The Fault Tolerant Epigenome
&
its Data Profile

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2003

The feat made headlines around the world: "Scientists Say Human Genome is Complete," the New York Times announced in 2003. "The Human Genome," the journals Science and Nature said in identical ta-dah cover lines unveiling the historic achievement.

Fake News

There was one little problem.

"It's very fair to say the human genome was never fully sequenced," **Craig Venter**

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Human variation

It turns out, in the grand scheme, we're all very, very similar, genetically: **99.9 percent of people's genes are identical**. It's in that last one-tenth of 1 percent where we find all of human variation.

More than 98% of the human genome does not encode protein sequences, including most sequences within introns and most intergenic DNA.

98% of human genome is "**Junk DNA**"

Wait there is more: Epigenome!

Fake News

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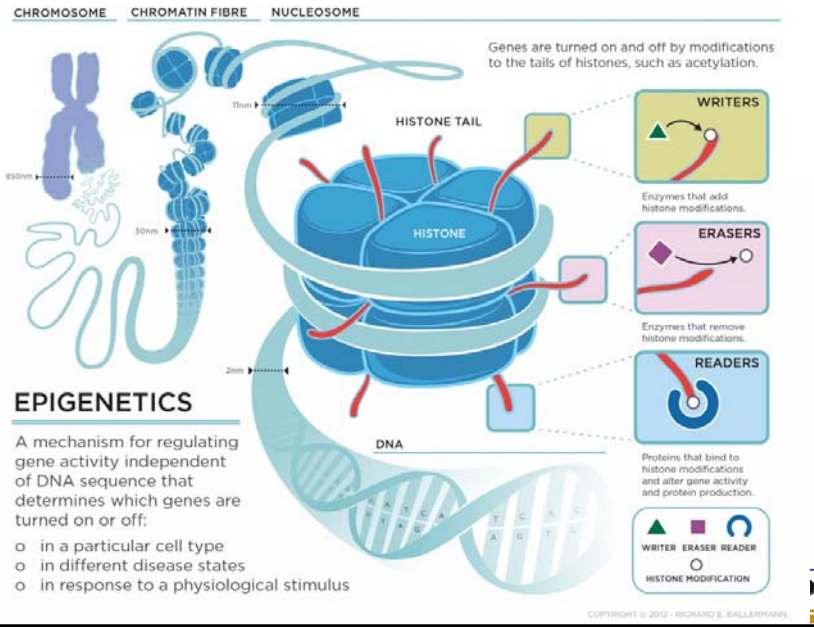
Epigenetics: What does the epigenome look like?



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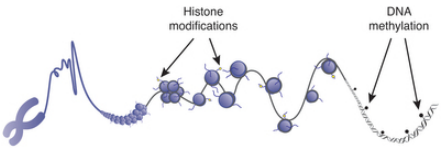
Why do we need to analyze the epigenome now?

- Lots and lots of epigenetic data



- Promise that this data can be mined to create personalized models of health and disease
- Ability to create very flexible models
  - Nonparametric Bayesian Models
  - Neural Networks
- Enough computing power
- Powerful priors that can defeat the curse of dimensionality

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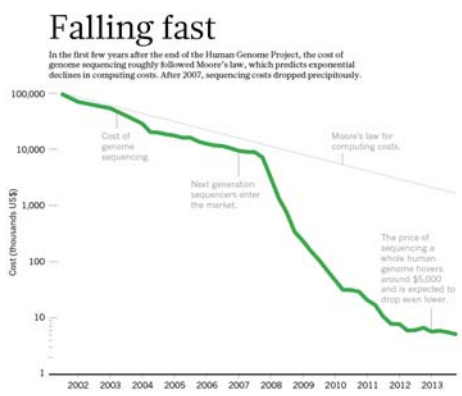
Driver: Big Data Explosion in Genomics



- Amount of genomics data is increasing rapidly
- Can we use this data to make personalized medicine approaches more disciplined?
- What are the ML classifiers best suited to this problem area
- What does the input space look like?
- Can we speed up the slow training process?
  - New datasets are being generated through genomics experiments at a fast rate
  - Diverse datasets need separate models to be trained
- Can we make use of large distributed clusters to speed up training?
- Can we make the overall development of computational genomics algorithms speedier and more efficient

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Epigenomic data for personalized medicine

- Create different models for classes of individuals or cell types based on their features (demographics, -omics data, …) (*Training phase*)
- Use model on hitherto unseen individual or cell type – then predict the individual's predilection for disease, etc. (*Prediction phase*)

$$X \longrightarrow \boxed{W_{Y|X}} \longrightarrow Y$$

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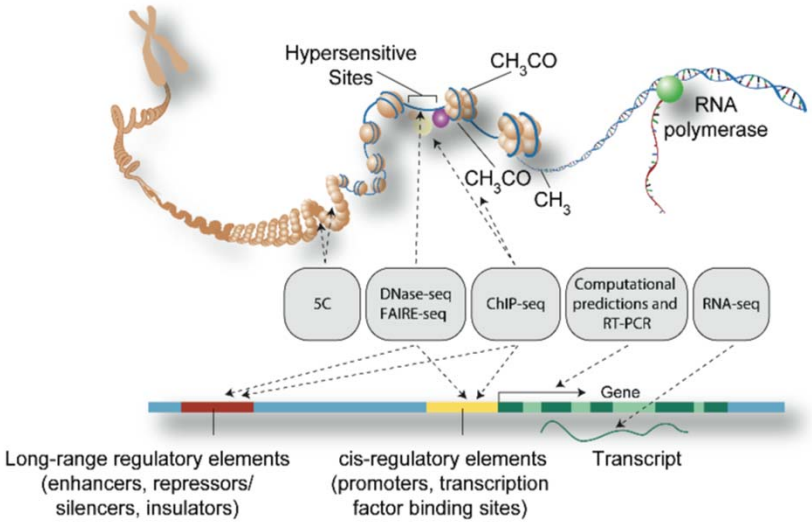
Epigenomic big data



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Precision epigenome-based therapeutics

- Which are the hotspots of genetic variants?
  - Genomic enhancers (Non-coding regulatory DNA)
- Which are the mobile, endogenous fine-tuners of gene expression?
  - MicroRNA (Non-coding regulatory RNA)

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AVISHKAR

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MicroRNA-based targeting

- miRNA are 22 nucleotide (nt) strings of RNA, base-pairing with messenger RNA (mRNA) to cause mRNA degradation or translational repression
- Can be thought of as biology's dark matter: small regulatory RNA that are abundant and encoded in the genome
- Dysregulation of miRNA may contribute to diverse diseases
- Canonical (i.e., exact) matches involve the **miRNA's seed region (nt 2-7)** and the 3' untranslated region (UTR) of mRNA and were thought of as the only form of interaction
- Recent high-throughput experimental studies have indicated the high-preponderance of "non-canonical" miRNA targets

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Our Contributions in microRNA Target Prediction

- Many tools are available for miRNA target prediction
  - However, they require complicated configurations and are computationally expensive
- Our contributions:
  1. Most general microRNA targeting algorithms
  2. Distributed pattern mining algorithm
  3. Visualizing the predicted miRNA-mRNA mappings

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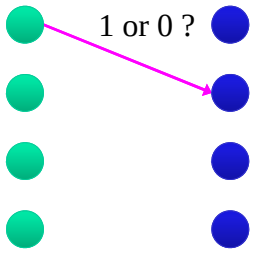
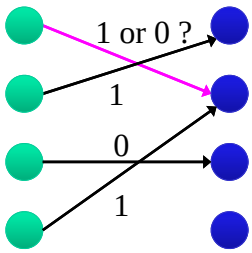
Problem Statement

- Predict if a miRNA targets an mRNA (segment)



- Ideally we would want some experimentally verified edge labels to train on



Edges with ground truth labels

Edges whose labels have to be predicted

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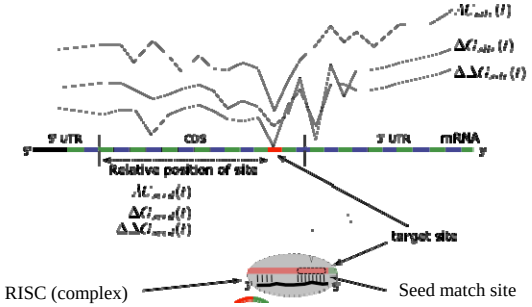
Methods: Feature Construction



- The alternating blue and green regions denote the 13 consecutive windows around the miRNA target site (red). These are the windows where the average thermodynamic and sequence features are computed.
- Compute interaction profiles at two different resolutions
  - Window size of 46 and using the entire miRNA: **"site" curves**
  - Window size of 9 and only using the seed region of the miRNA: **"seed" curves**
- Use coefficients of B-spline basis functions as features for classifier
- We hypothesize that the curves are different for the positive and negative samples.

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Improving Classification Performance with Kernel SVM

- Linear classifier suffers from high bias (large error even on training set)
- Solution: Use more complex learning model
  - Non-linear or Kernel SVM
- SVMs suffer from a widely recognized scalability problem in both memory use and compute time.
- Kernel SVM computational cost: $O(n^3)$
- Does not scale beyond a few thousand examples for feature vector of dimension ~ 150
- Running serial version on entire dataset (300 GB) will take 45.4×10^3 years!

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Making Kernel SVM Scale Up

- Biological insight: miRNAs within an miRNA family share structural similarities
- Therefore, we create a separate non-linear classifier for each miRNA family
- Within each family, we train in parallel using Cascade SVM approach

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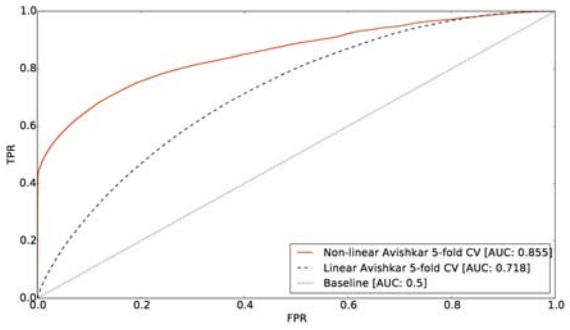
Results: ROC Curve for Linear and Non-linear SVM



- ROC curves for the ensemble linear model and ensemble non-linear model, obtained by varying the probability threshold for the output of the SVM.
- One possible operating region is FPR = 0.2: TPR for the linear model is 0.469, while the TPR for the non-linear model is 0.756.
- TPR is 150% better than competition.

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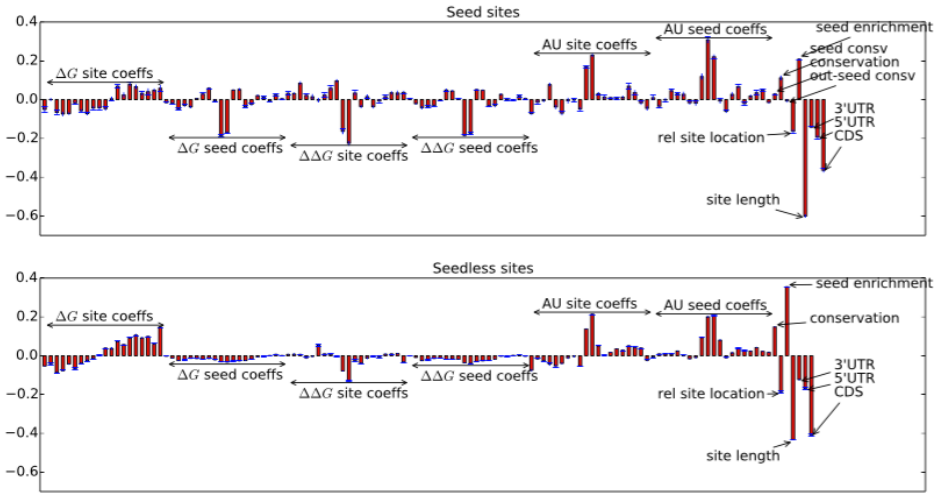
Results: Feature Importance



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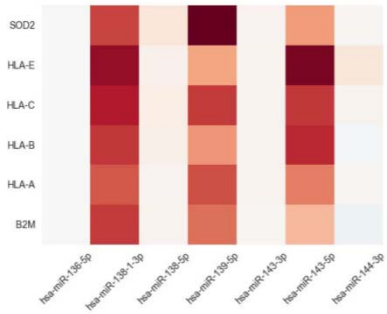
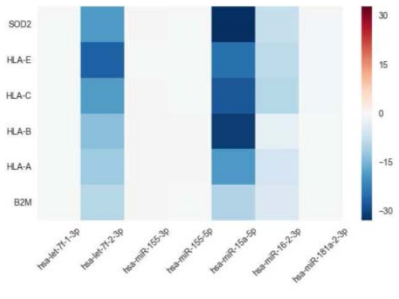
Visualization Snapshots

- Provided through a web server: http://cygnus.ecn.purdue.edu/



Upregulation



Downregulation

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TIRESIAS

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Context-Specific Prediction

- Goal
  - Integrate expression data about miRNA-mRNA, with prior sequence data, for predictions
  - Perform prediction under dynamic conditions of interest, such as in disease conditions and in specific tissues
- Prior work
  - Little prior work can achieve the two goals above
  - [Bioinformatics 2013][§] can only handle linear effects and downregulation
  - Recent results show that the effects from multiple interacting miRNAs is non-linear
  - Recent results show that miRNA regulation can be upregulation

[§] Integrating sequence, expression and interaction data to determine condition-specific miRNA regulation: Hai-Son Le, Ziv Bar-Joseph

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Our Solution Approach: *Tiresias*

- Tiresias computationally predicts miRNA targets under context-specific conditions by incorporating expression-level data into sequence-based prediction results
- Tiresias decouples the problem making the learning easier
  - The first stage estimates miRNA targets (as in *Avishkar*)
  - The second stage estimates regulation weights based on the previous stage's outputs
- Tiresias considers up-regulation and down-regulation simultaneously
- Tiresias extends prediction to a complex non-linear regulation model using two Artificial Neural Networks (ANNs)
- Tiresias characterizes the density of miRNA-mRNA interactions by one single hyper-parameter (ρ) unlike prior work

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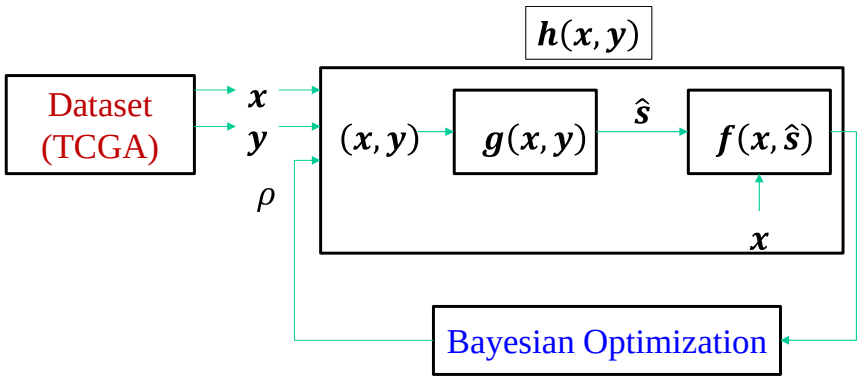
Our Solution Approach: *Tiresias*



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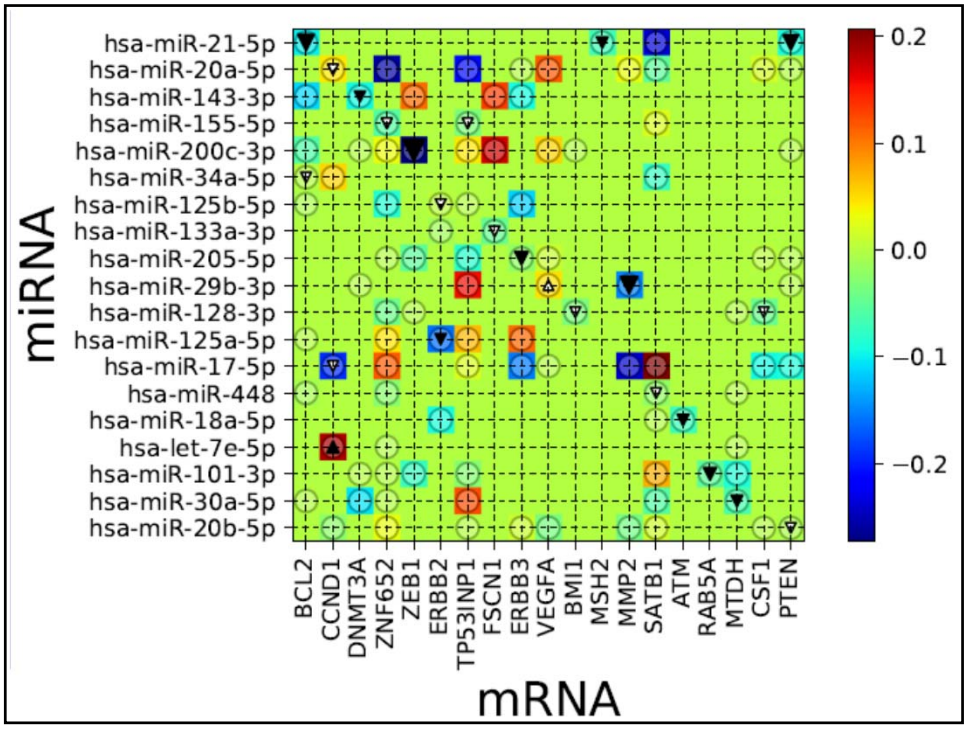
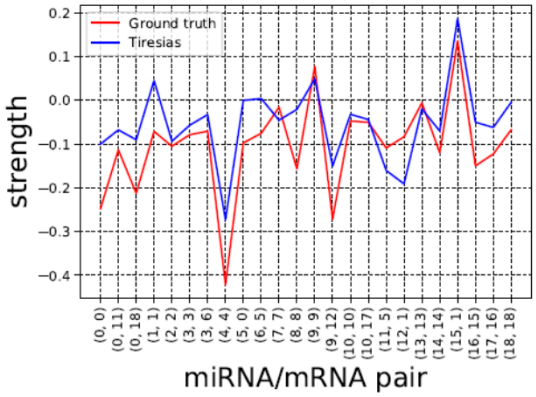


Regulation strength and direction



Experimental results showed that Tiresias performs better than existing computational methods such as GenMiR++, Elastic Net, and PIMiM.
For the TCGA breast cancer dataset, Tiresias showed a true positive rate of about 88% in recovering the ground truth regulatory interactions between miRNAs and mRNAs.

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Expertise

- Computational biology
  - Mining epigenomics and metagenomics data
  - Data structures for efficient computing in genomics
  - Federation of infrastructures for genomics
  - Faster and more efficient evolution of new algorithms
  - Predictive analytics for genome editing and therapeutic targeting
- Data-driven cell engineering
  - Efficient and precise genome editing
  - Bridging the gap between systems biology and synthetic biology
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