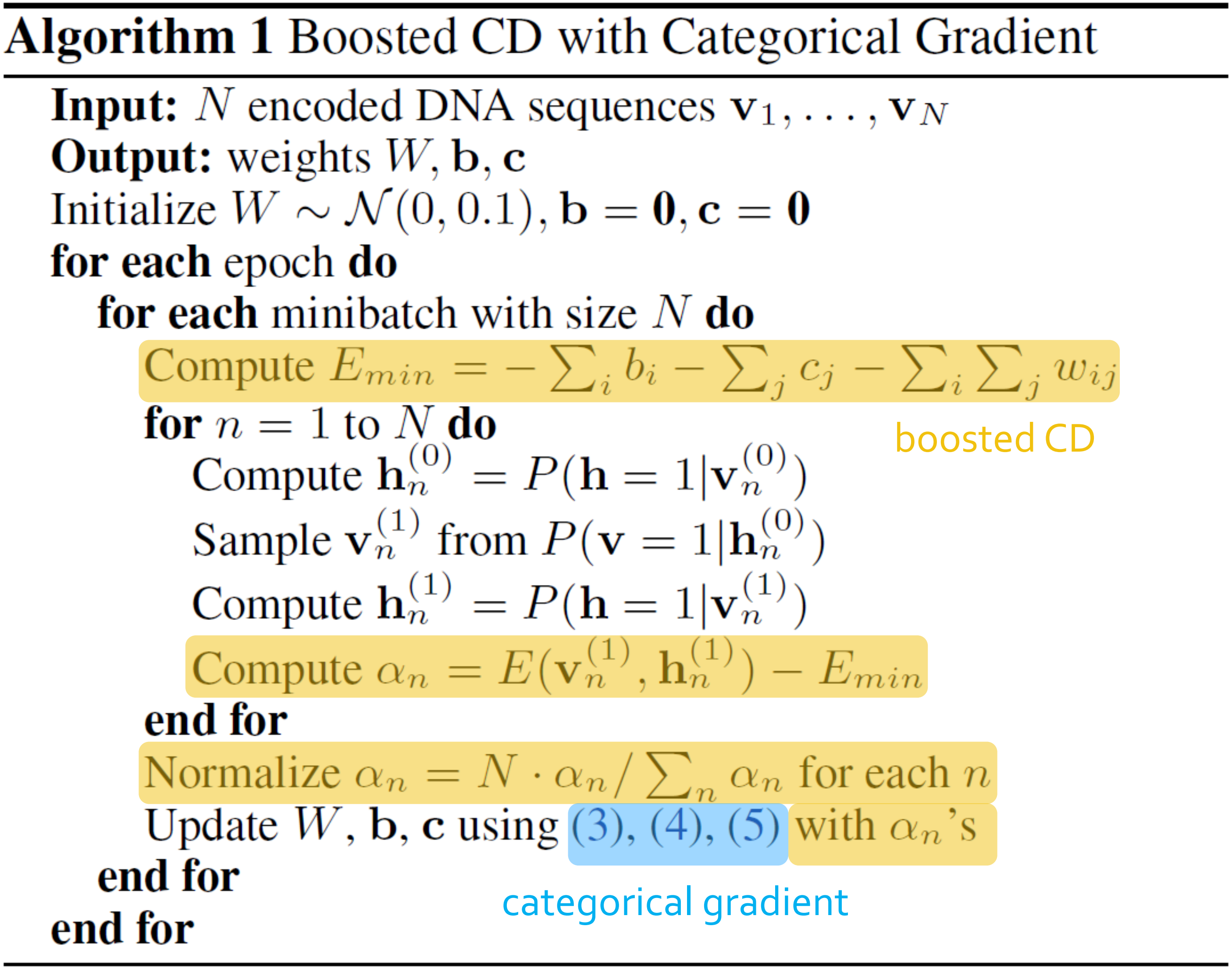
$$f(\mathbf{v}) = \mathbf{v} \circ (1-\mathbf{v}) \circ g(\mathbf{v}), \;\; g(\mathbf{v})_i = \sum_{j=1}^{n_c} v_{n_c[\frac{i-1}{n_c}]+j} - 1$$





reconstruction with and w/o the sparsity term

Proposed Training Algorithm



Algorithm 1 Boosted CD with Categorical Gradient

```
Input: $N$ encoded DNA sequences $\mathbf{v}_1, \ldots, \mathbf{v}_N$
Output: weights $W$, $\mathbf{b}$, $\mathbf{c}$
Initialize $W \sim \mathcal{N}(0, 0.1)$, $\mathbf{b} = \mathbf{0}$, $\mathbf{c} = \mathbf{0}$
for each epoch do
    for each minibatch with size $N$ do
        Compute $E_{min} = -\sum_i b_i - \sum_j c_j - \sum_i \sum_j w_{ij}$
        for $n = 1$ to $N$ do
            Compute $\mathbf{h}_n^{(0)} = P(\mathbf{h} = 1 | \mathbf{v}_n^{(0)})$
            Sample $\mathbf{v}_n^{(1)}$ from $P(\mathbf{v} = 1 | \mathbf{h}_n^{(0)})$
            Compute $\mathbf{h}_n^{(1)} = P(\mathbf{h} = 1 | \mathbf{v}_n^{(1)})$
            Compute $\alpha_n = E(\mathbf{v}_n^{(1)}, \mathbf{h}_n^{(1)}) - E_{min}$
        end for
        Normalize $\alpha_n = N \cdot \alpha_n / \sum_n \alpha_n$ for each $n$
        Update $W$, $\mathbf{b}$, $\mathbf{c}$ using (3), (4), (5) with $\alpha_n$'s
    end for
end for
```

boosted CD

categorical gradient

Outline

- Motivation
- Preliminary
- Boosted contrastive divergence
- Categorical restricted Boltzmann machine
- Experiment results
- Conclusion

Results

Effects of categorical gradient

Effects of boosting

Effects on the splicing prediction

- Data preparation:
  - **Real human DNA** sequences with known boundary information.

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CGTAGCAGCGATACGTACCGATCGTCACTATCATCGAGGTACGAGAGATCGATCGGCAACG

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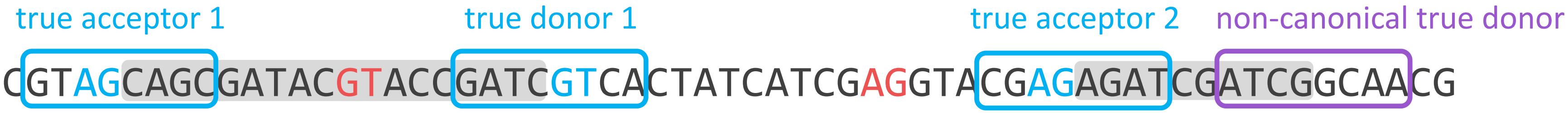

true acceptor 1

true donor 1

true acceptor 2

non-canonical true donor

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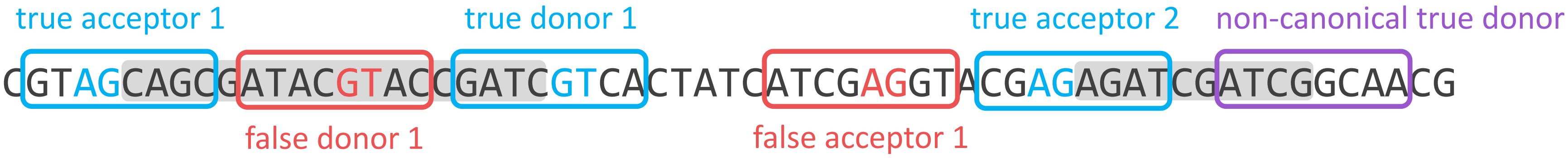

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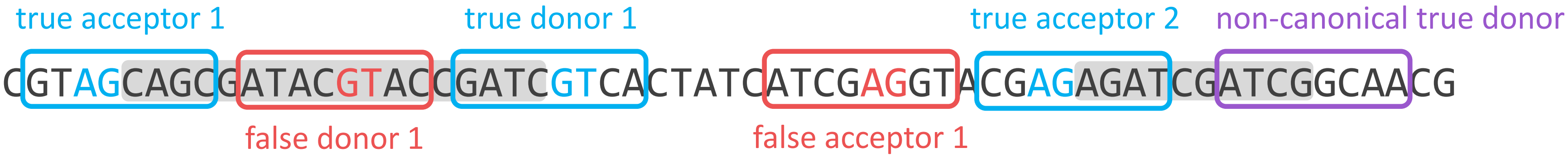


  - GWH dataset: **2-class** (boundary or not).
  - UCSC dataset: **3-class** (acceptor, donor, or non-boundary).

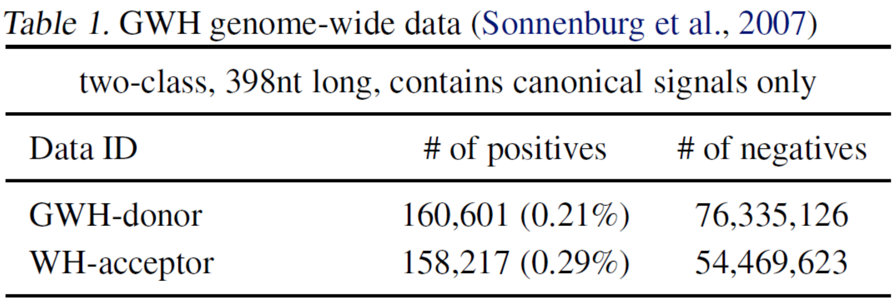


Table 1. GWH genome-wide data (Sonnenburg et al., 2007)

two-class, 398nt long, contains canonical signals only		
Data ID	# of positives	# of negatives
GWH-donor	160,601 (0.21%)	76,335,126
WH-acceptor	158,217 (0.29%)	54,469,623

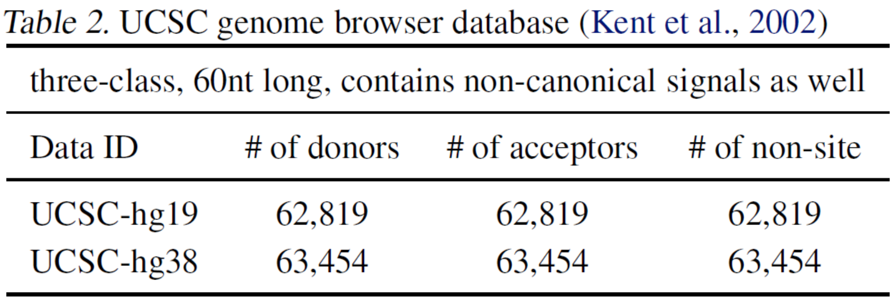
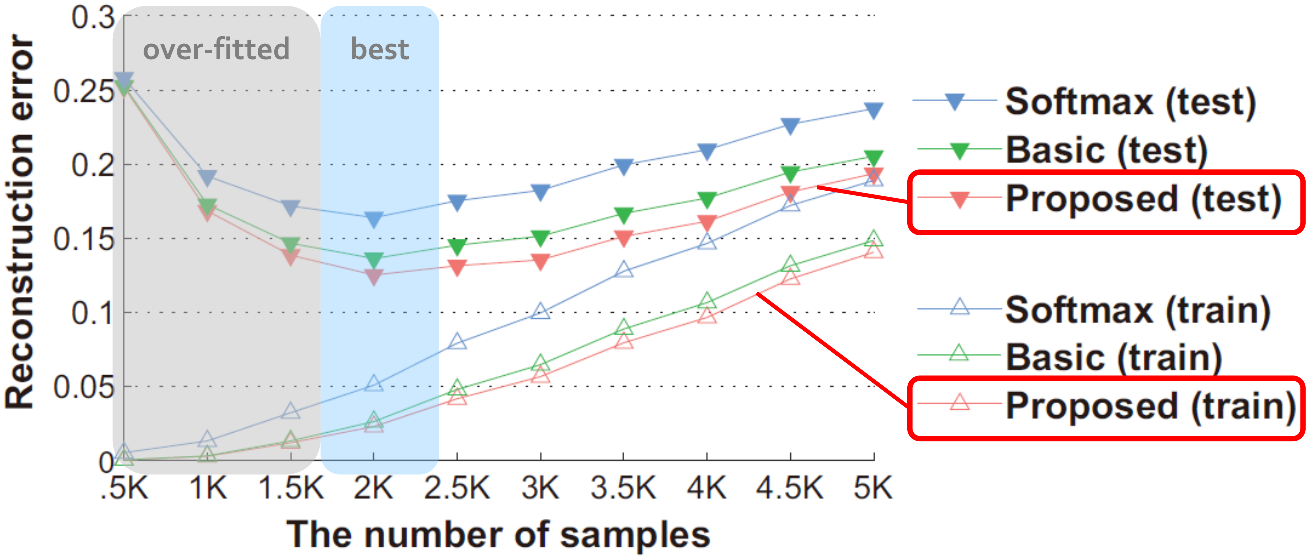


Table 2. UCSC genome browser database (Kent et al., 2002)

three-class, 60nt long, contains non-canonical signals as well			
Data ID	# of donors	# of acceptors	# of non-site
UCSC-hg19	62,819	62,819	62,819
UCSC-hg38	63,454	63,454	63,454

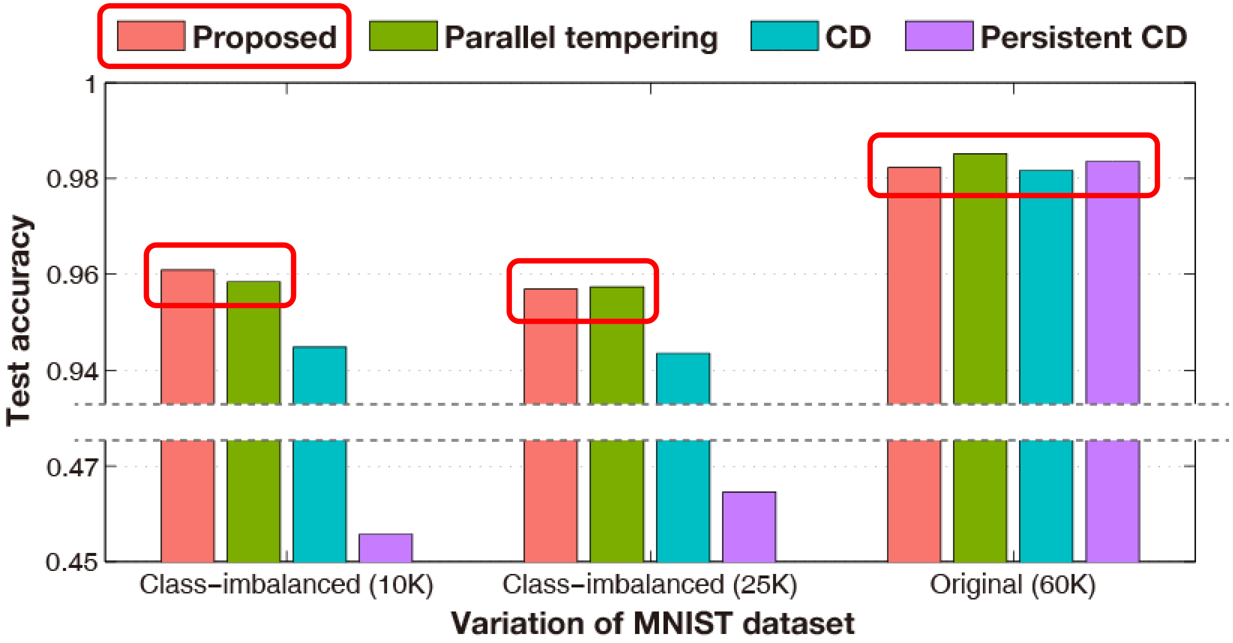
Results: Effects of Categorical Gradient



Data: chromosome 19 in GWH-donor
Sequence Length: 200nt
(800 dimension)
# of iterations: 500
Learning rate: 0.1
L2-decay: 0.001

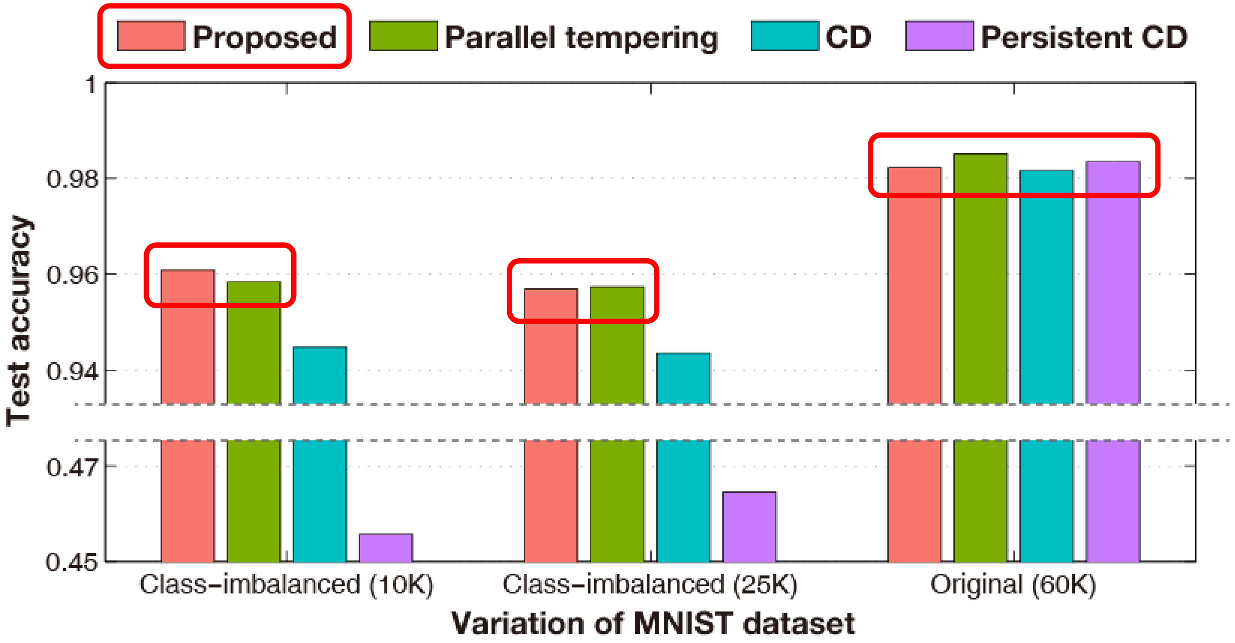
- The proposed method shows the **best** performance in terms of **reconstruction error** for both training and testing.
- Compare to the softmax approach, the proposed regularized RBM succeeds in **achieving lower error by slightly sacrificing the probability sum constraint**.

Results: Effects of Boosting



- For **simulating a class-imbalance** situation
  - we randomly dropped samples with different drop rates for different classes.

Results: Effects of Boosting



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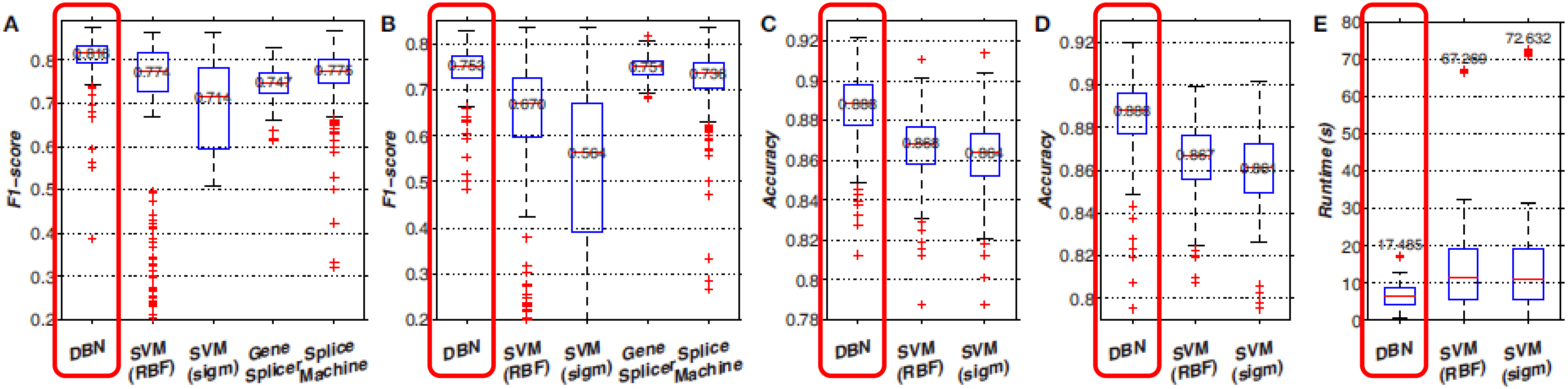
	Description	Training cost	Noise handling	Class-imbalance handling
CD (Hinton, Neural Comp. 2002)	Standard and widely used	-	-	-
Persistent CD (Tieleman, ICML 2008)	Use of a single Markov chain	-	☺	-
Parallel tempering (Cho et al., IJCNN 2010)	Simultaneous Markov chains generation	☹	☺	☺
Proposed boosted CD	**Reweighting samples**	**-**	☺	☺

Results: Improved Performance and Robustness

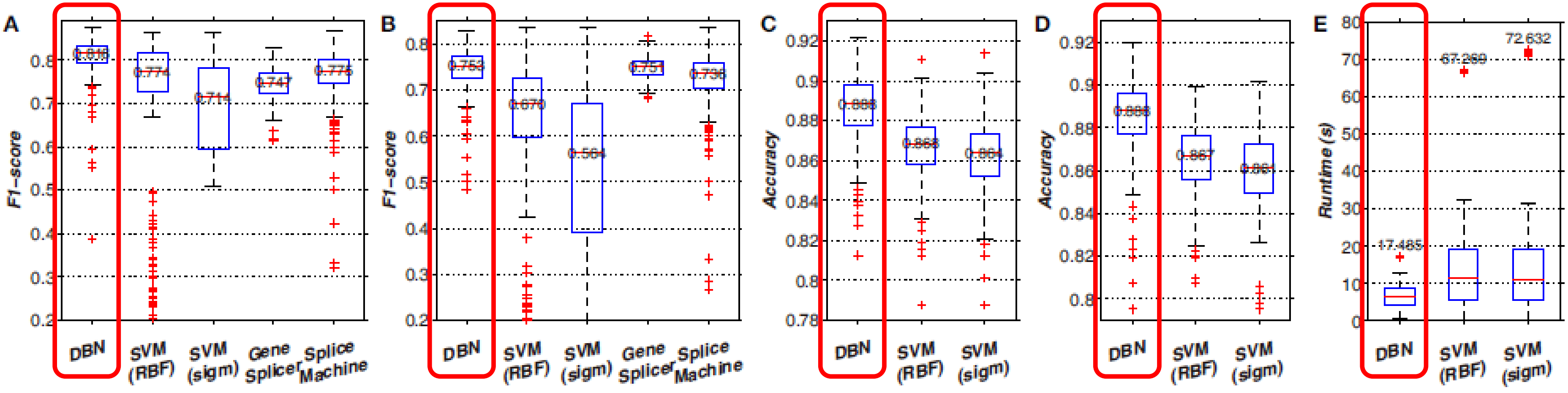


2-class classification performance

3-class classification

Runtime

Results: Improved Performance and Robustness



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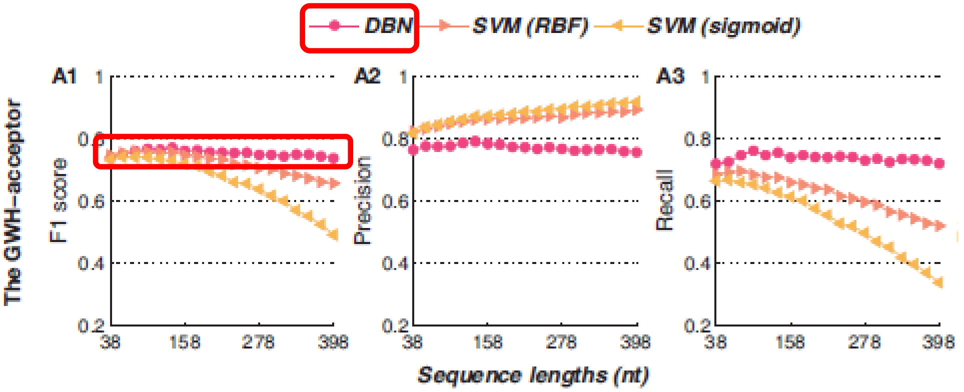

Insensitivity to sequence lengths

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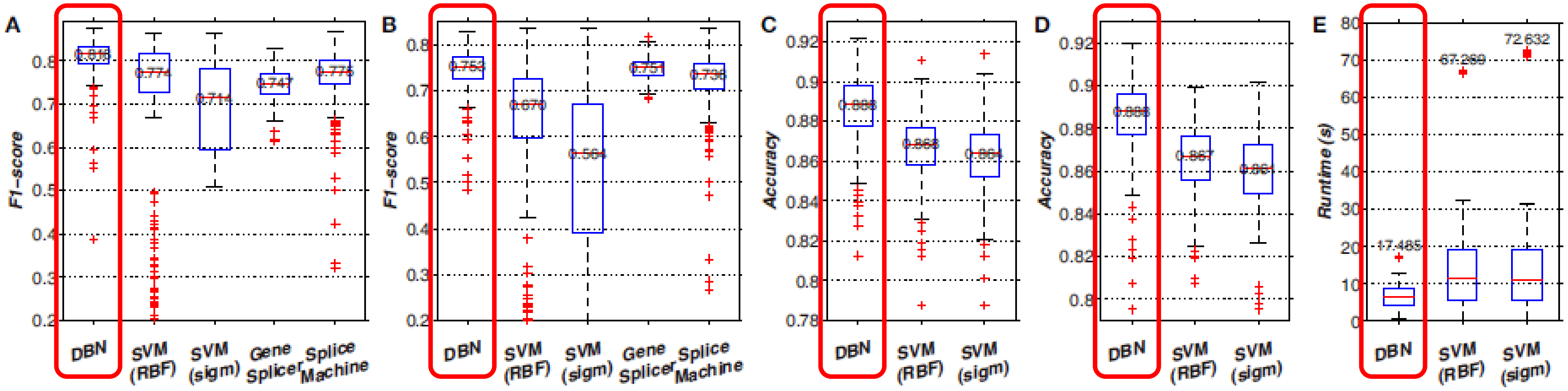

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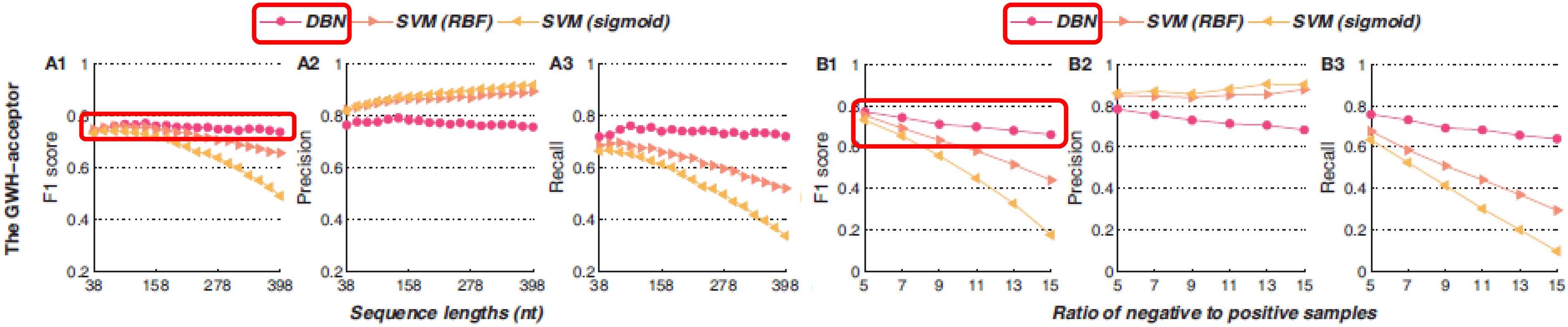
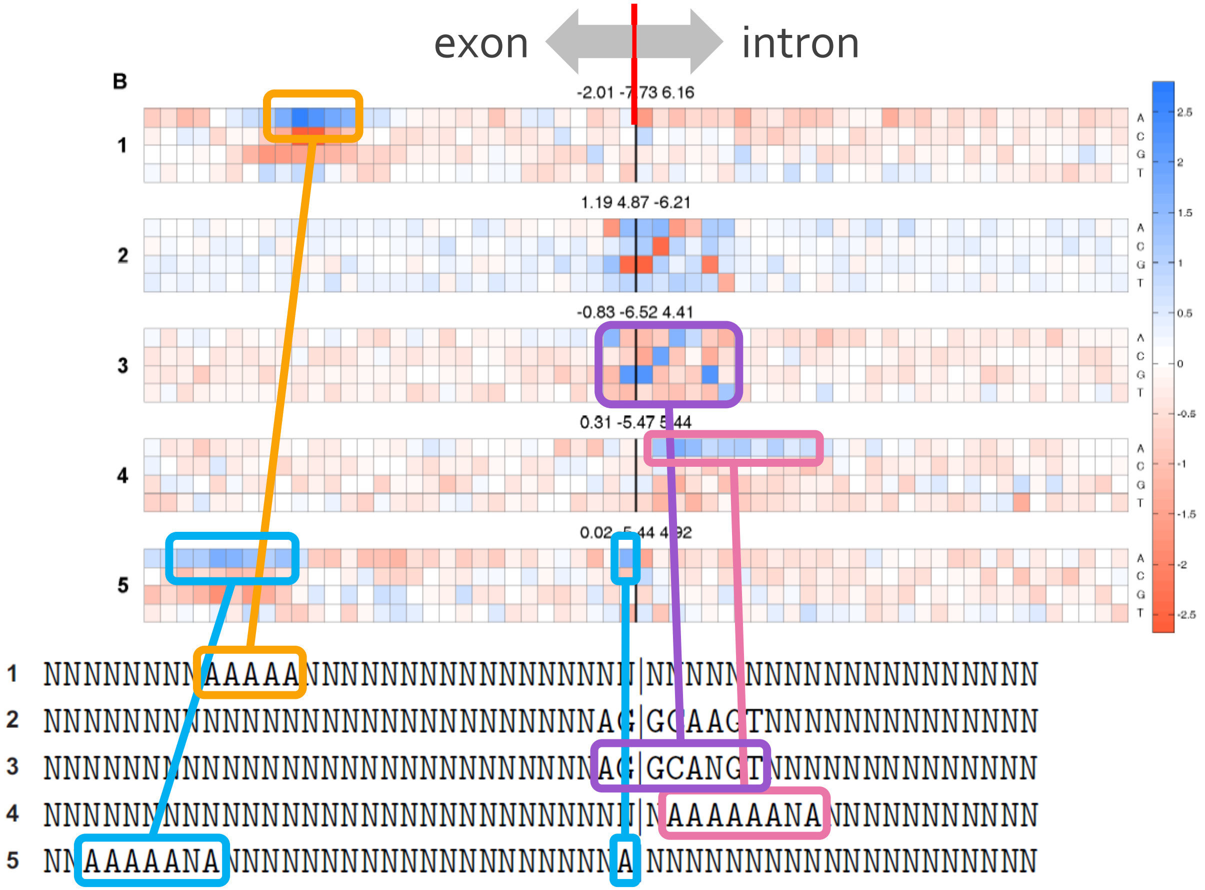


Insensitivity to sequence lengths

Robustness to negative samples

Results: Identification of Non-Canonical Splice Sites

- **(Important biological finding)** non-canonical splicing can arise if:
  - Introns contain GCA or NAA sequences at their boundaries.
  - Exons include contiguous A's around the boundaries.

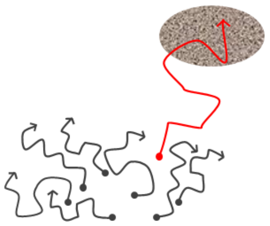


We used 162,951 examples excluding canonical splice sites.

Conclusion

- We proposed a **new RBM training method called boosted CD** with categorical gradients that improves conventional CD for class-imbalanced data.
  - **Significant boosts in splicing prediction** in terms of accuracy and runtime.
  - Increased **robustness** to high-dimensional **class-imbalanced** data.

- The proposed scheme shows the ability to detect subtle **non-canonical splicing signals** that often could not be identified by traditional methods.
  - Future work: additional validation using various class-imbalance datasets.



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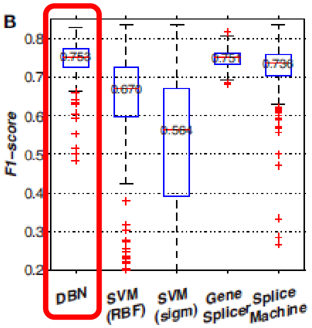

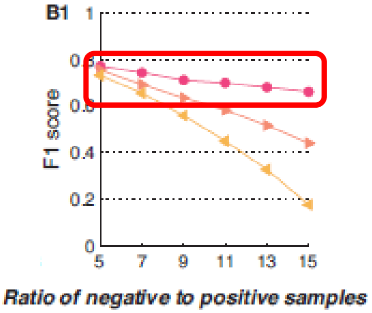

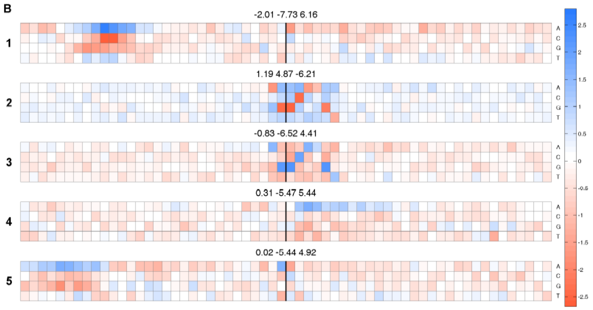

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June 2, 2015

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Backup: Comparison with Recurrent Neural Networks (RNNs)

To be placed

- The proposed DBN showed xx% higher performance in terms of the F1-score.
- RNN is appropriate for sequence modeling. However, splicing signals are often too far from the boundaries and hard to maintain splicing information.