Functional transcription factor target discovery via compendia of binding and expression profiles

Chris Banks, Anagha Joshi, Tom Michoel

The Roslin Institute

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- Our method:
  - "Guilt by association" method;
  - Our data;
  - Power of different statistics and the "wisdom of crowds".

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  - Our data;
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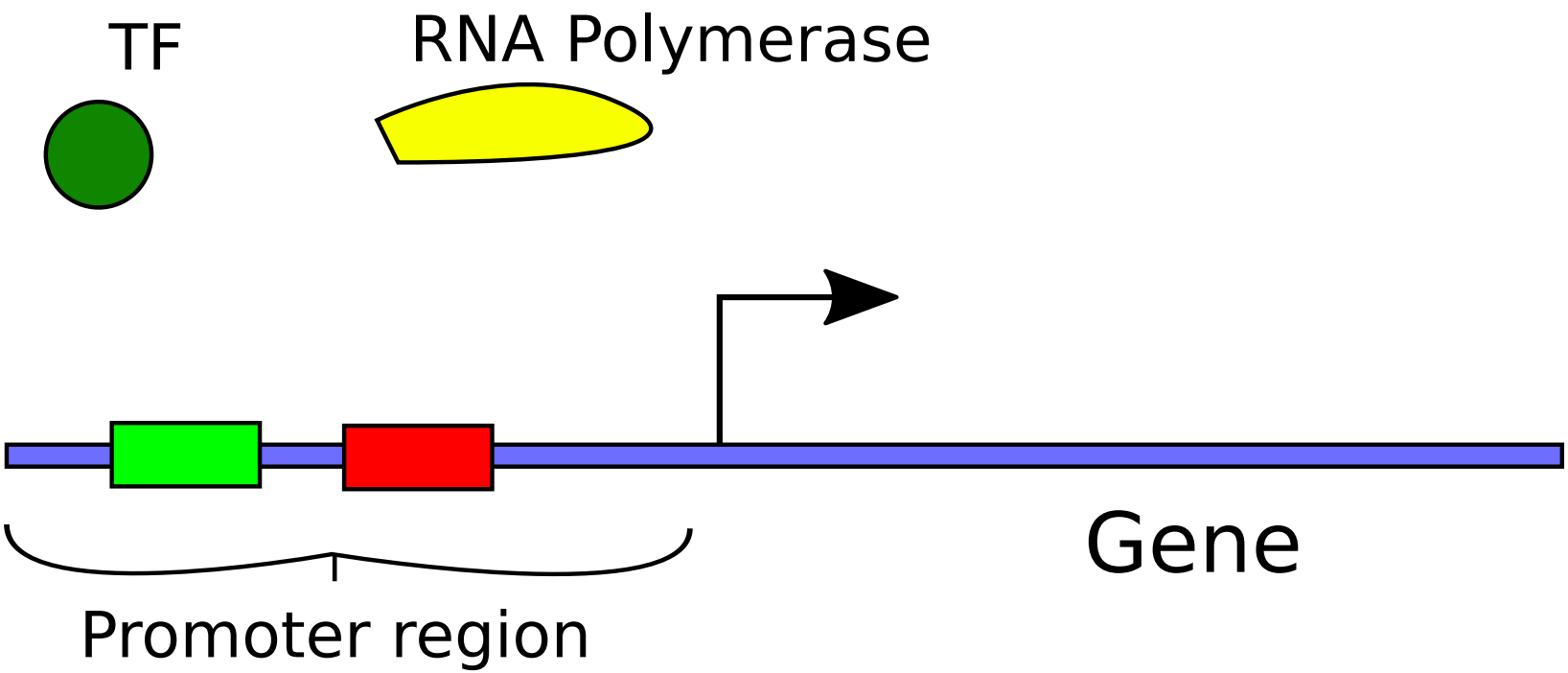
- Results.
- Future work.

Gene regulation—a computer scientist's view

Transcriptional regulation by DNA-binding transcription factors (TFs) is a fundamental process governing all cell behaviour.



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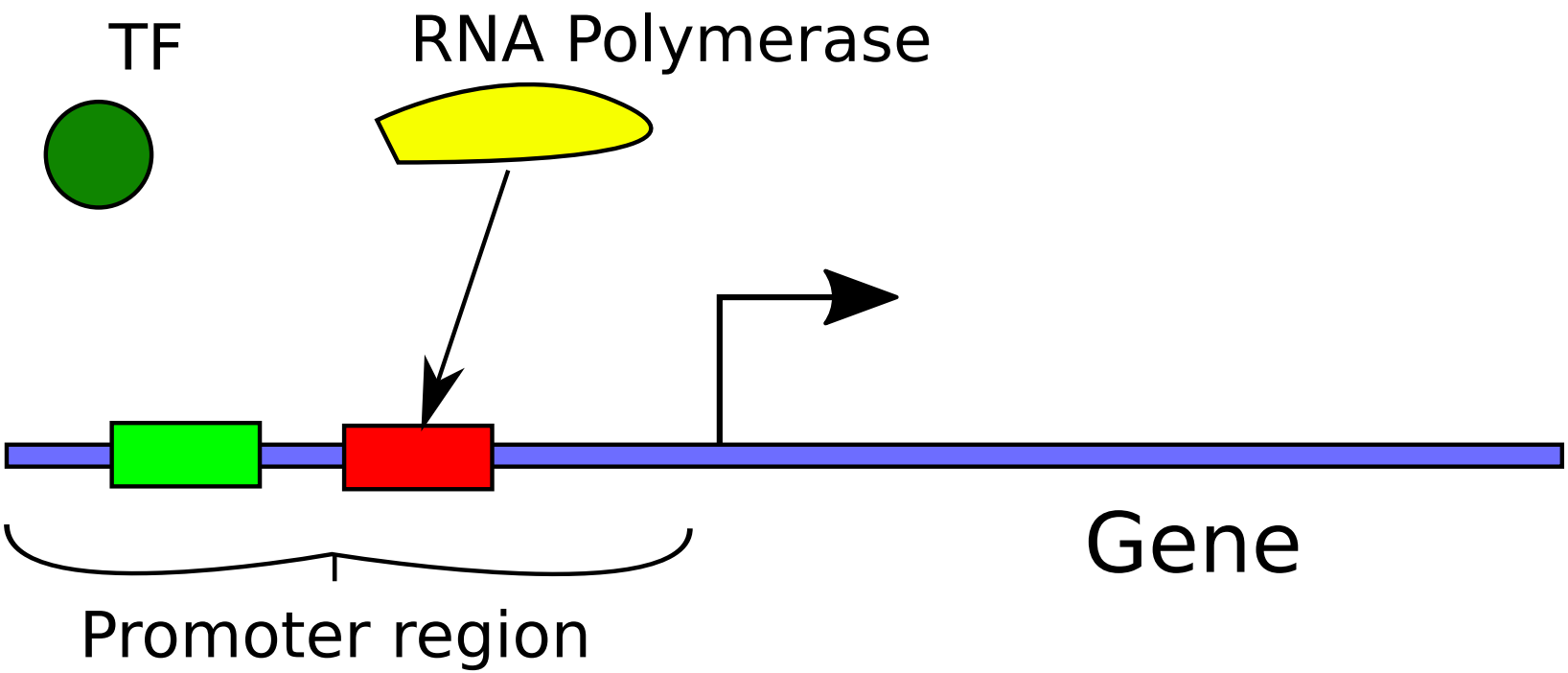

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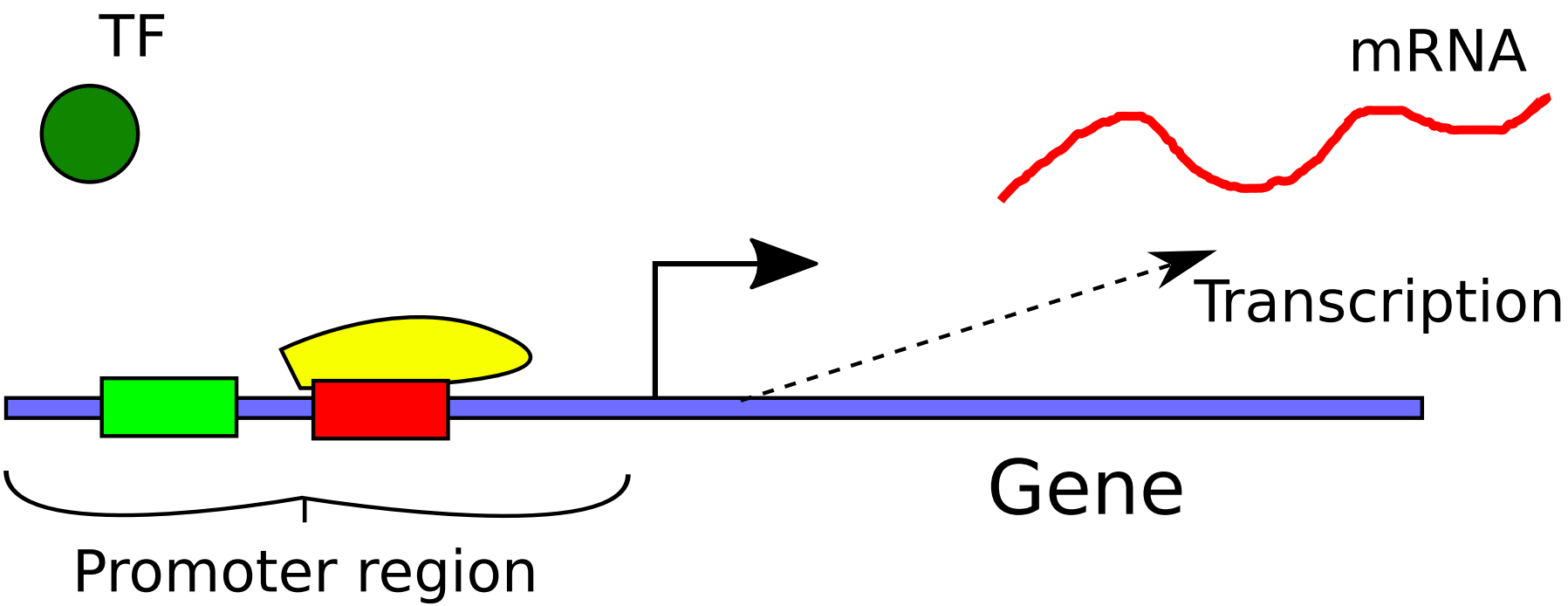

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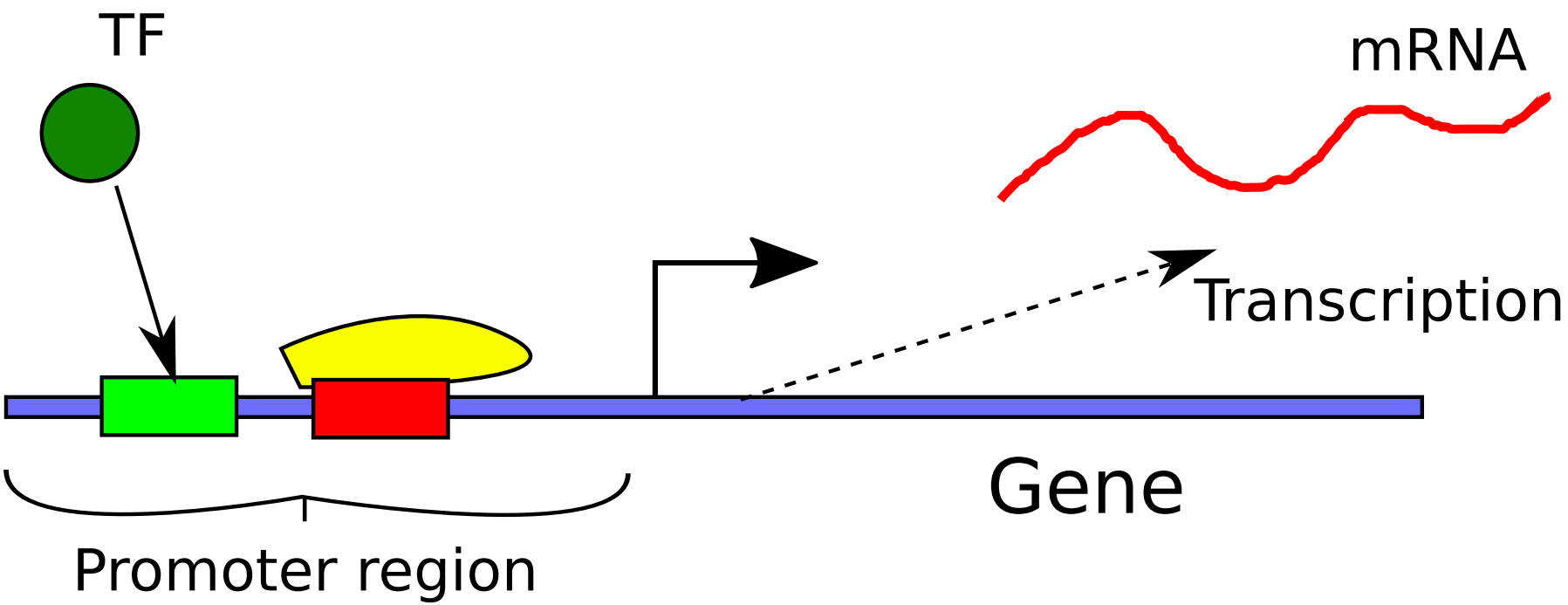

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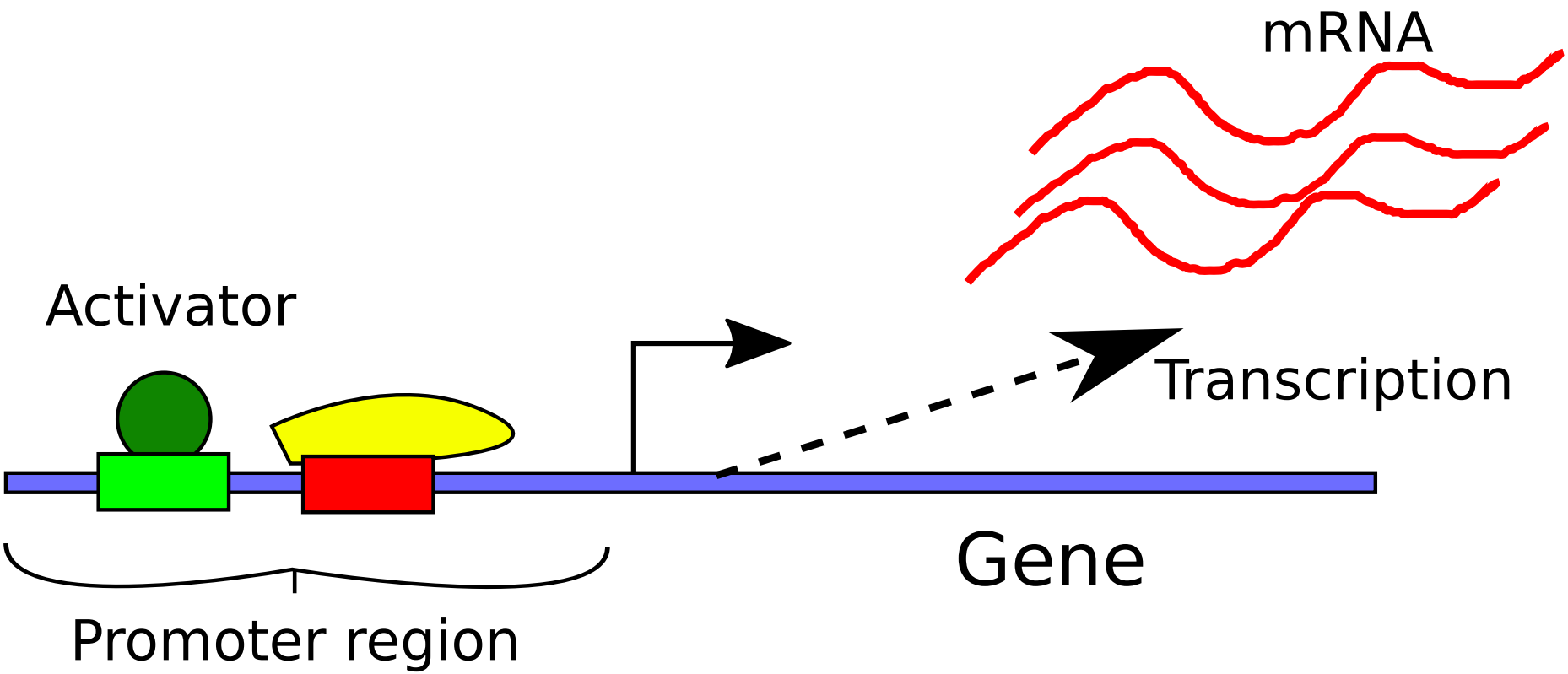

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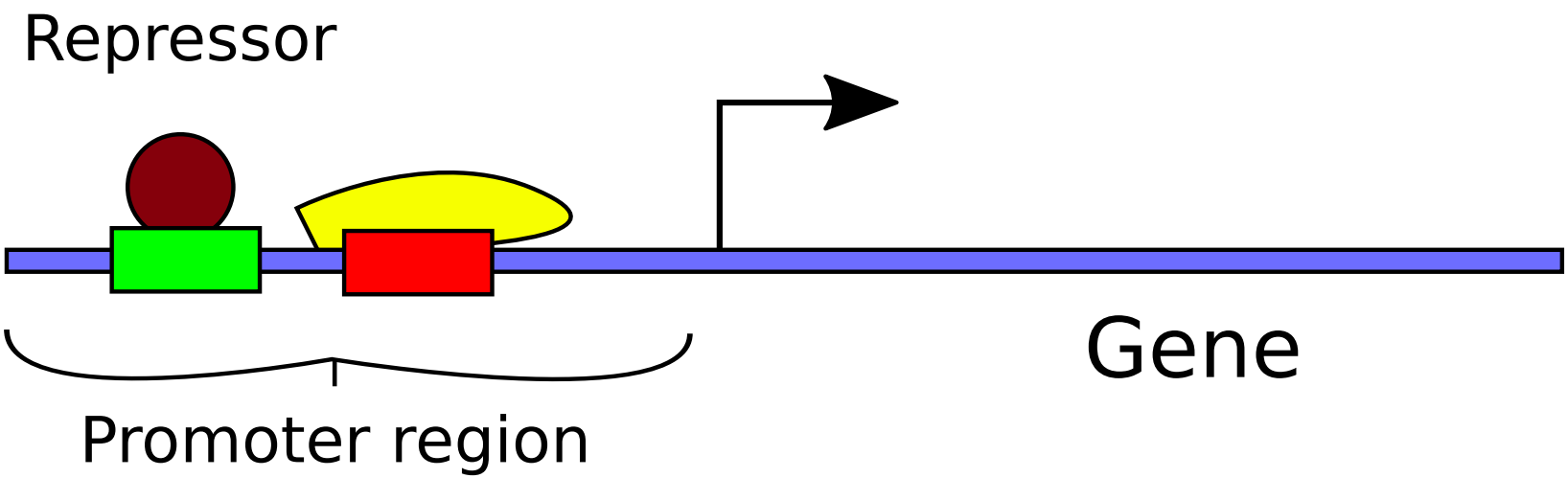
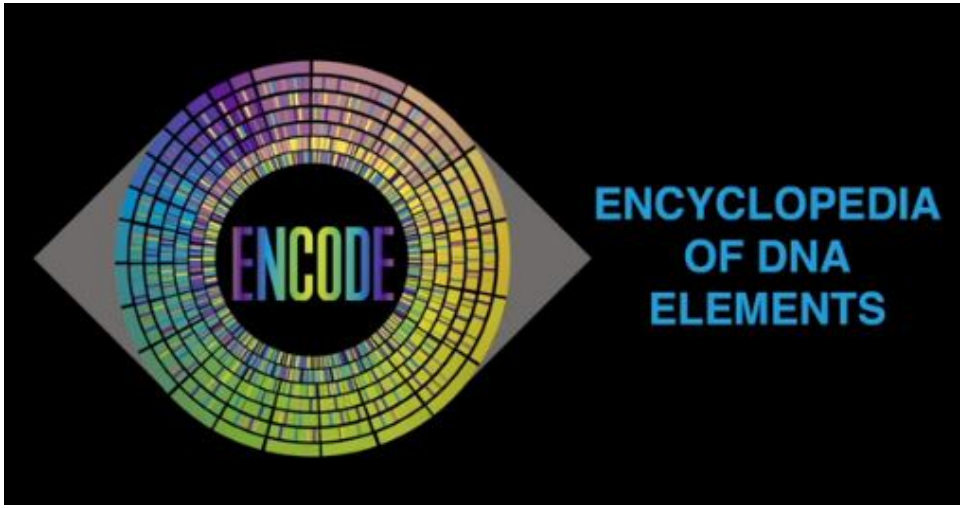


ChIP-sequencing



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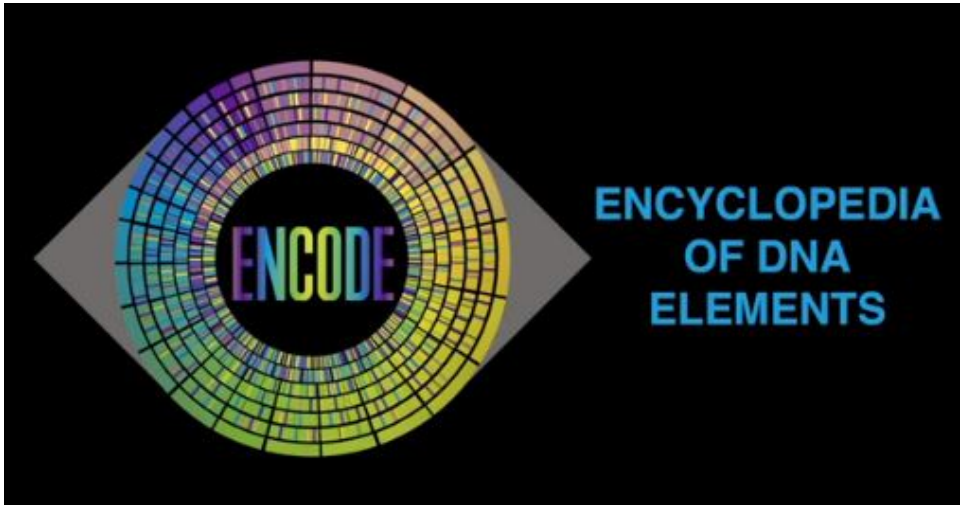

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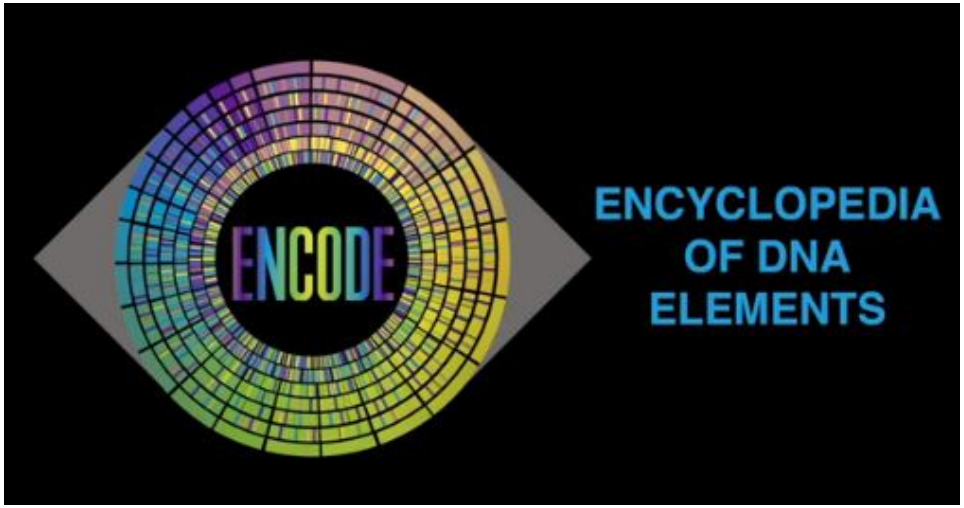

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  - using ChIP-sequencing technology.

- **However:** it has been found that **most** TF binding within the promoter region of a gene **does not cause differential expression** of that gene. (*Cusanovich et al., 2014*)

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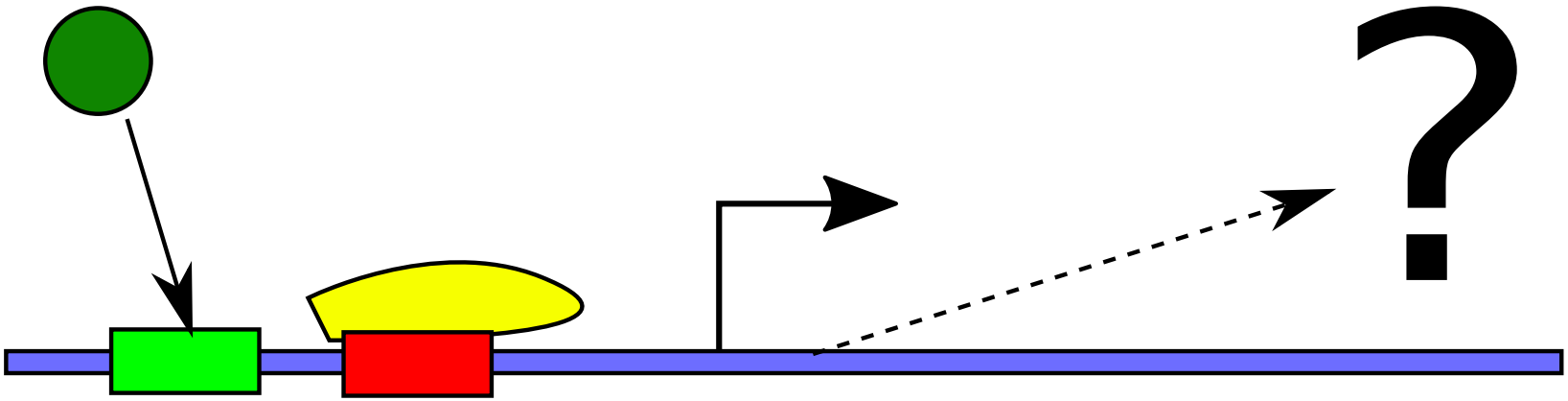

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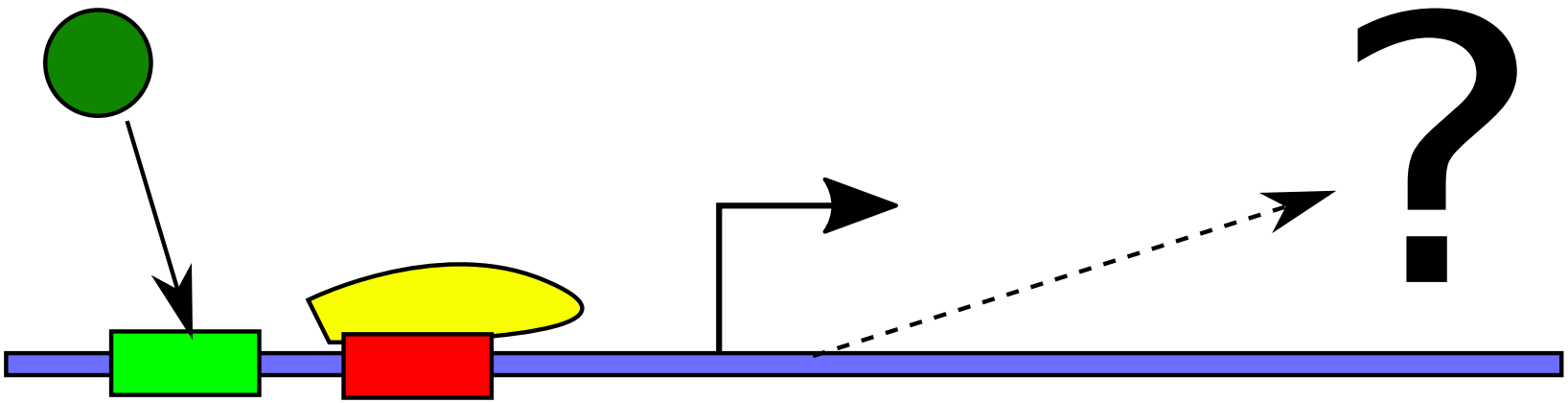

- **Predicting** when a **TF binding** will cause a **biologically significant response** in the **neighbouring gene**.

"Guilt-by-association"

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- **Can we apply the same principle to our ChIP-sequencing data?**
- Can the relationship between binding and expression predict function?

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  - RNA-sequencing data—normalised to compare expression levels for each cell-line.
- Differential expression in a knock-out cell-type for five factors—
  - proxy gold-standard for functional DNA-binding,
  - for one of the ENCODE cell-lines.

Data matrices

For each factor and each peak-to-gene model:

	Cell-line 1 $\cdots$ Cell-line n
Gene 1 $\vdots$ Gene m	ChIP Peak counts

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- Does correlation between ChIP and RNA predict KO expression?

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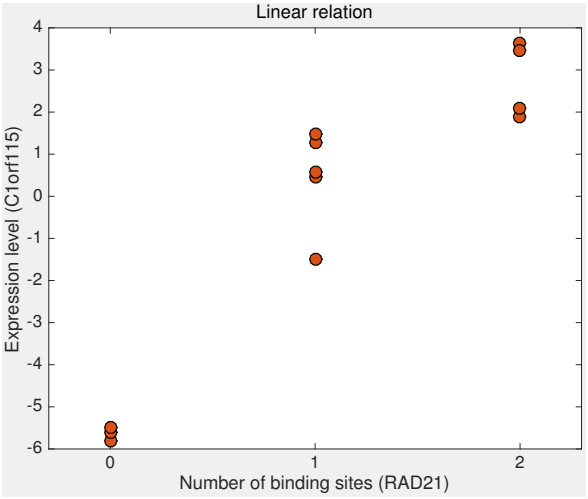
- High confidence for the top few hundred of targets.
- And we did find a way to improve this further...

Correlation methods

- We found a number of different patterns for correlation:

a



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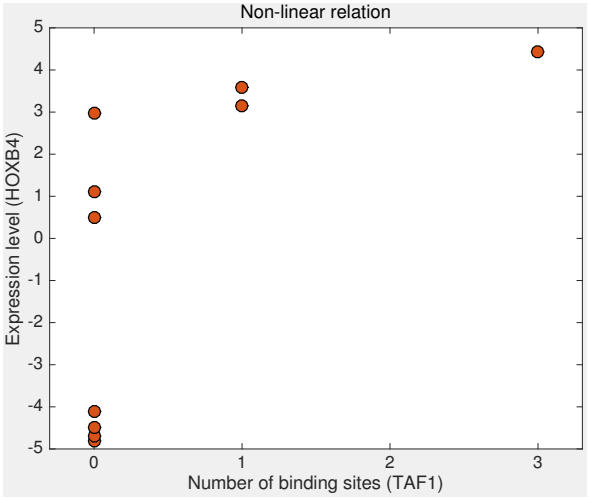

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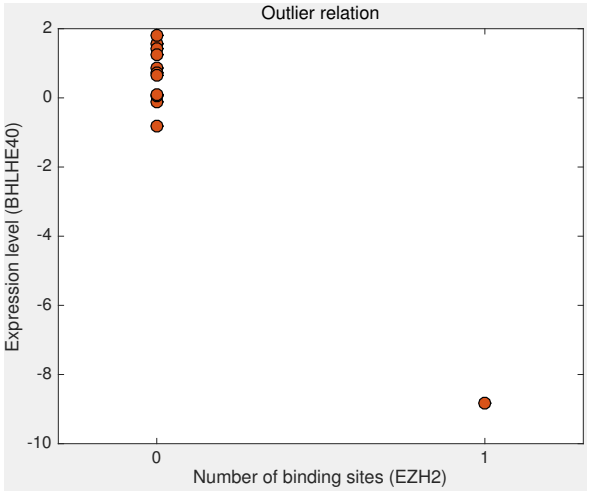

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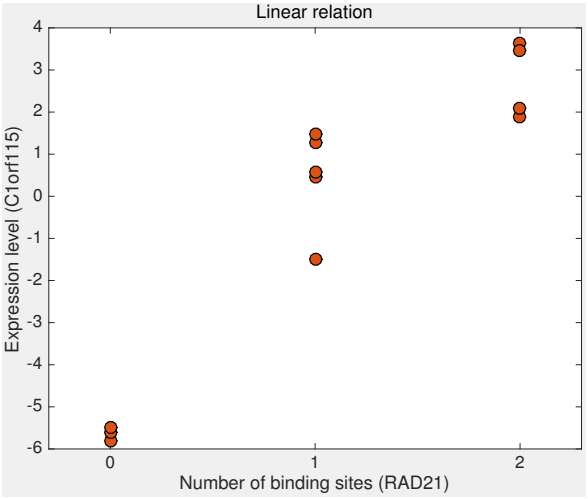

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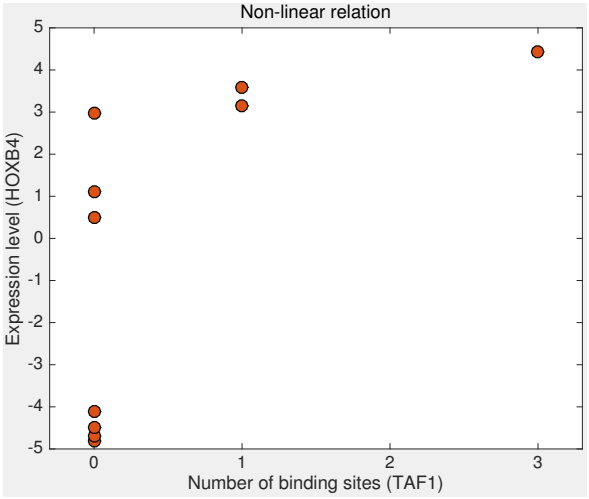

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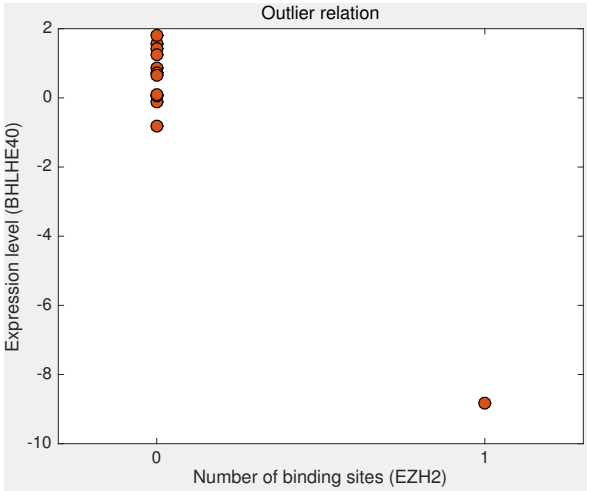
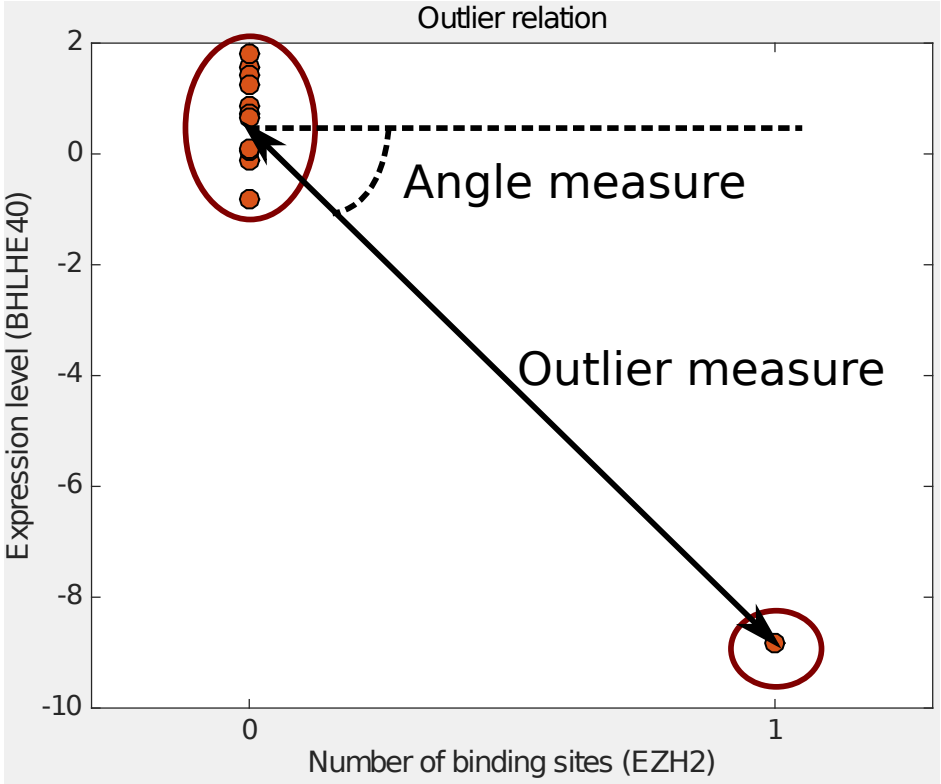


- Best accounted for by:
  - (a) Pearson,
  - (b) Spearman,
  - (c) Combined Angle Ratio Statistic.
    - Based on ARS (*Marstrand and Storey, 2014*), but with negative associations.

CARS

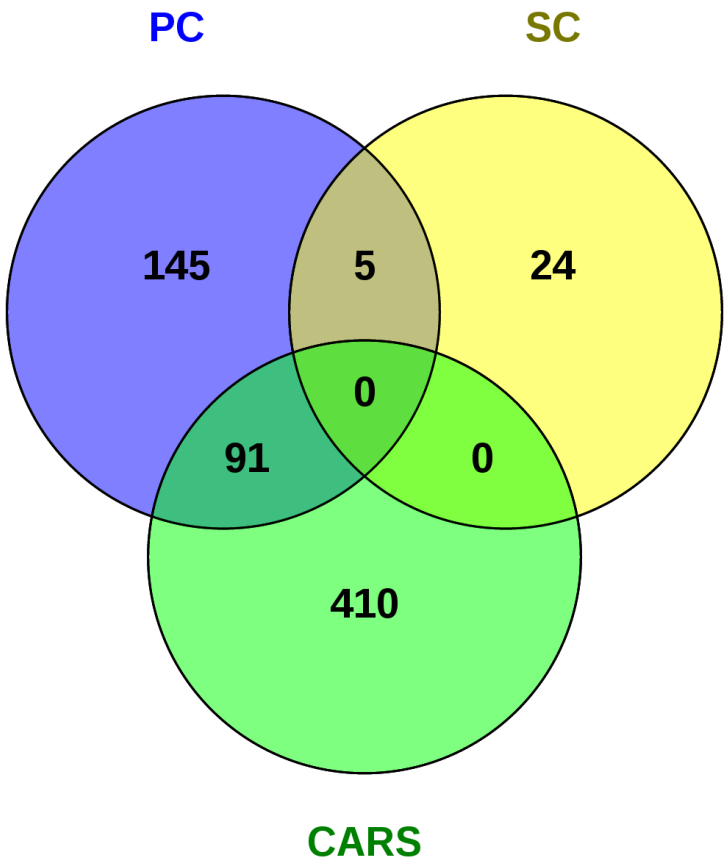
- Combined Angle Ratio Statistic (CARS)



- For each point:
- $\text{Angle}_i \times \text{Outlier}_i$
- CARS = max score for any point.

Wisdom of crowds

EP300:



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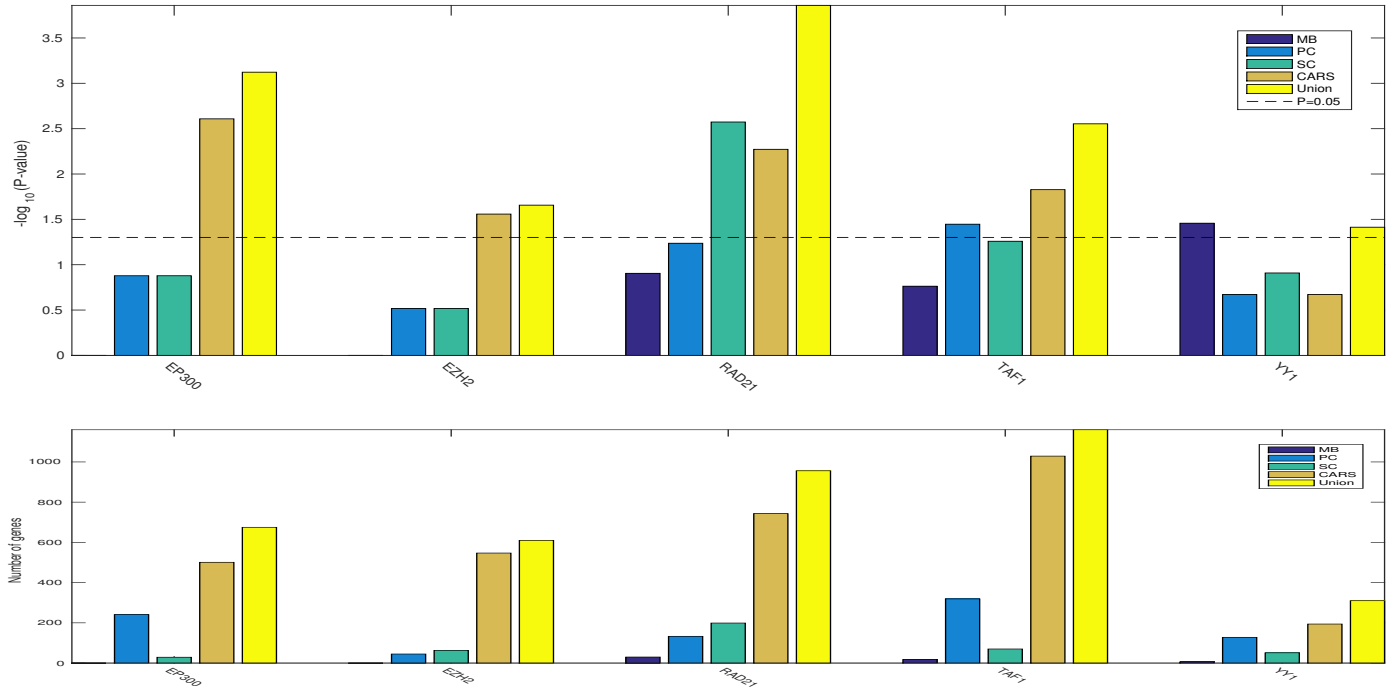
Wisdom of crowds

- Different correlation measures find different relationships, so why not combine their strengths?
- Taking the union of the top results from each measure:



- Significance is the hypergeometric overlap with the gold standard.

Other findings

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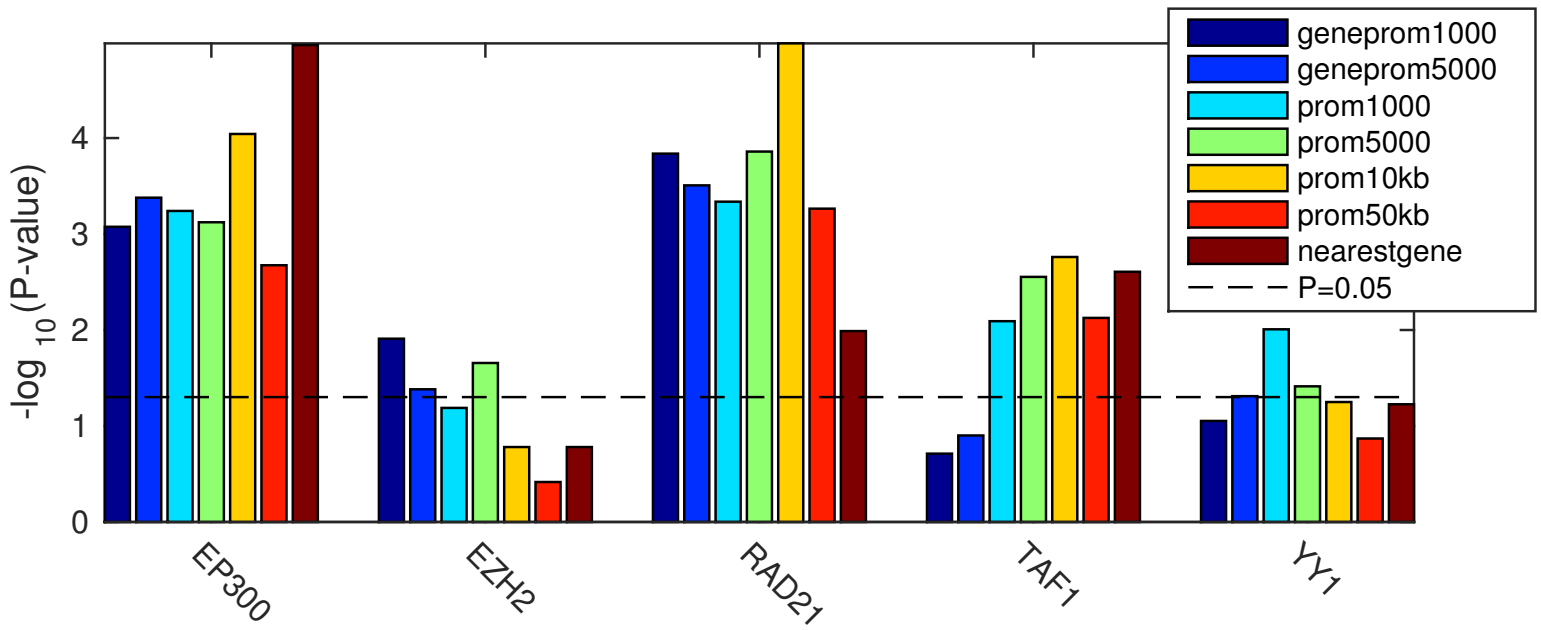

- EZH2 binds closer to the TSS; EP300 binds further away.

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- Plenty of data is available from the ENCODE resource—
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- A wisdom-of-crowds approach to correlation measures gives better precision.
- The method works with time-series data, as well as multiple cell-lines.

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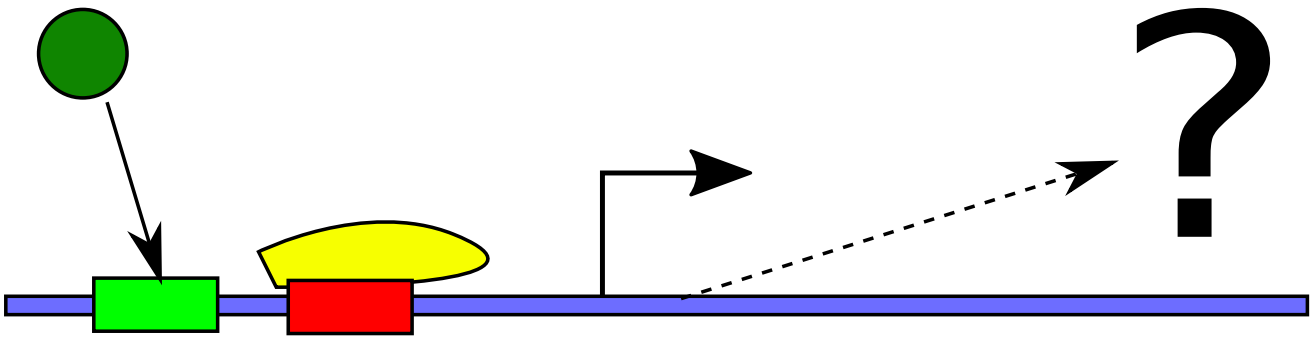

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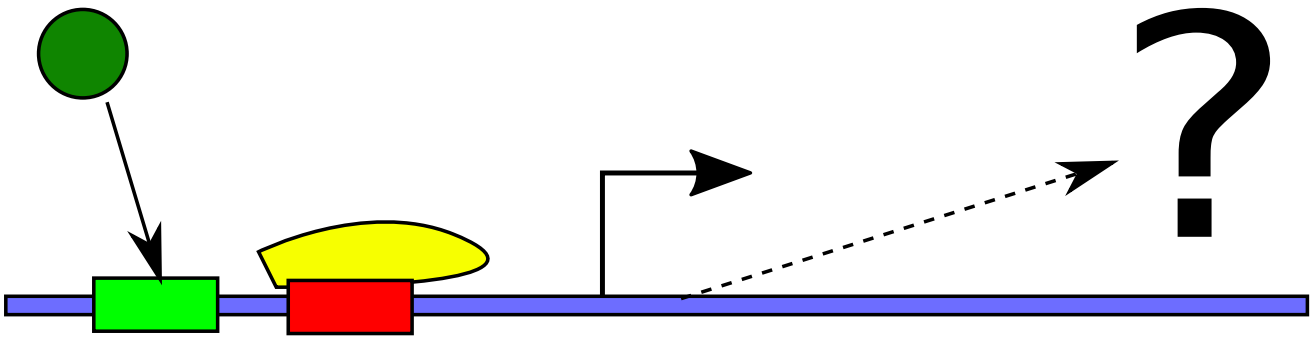

- What makes our predictions functional?
  - More investigation required on the idea of cumulative/combinatorial binding.