Towards the Understanding of Transcriptome Complexity and Plasticity

Gunnar Rätsch

Friedrich Miescher Laboratory

Max Planck Society

Tübingen, Germany

Symposium "40 Years FML"

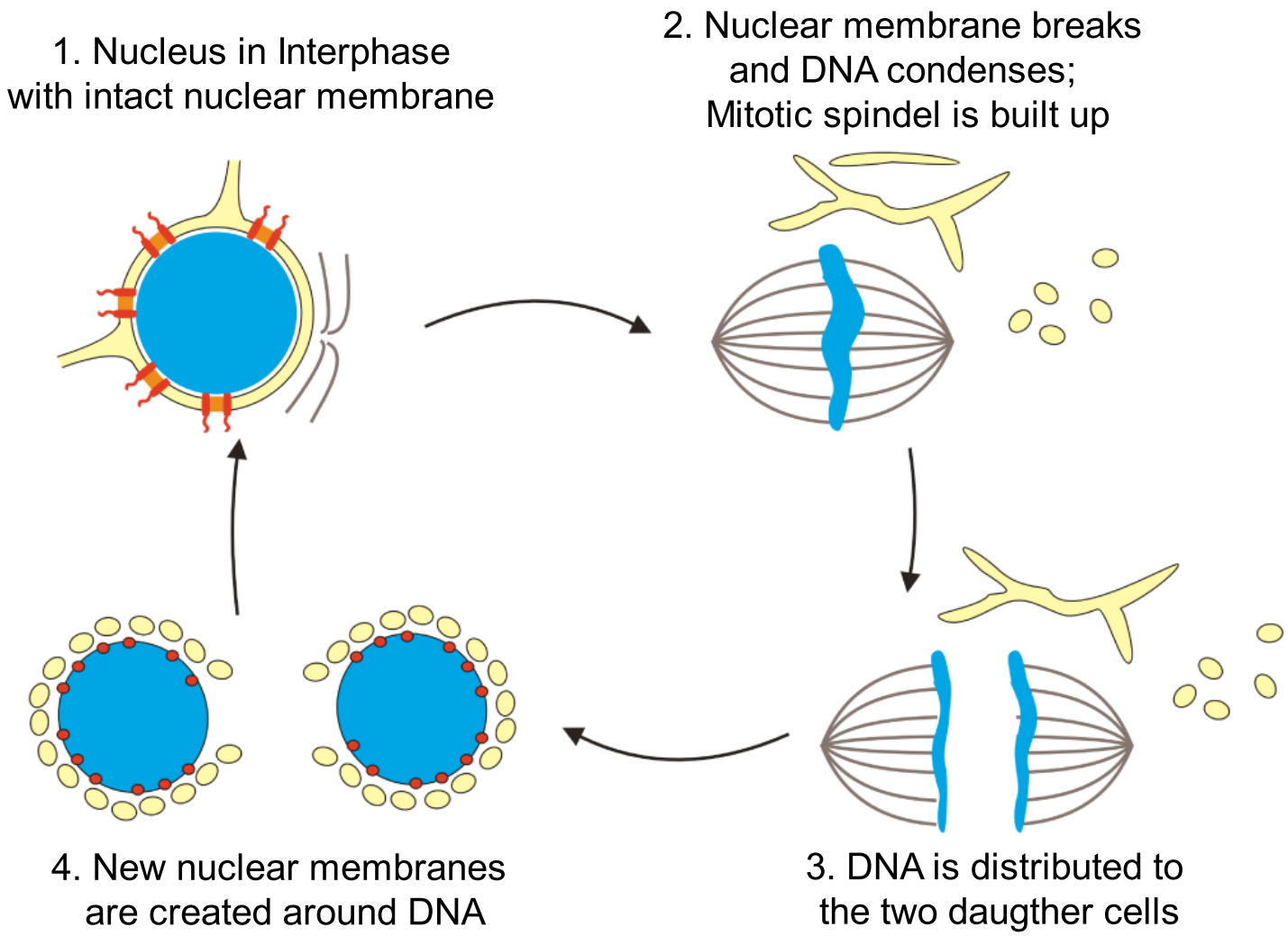
Tübingen, July 3, 2009



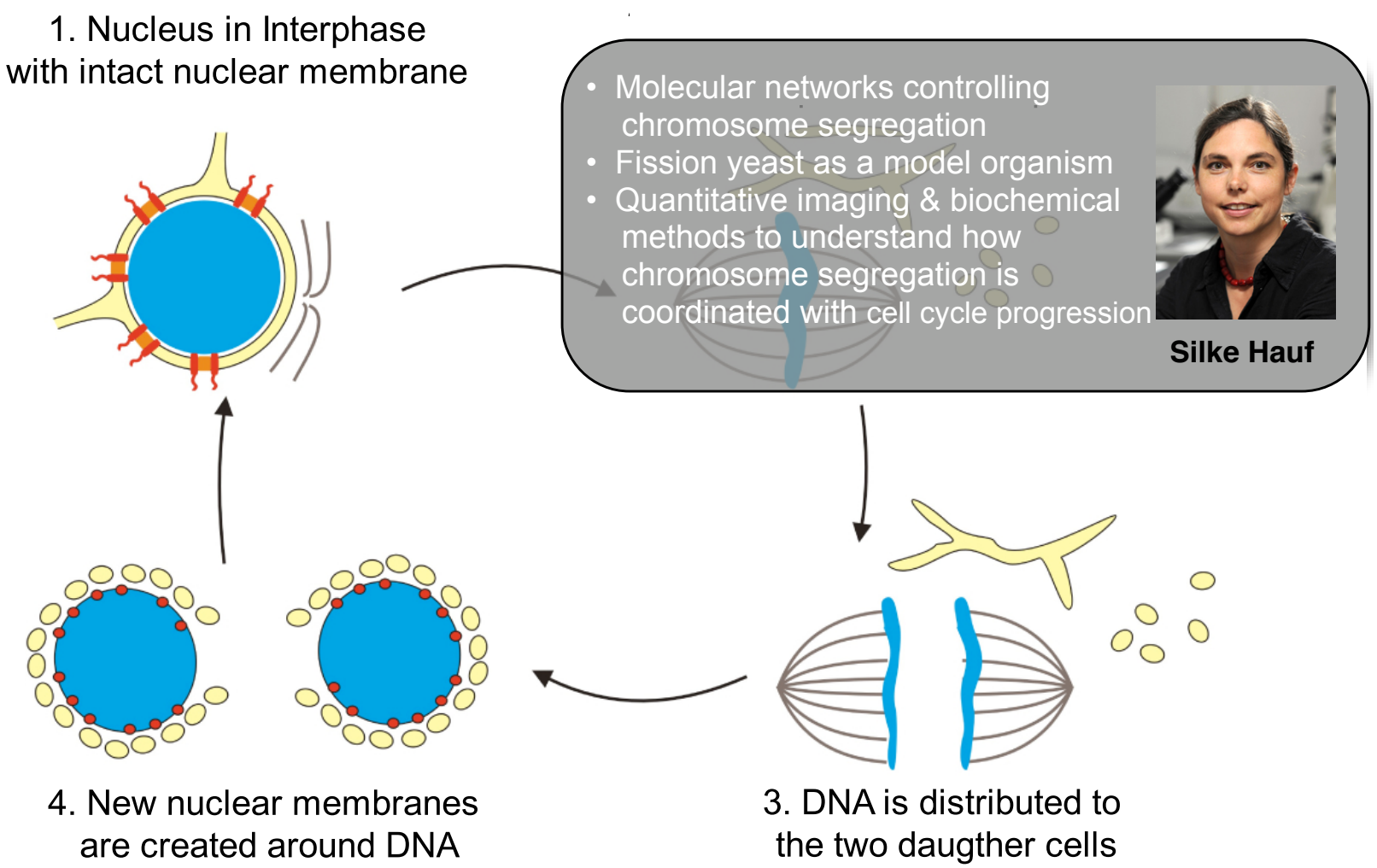
Friedrich Miescher Laboratory
of the Max Planck Society



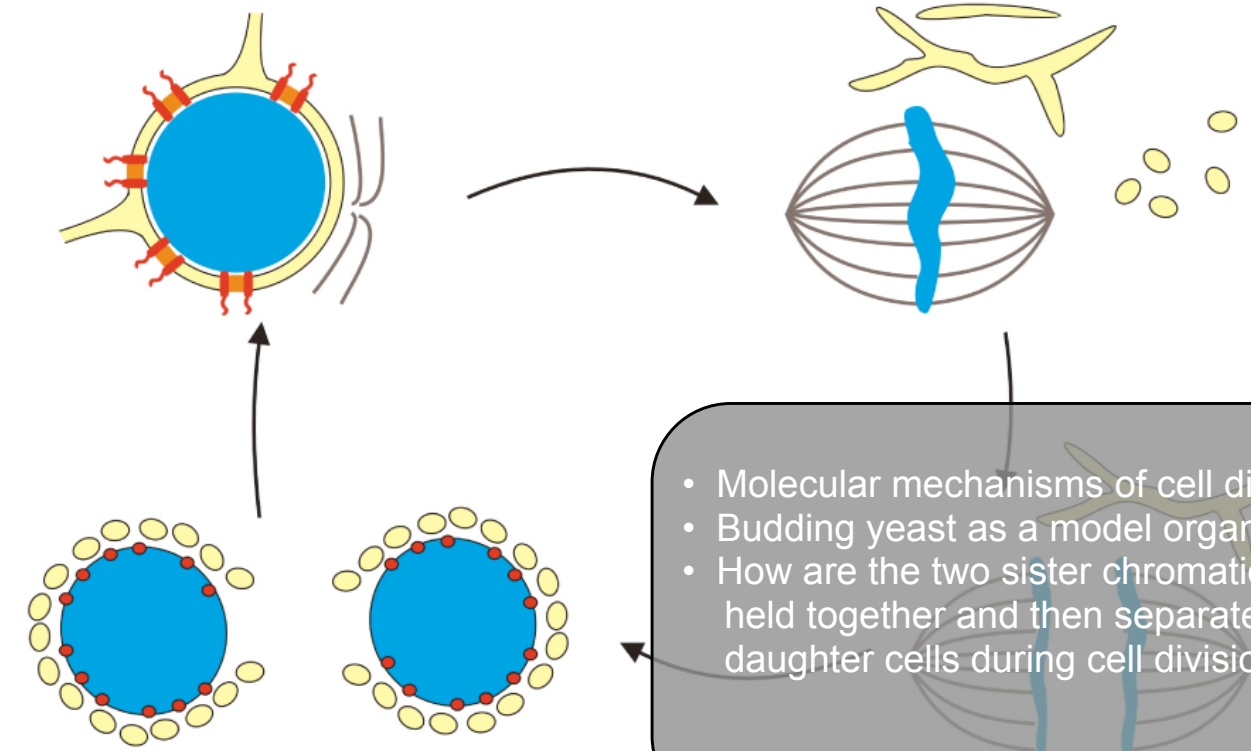
Research Groups at the FML



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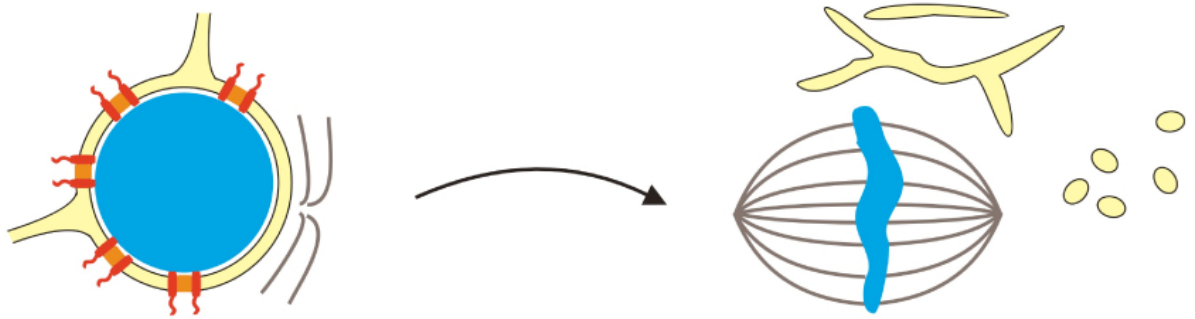
Silke Hauf

- Molecular mechanisms of cell division
- Budding yeast as a model organism
- How are the two sister chromatids held together and then separated to daughter cells during cell division?



Dmitri Ivanov

Research Groups at the FML





Silke Hauf



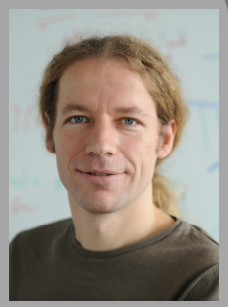
- Biochemical and cell biological research
- Egg extracts from Xenopus laevis for reconstitution of cellular processes
- How is nuclear envelope created at end of mitosis?

Wolfram Antonin



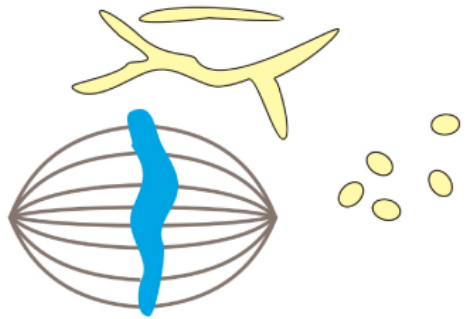
Dmitri Ivanov

Research Groups at the FML



Gunnar Rätsch

- Bioinformatics with machine learning
- Efficient methods for processing of genomic data
- Analysis of mechanisms of gene identification and processing

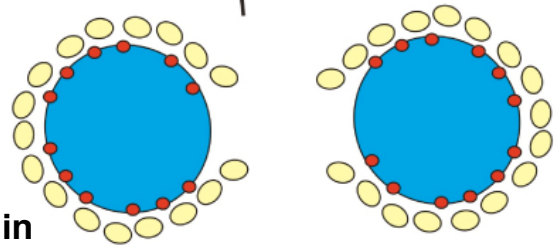


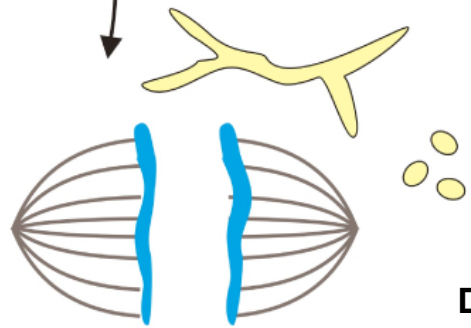


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Wolfram Antonin







Dmitri Ivanov

Research Groups at the FML

The FML Today: Science Around the DNA



Gunnar Rätsch



Silke Hauf



Wolfram Antonin



Dmitri Ivanov

Machine Learning in Biology

Research Topics

Machine Learning

1. Inference methods for structured data
   ⇒ *Develop fast and accurate learning methods*

Molecular Biology

2. Genome annotation
   ⇒ *Predict features encoded on DNA*
3. Biological networks
   ⇒ *Understand interactions between gene products*
4. Analysis of polymorphisms
   ⇒ *Discover polymorphisms and associate with phenotypes*

Machine Learning

$\rightsquigarrow$ Develop fast, accurate and interpretable learning methods



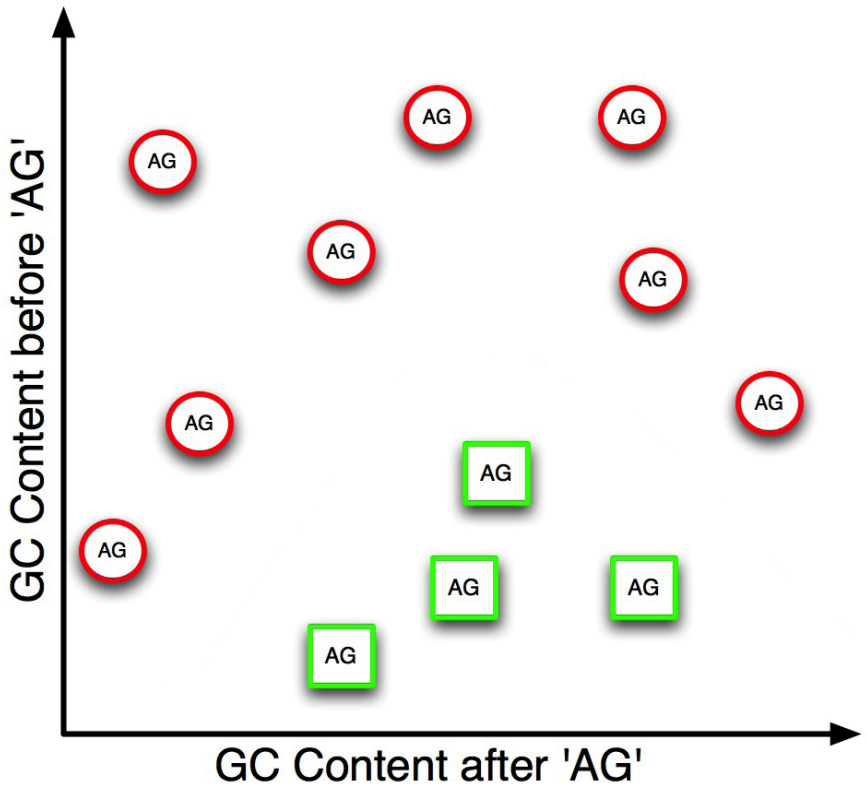
Given: Observations of some complex phenomenon
Goal: Learn from data & build predictive models

Machine Learning

⇝ Develop fast, accurate and interpretable learning methods

Given: Observations of some complex phenomenon
Goal: Learn from data & build predictive models

Example:



Two different classes of observations

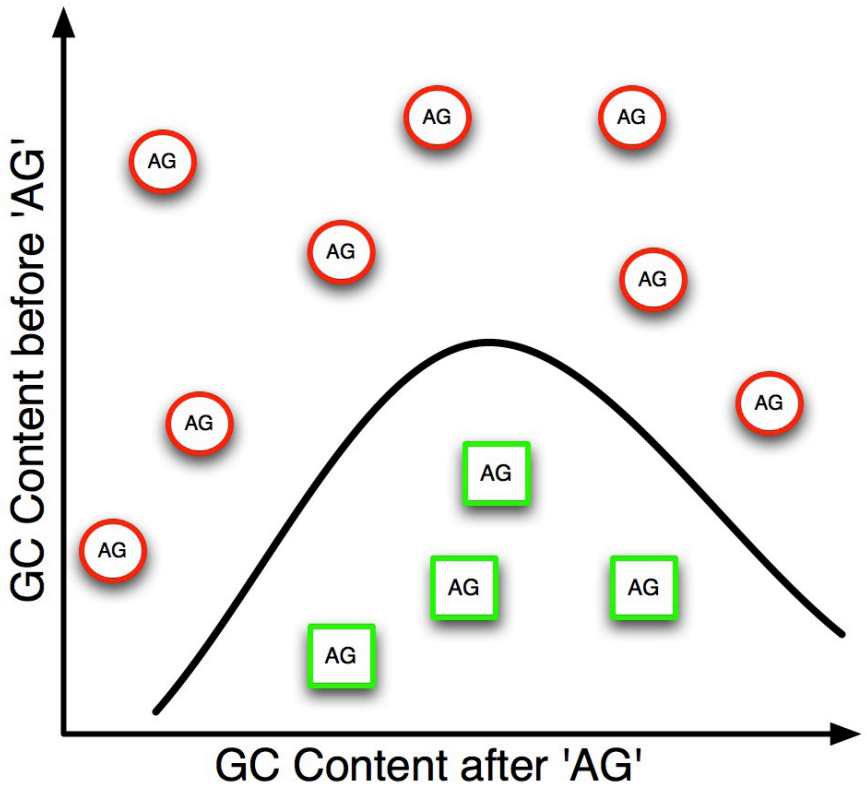
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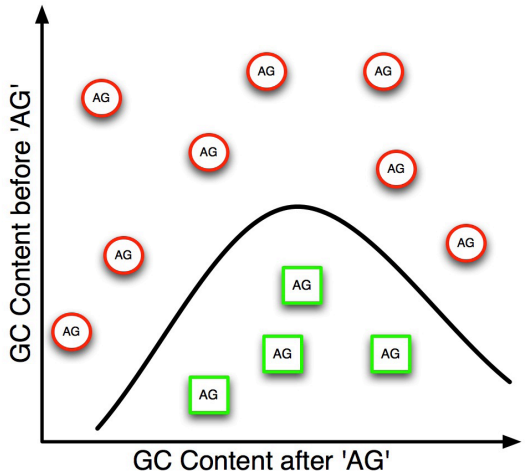
Inferred classification rule

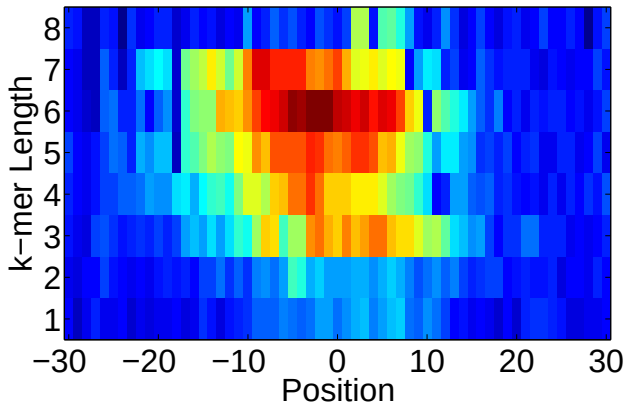
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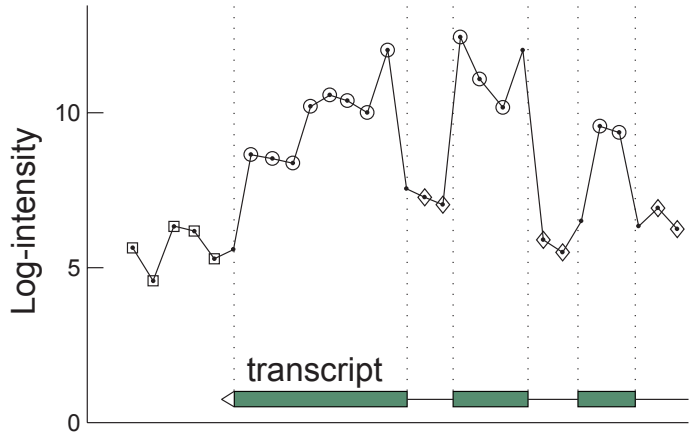
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1. Large scale sequence classification
   with Sonnenburg (Fraunhofer, Berlin) & Schölkopf (MPI Biol. Cybernetics)
2. Analysis and explanation of learning results
   with Sonnenburg (Fraunhofer, Berlin)
3. Sequence segmentation & structure prediction
   with Altun (MPI Biol. Cybernetics)

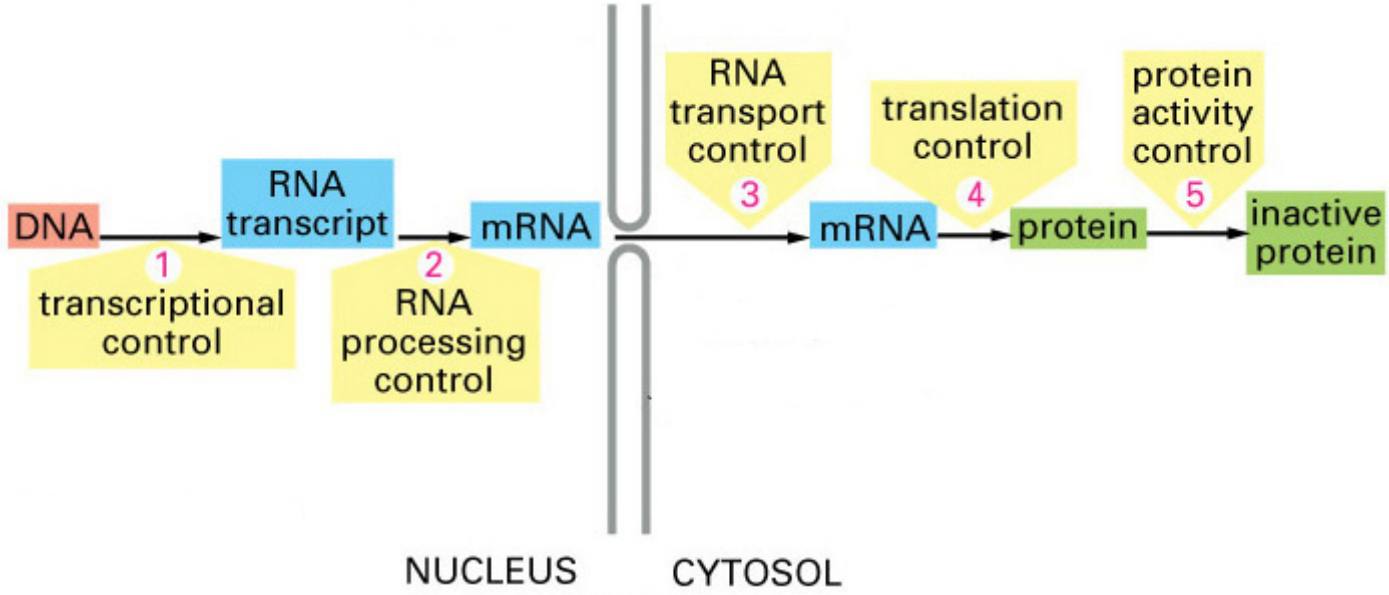






Learning about the Transcriptome

⇝ What is encoded on the genome and how is it processed?



Machine Learning View

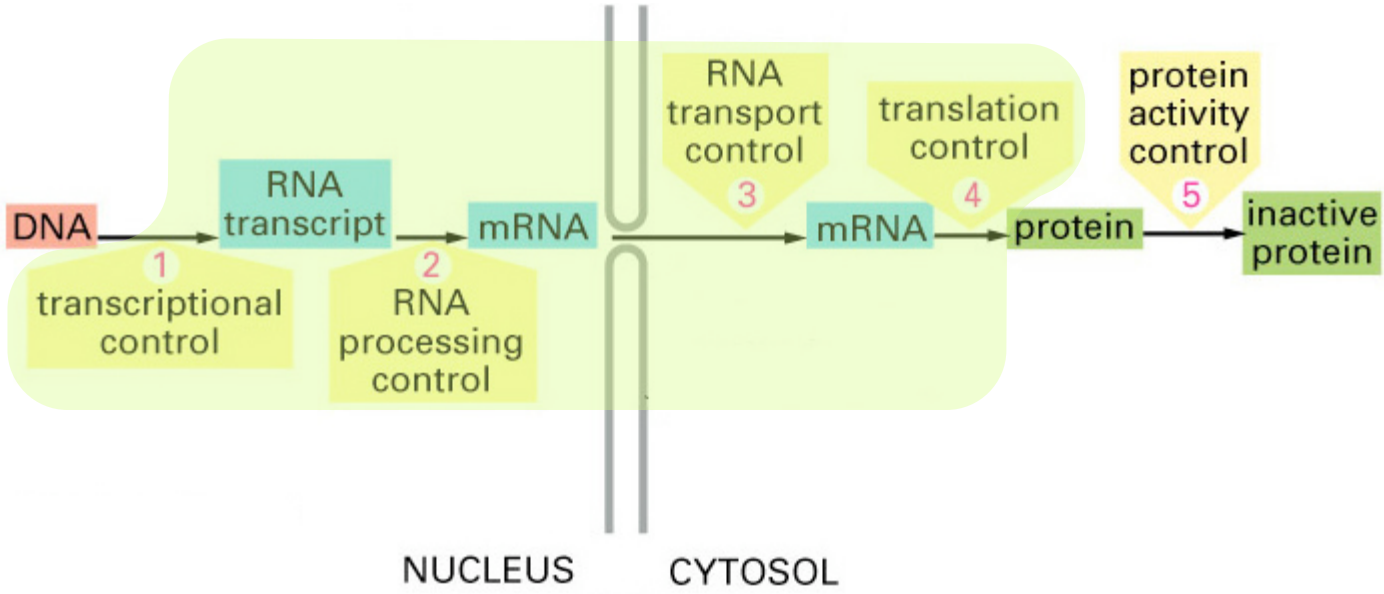
- How to learn to predict what these processes accomplish?
- How well can we predict it from the available information?

Biological View

1. What can we not predict yet? What is missing?
2. Can we derive a deeper understanding of these processes?

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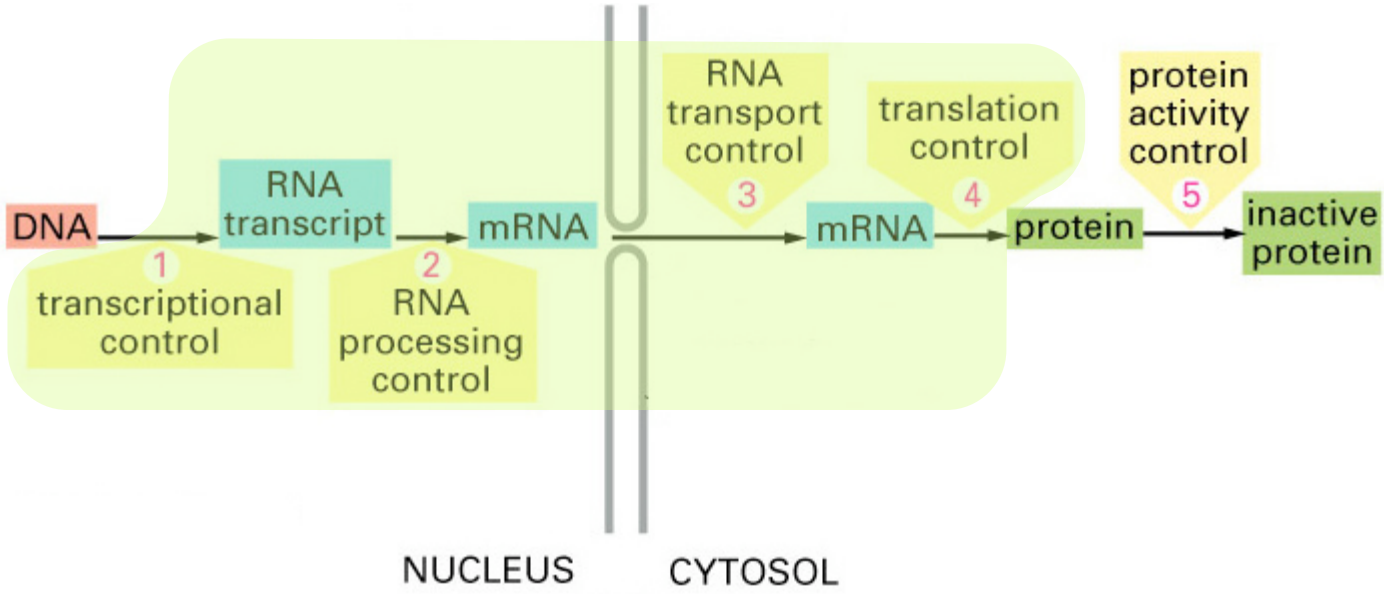
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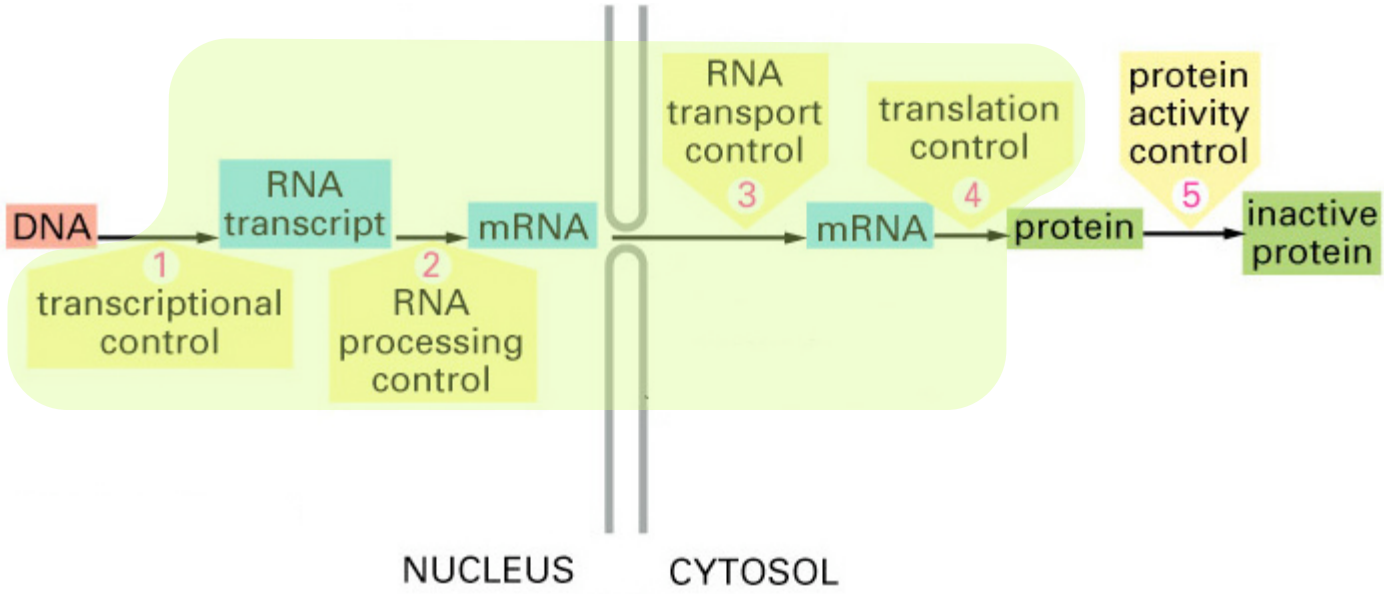
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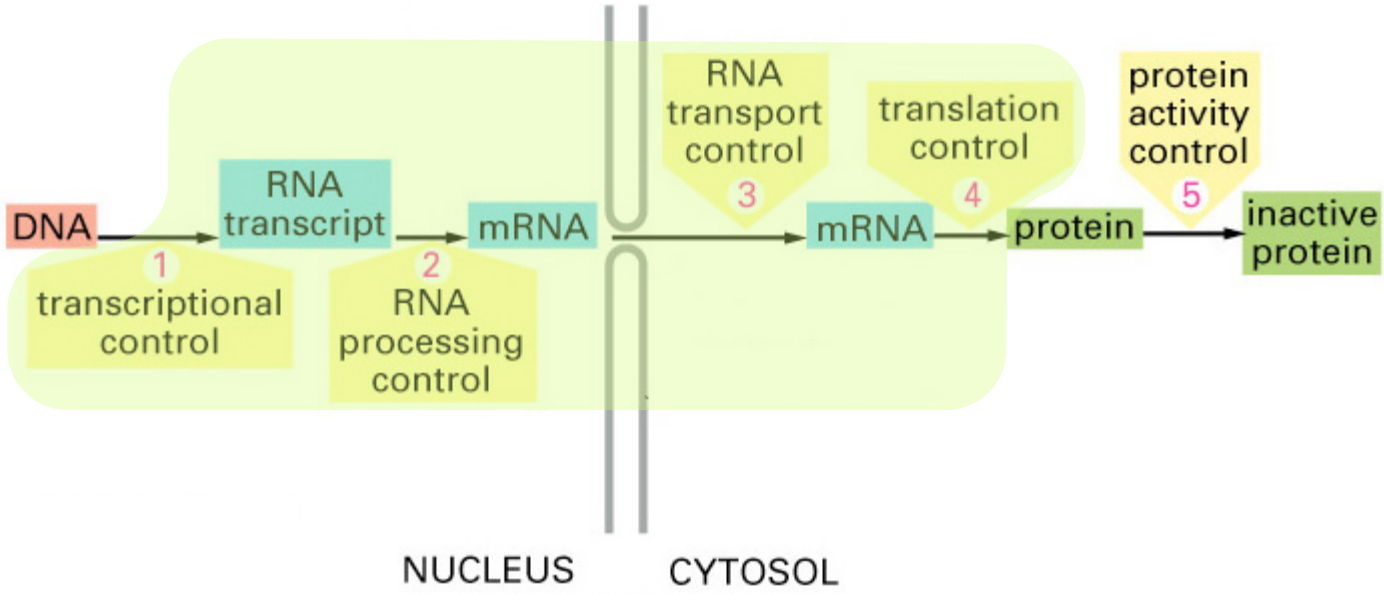
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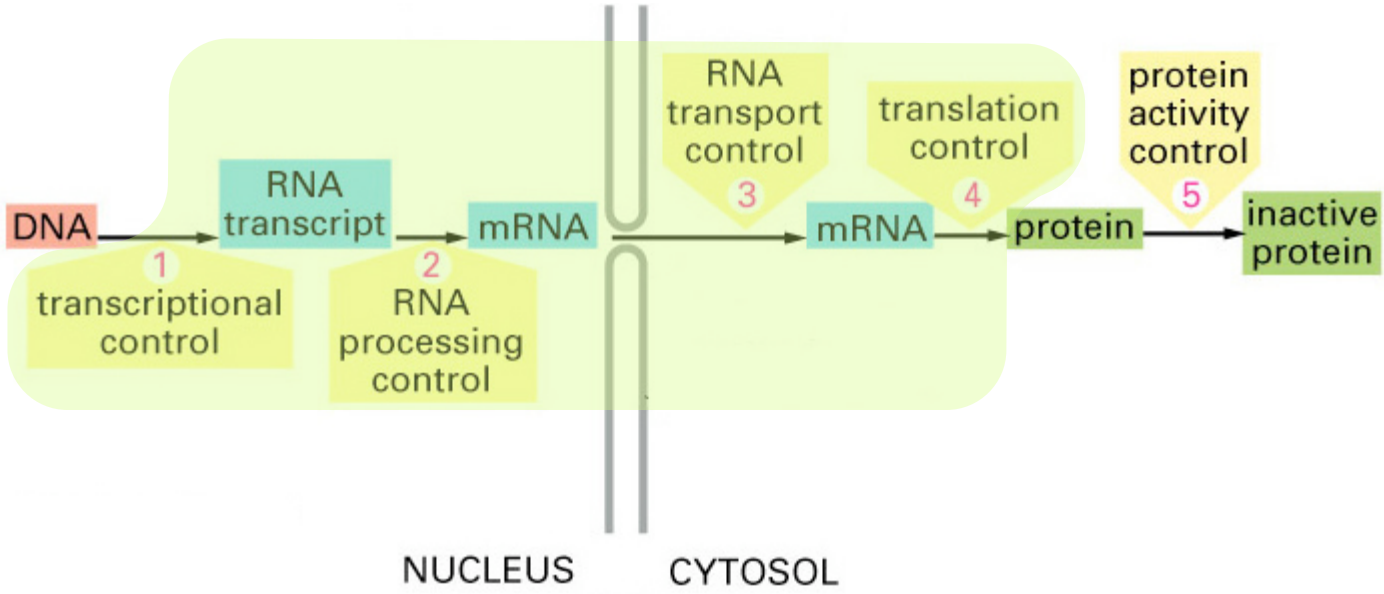
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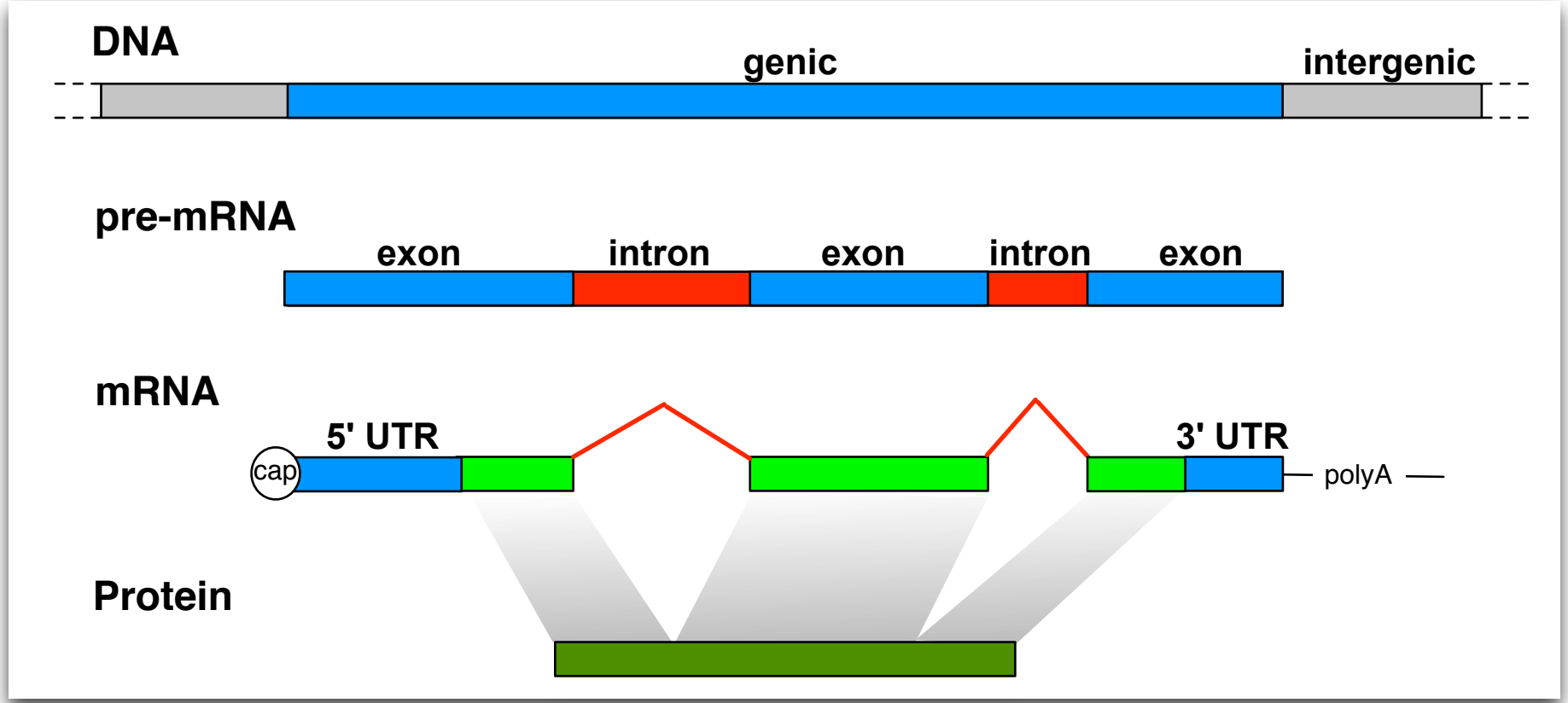
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1st Step: Gene Finding



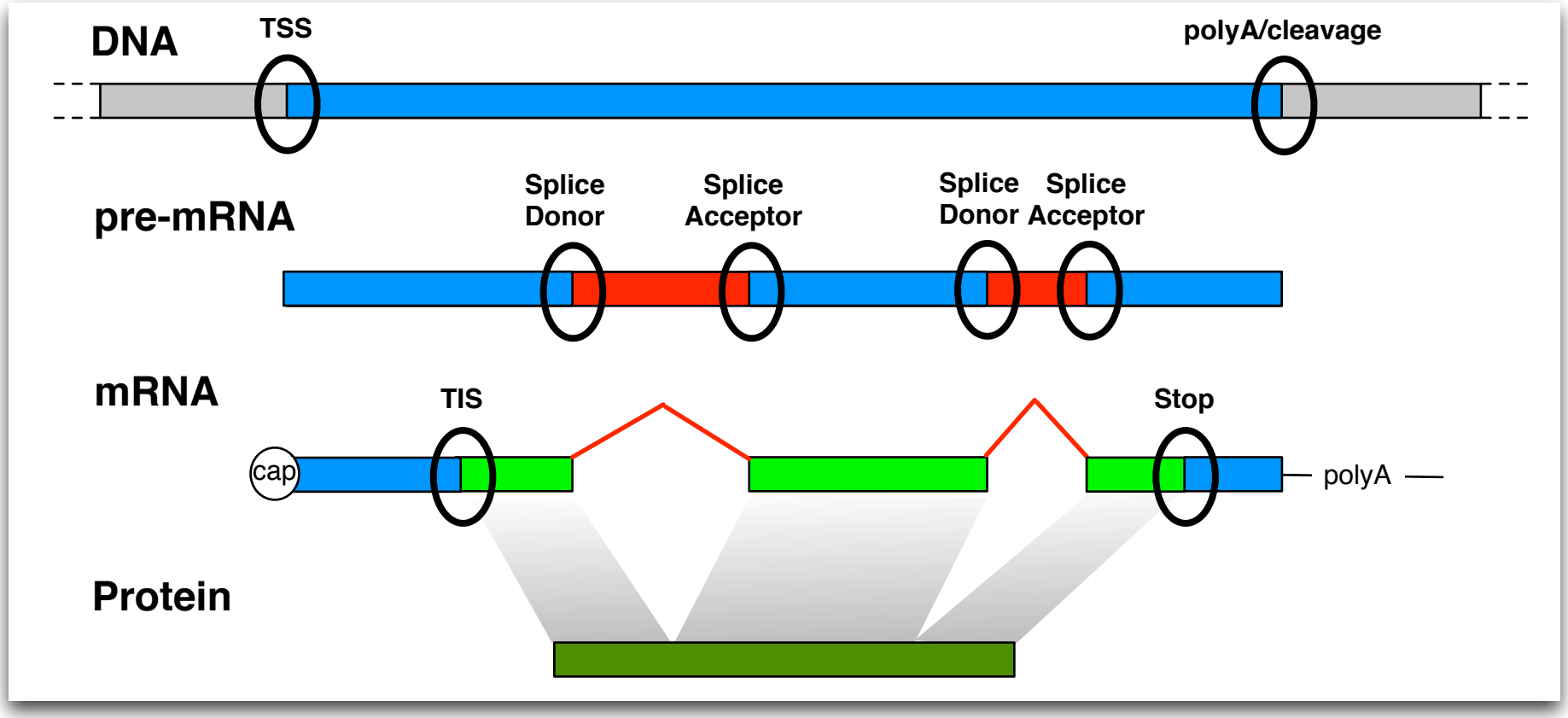
- Given a piece of DNA sequence
- Predict gene products

1st Step: Gene Finding



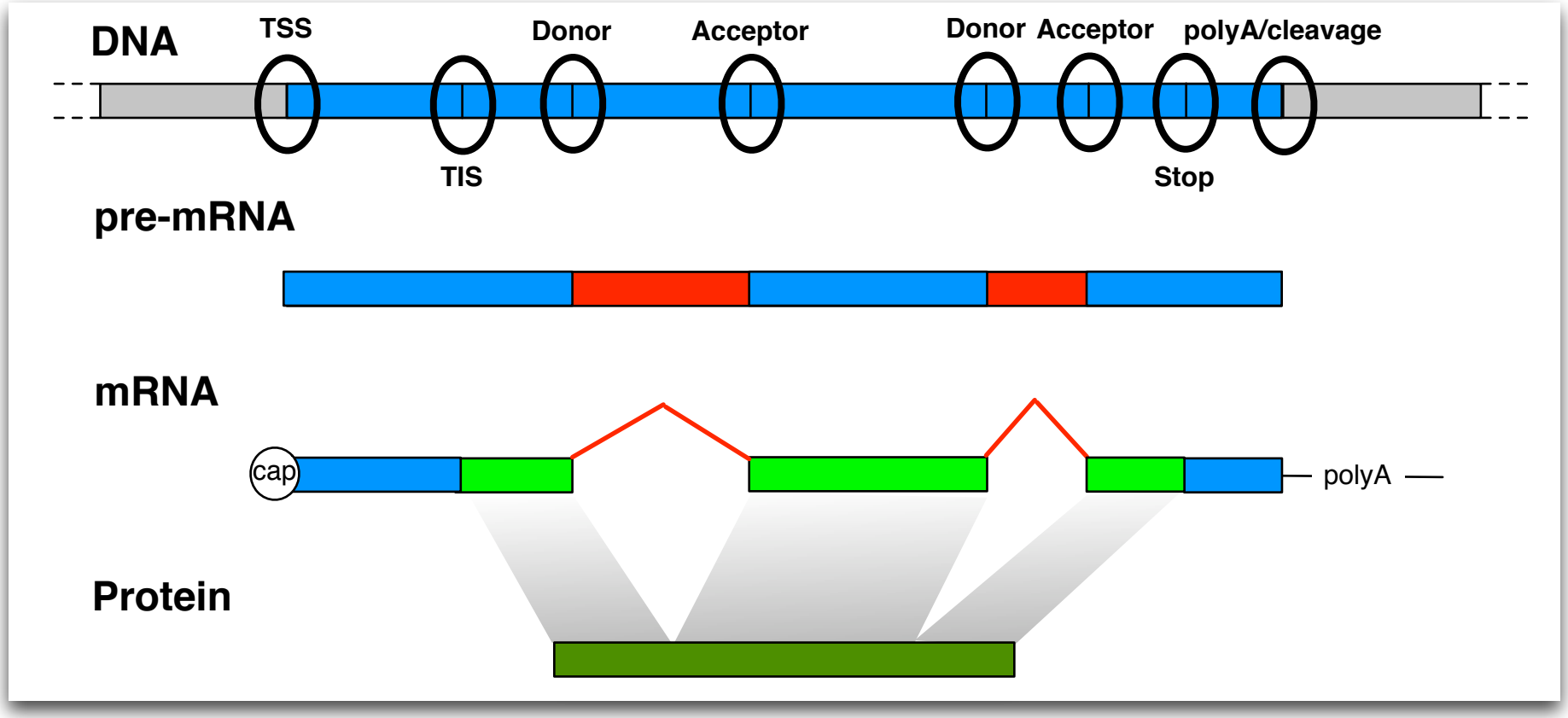
- Given a piece of DNA sequence
- Predict gene products inluding the intermediate processing steps

1st Step: Gene Finding



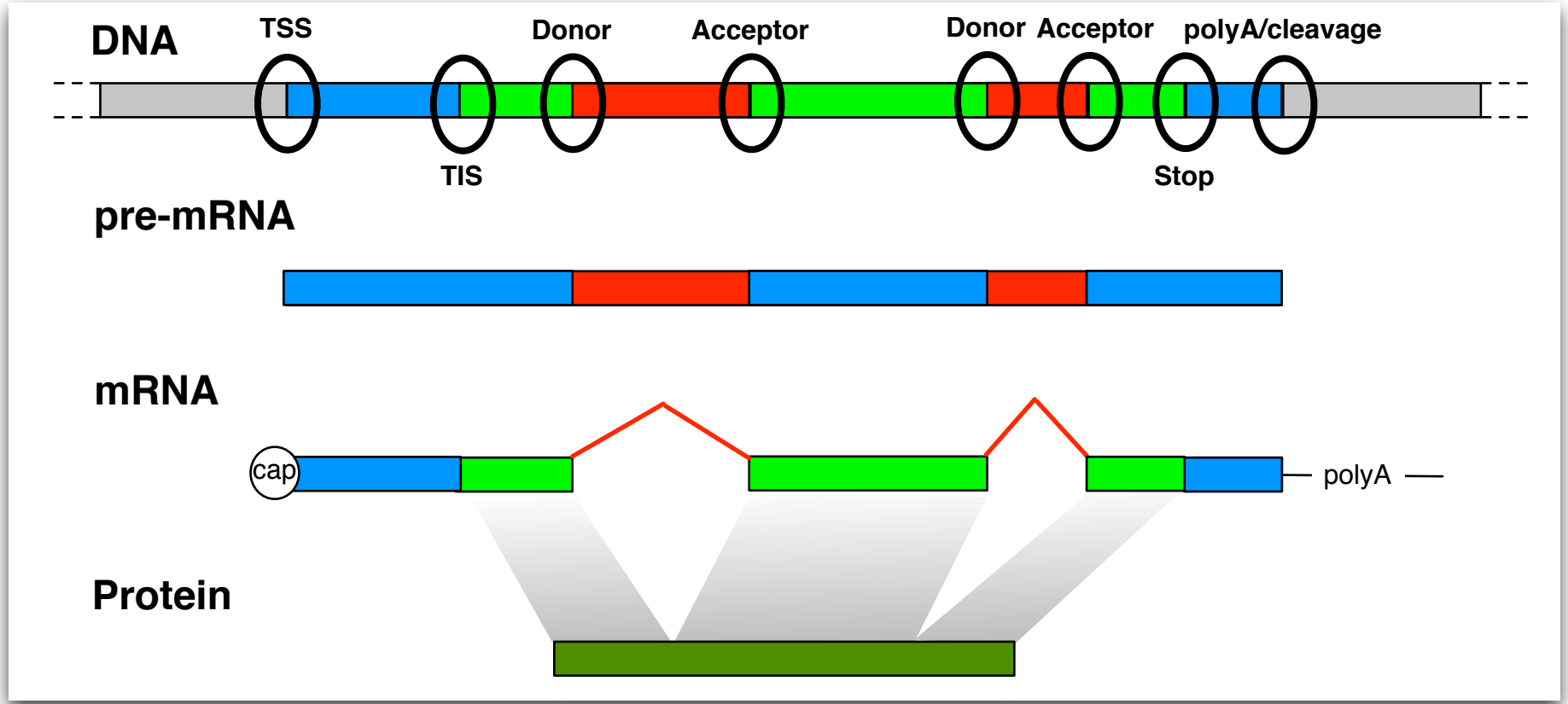
- Predict signals used during processing

1st Step: Gene Finding



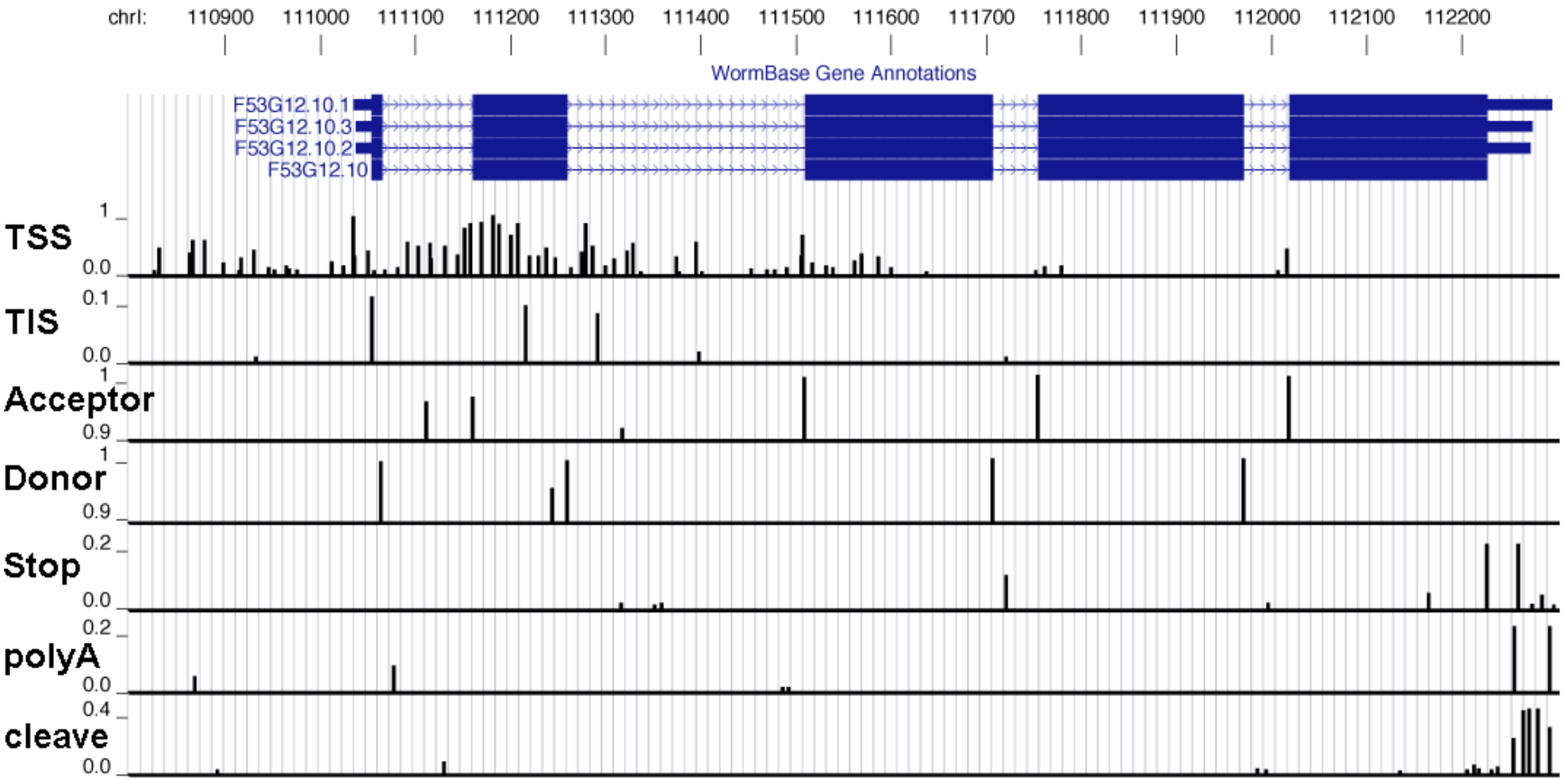
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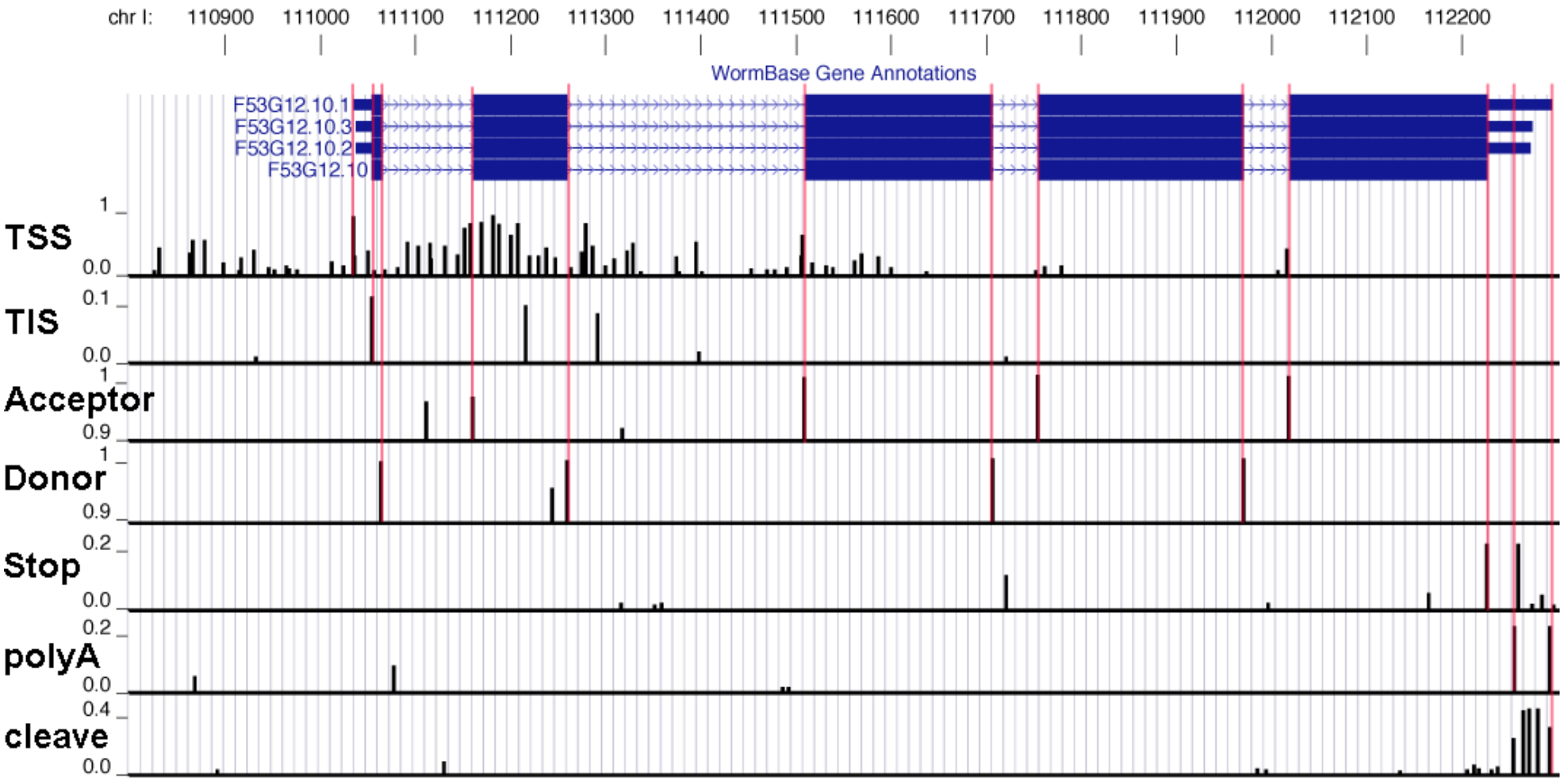
- Predict signals used during processing
- Predict the correct corresponding **label sequence** with labels "intergenic", "exon", "intron", "5' UTR", etc.

Example: Predictions in UCSC Browser



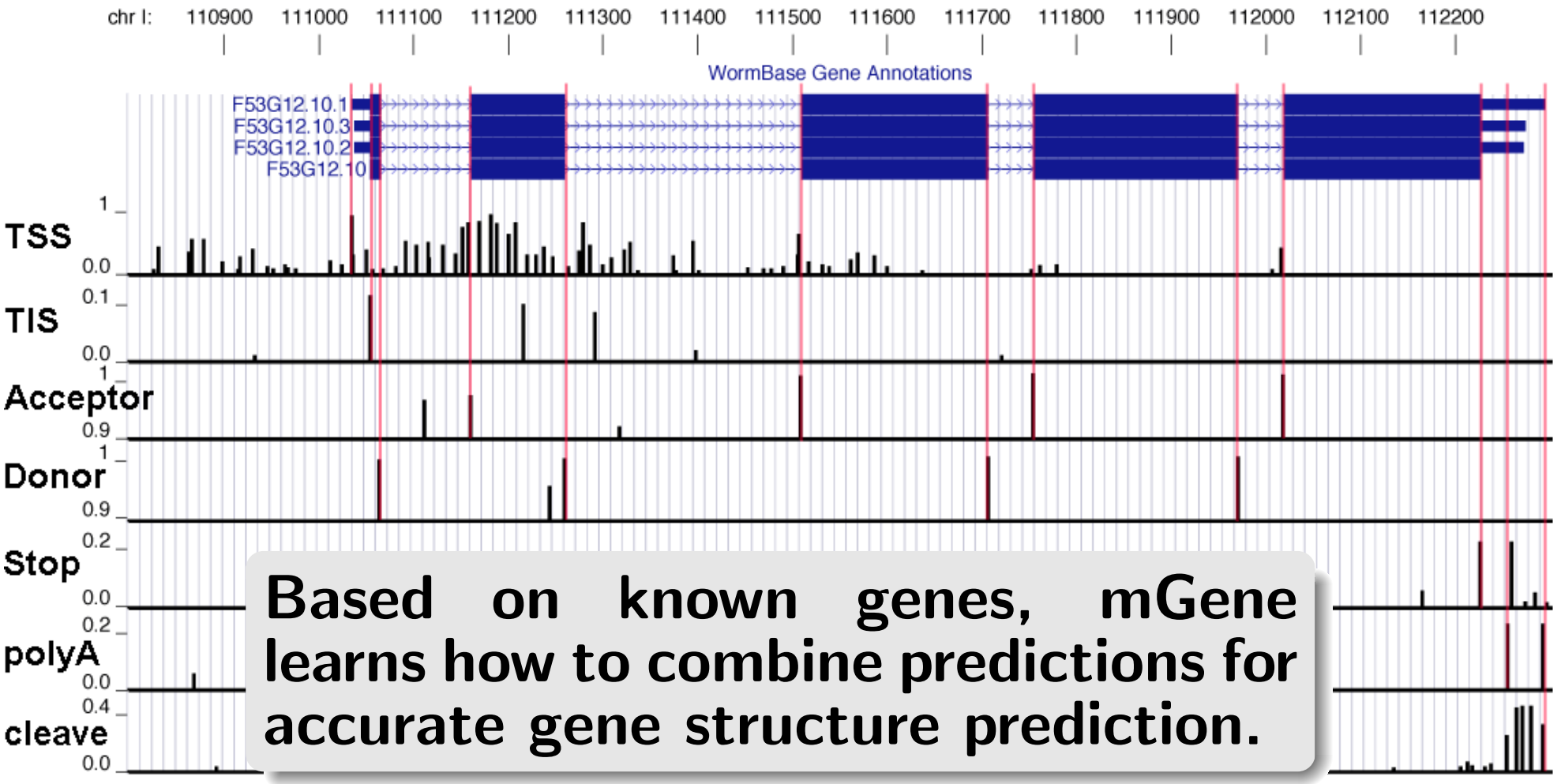
[Rätsch et al., 2007, Schweikert et al., 2009b]

Example: Predictions in UCSC Browser



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Example: Predictions in UCSC Browser



Based on known genes, mGene learns how to combine predictions for accurate gene structure prediction.

[Rätsch et al., 2007, Schweikert et al., 2009b]

Results using mGene

- Most accurate *ab initio* method in the nGASP genome annotation challenge for *C. elegans* [Coghlan et al., 2008]
- Validation of gene predictions for *C. elegans*: [Schweikert et al., 2009b]

	No. of genes	No. of genes analyzed	Frac. of genes w/ expression
New genes	2,197	57	$\approx 42\%$
Missing unconf. genes	205	24	$\approx 8\%$

- Annotation of other nematode genomes: [Schweikert et al., 2009b]

Genome	Genome size [Mbp]	No. of genes	No. exons/gene (mean)	mGene accuracy	best other accuracy
C. remanei	235.94	31503	5.7	**96.6%**	93.8%
C. japonica	266.90	20121	5.3	**93.3%**	88.7%
C. brenneri	453.09	41129	5.4	**93.1%**	87.8%
C. briggsae	108.48	22542	6.0	**87.0%**	82.0%

- Web service for *ab initio* gene predictions [Schweikert et al., 2009a]

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Limitations/Extensions

- Gene finding (by far) still not perfect
  - New *ab initio* techniques more accurate
  - Many genes mis-predicted (*C. elegans*: $\approx 50\%$; human: $\approx 80\%$)
  - What is missing?
    - Not enough examples for training?
    - Model complexity?
    - Other information?
- Transcriptome is the result of many complex processes
  - *Ab initio* methods cannot predict alternative transcripts
  - Current methods also ignore other important information:
    - Chromatin structure and methylation patterns
    - RNA structure and processing regulation ...
- New experimental data gives hope to towards more accurate predictive models

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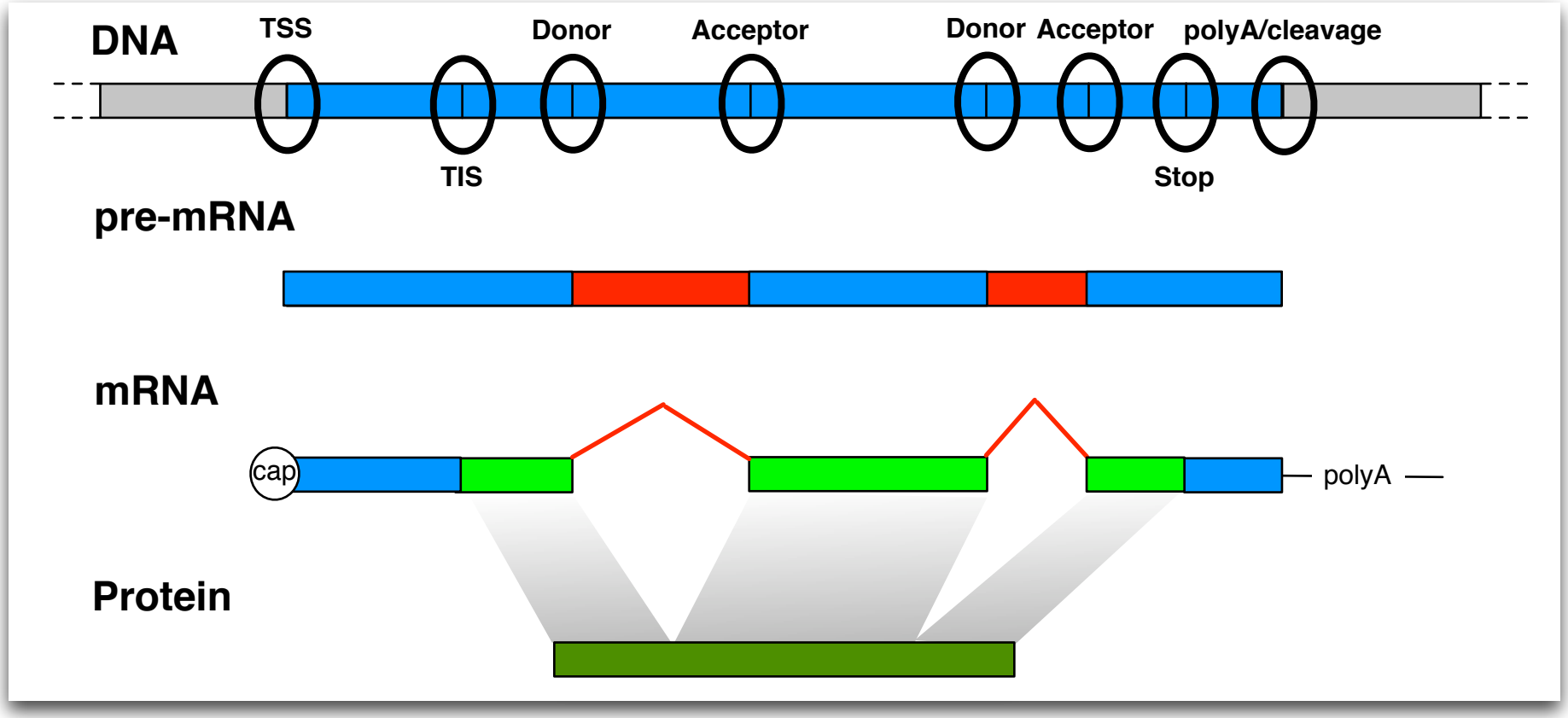
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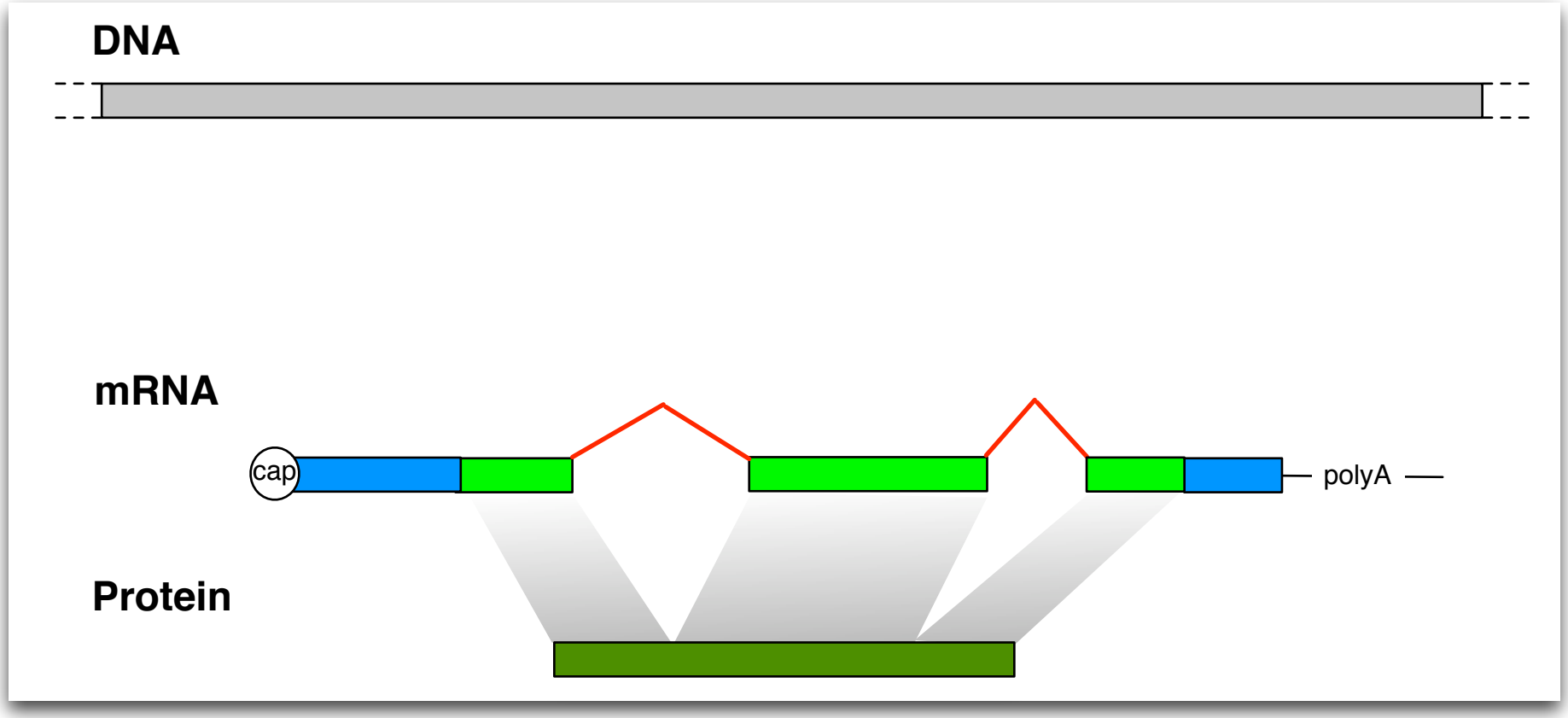
From Genome to Products



Directly measure the transcriptome

- Whole genome tiling arrays
- Transcriptome sequencing (Sanger or Next Generation Sequencing)

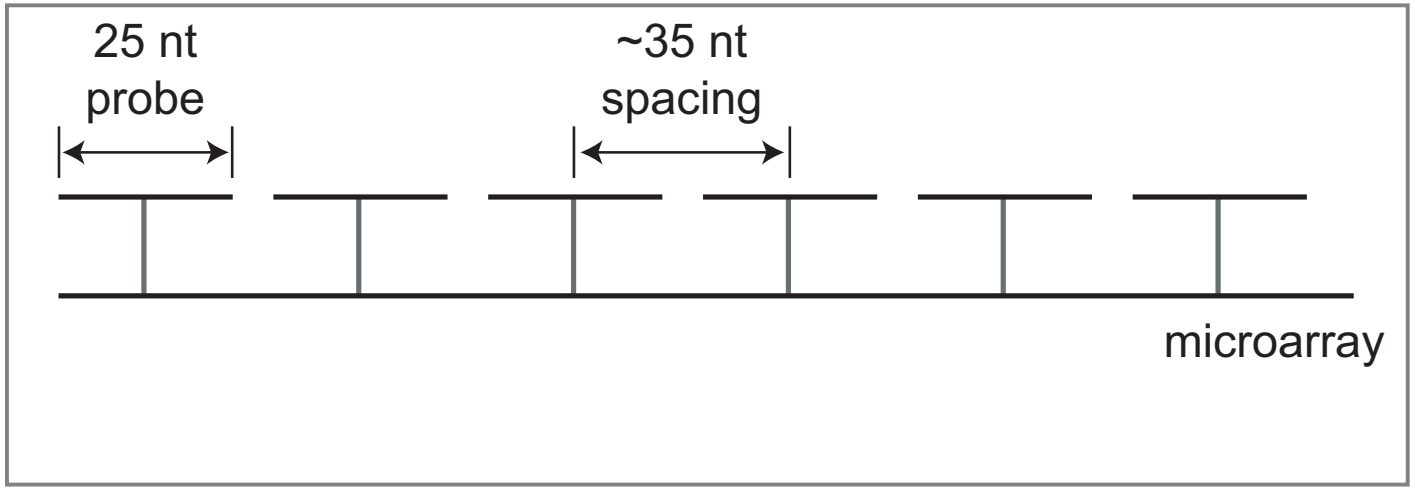
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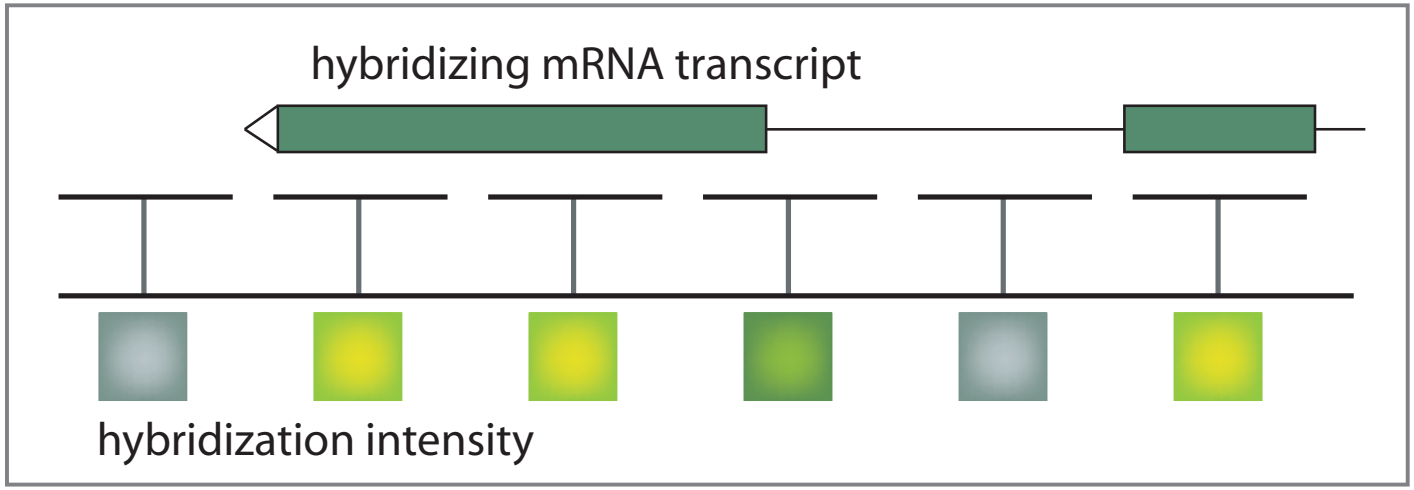
Tiling Arrays for Transcriptome Analysis



- Whole-genome quantitative measurements
- Cost-effective
  - ⇒ Replicates affordable, many tissues / mutants / conditions
- Unbiased
  - ⇒ Do not rely on annotations or known ESTs

(Work in collaboration with Detlef Weigel's lab, Max Planck Institute for Developmental Biology)

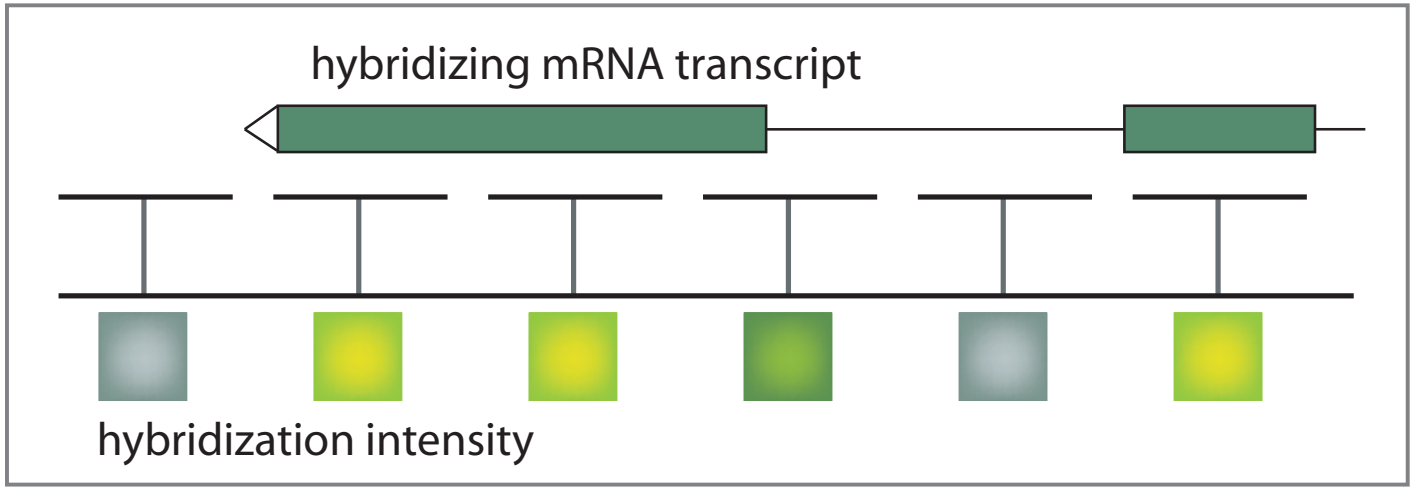
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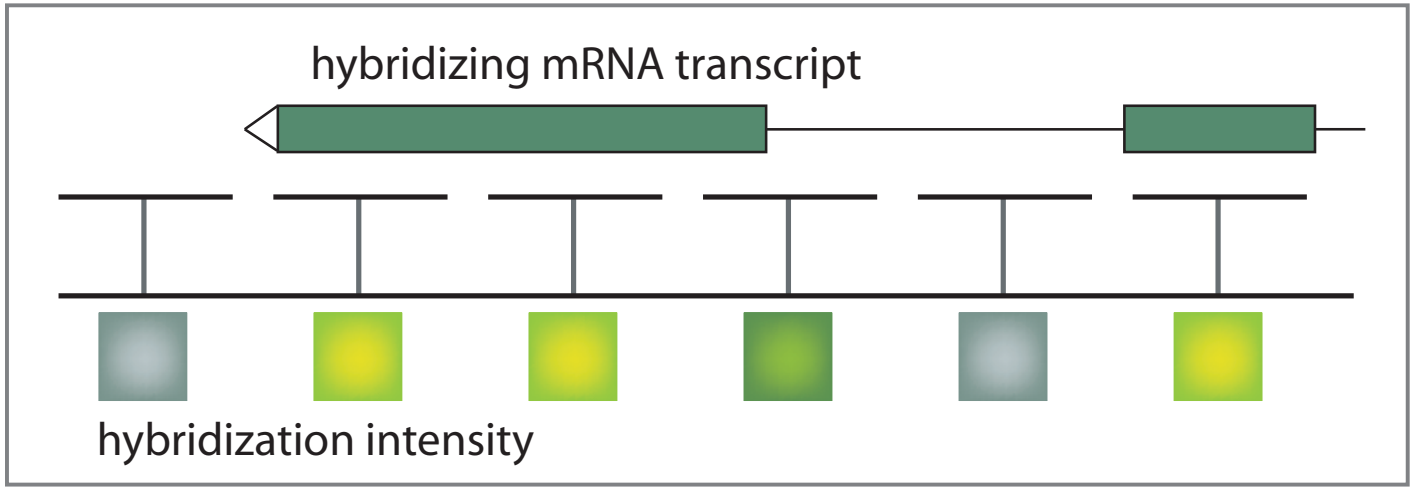
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[Laubinger et al., 2008b]

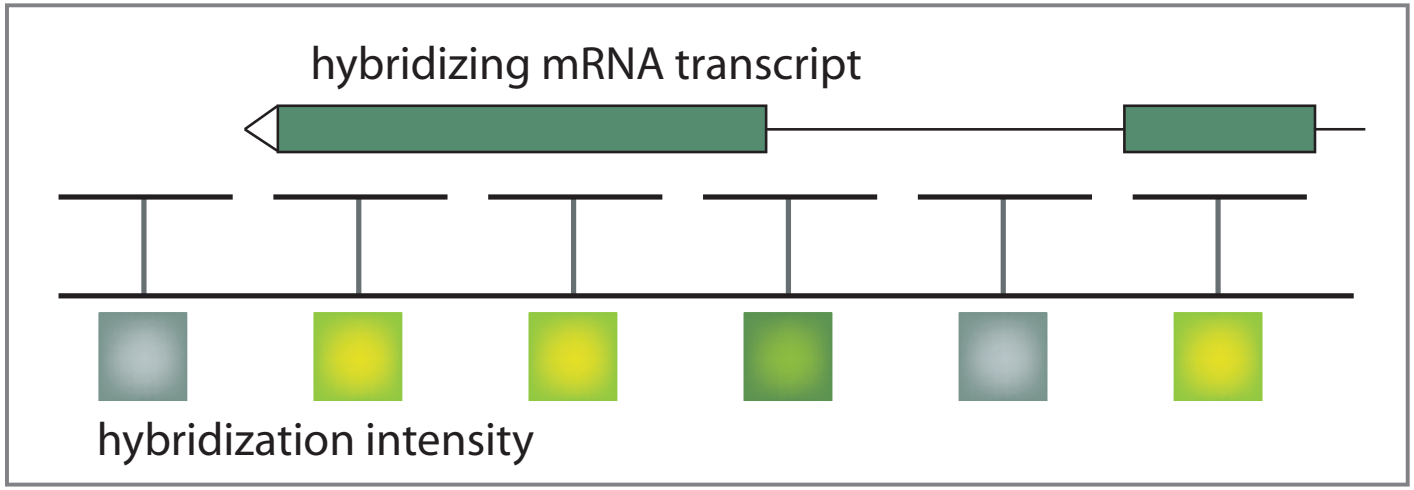
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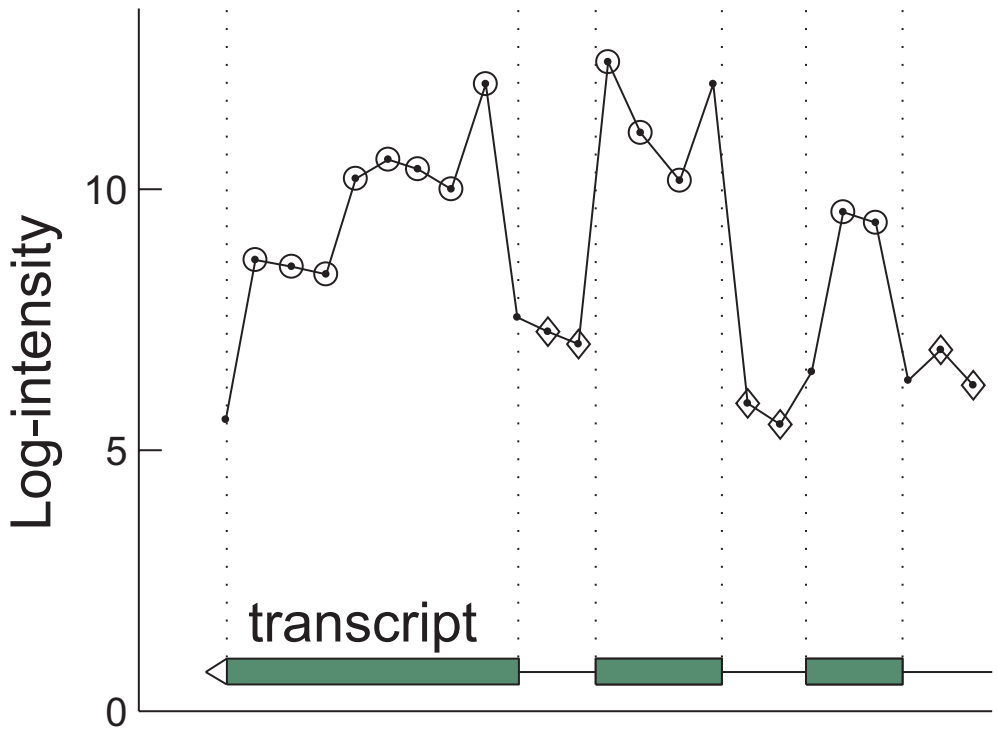
Tiling Arrays for Transcriptome Analysis



- Whole-genome quantitative measurements
- Cost-effective
  - ⇒ Replicates affordable, many tissues / mutants / conditions
- Unbiased
  - ⇒ Do not rely on annotations or known cDNAs
  - ⇒ For known genes, gives similar results as traditional microarrays

[Laubinger et al., 2008b]

Intensities are Noisy Measurements

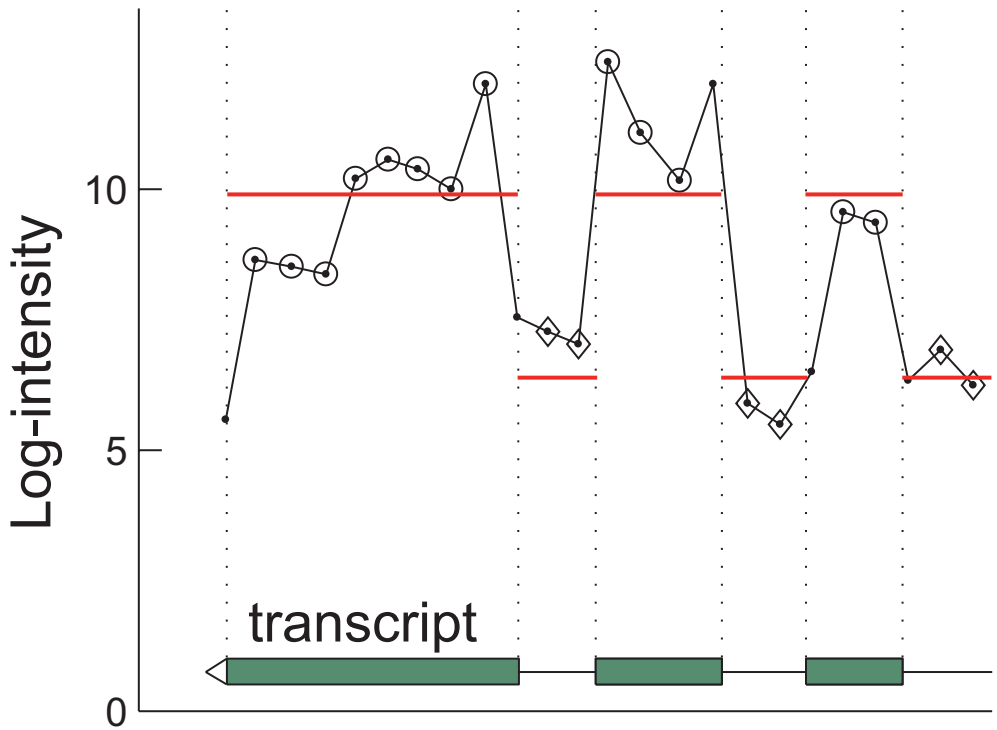


- observed intensity
- annotated exonic
- annotated intronic

Systematic bias induced by probe sequence effects

$\Rightarrow$ Model effect for normalization [Zeller et al., 2008b]

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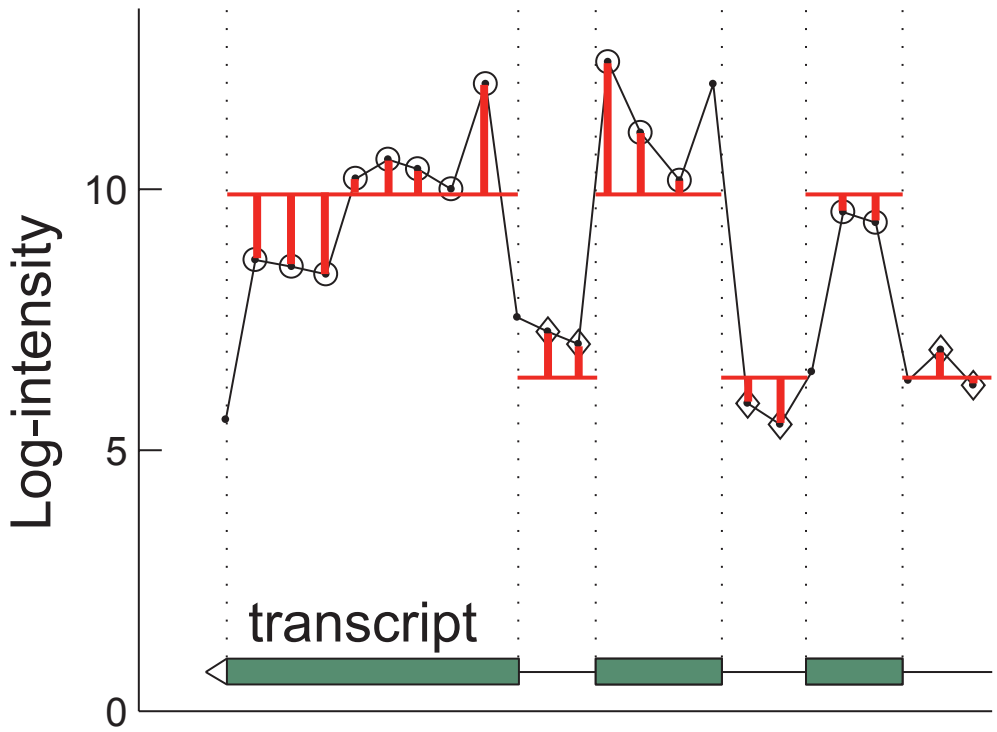


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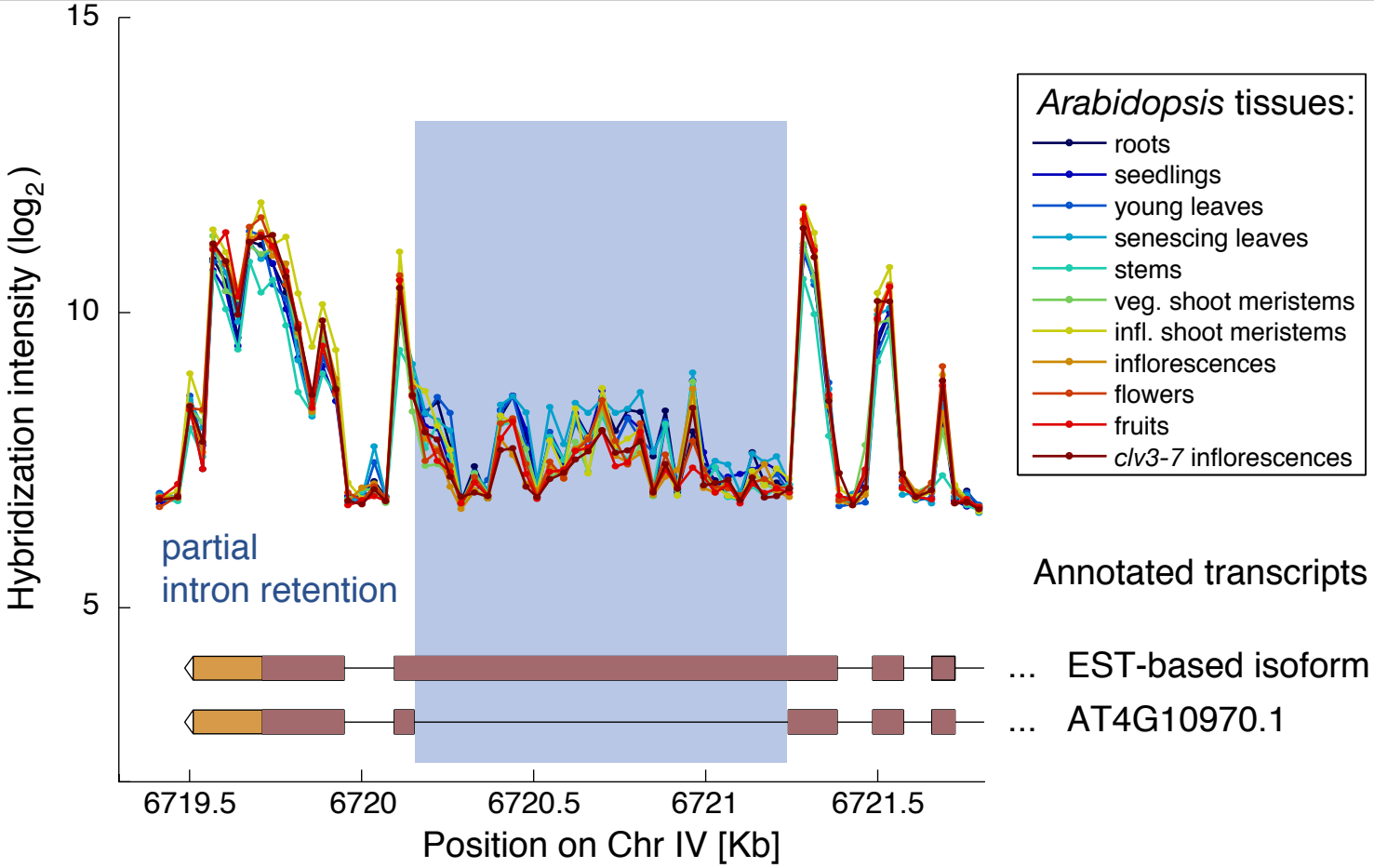


- observed intensity
- annotated exonic
- annotated intronic
- "ideal noise-free intensity"
- fold difference δ between observed and transcript intensity

Systematic bias induced by probe sequence effects

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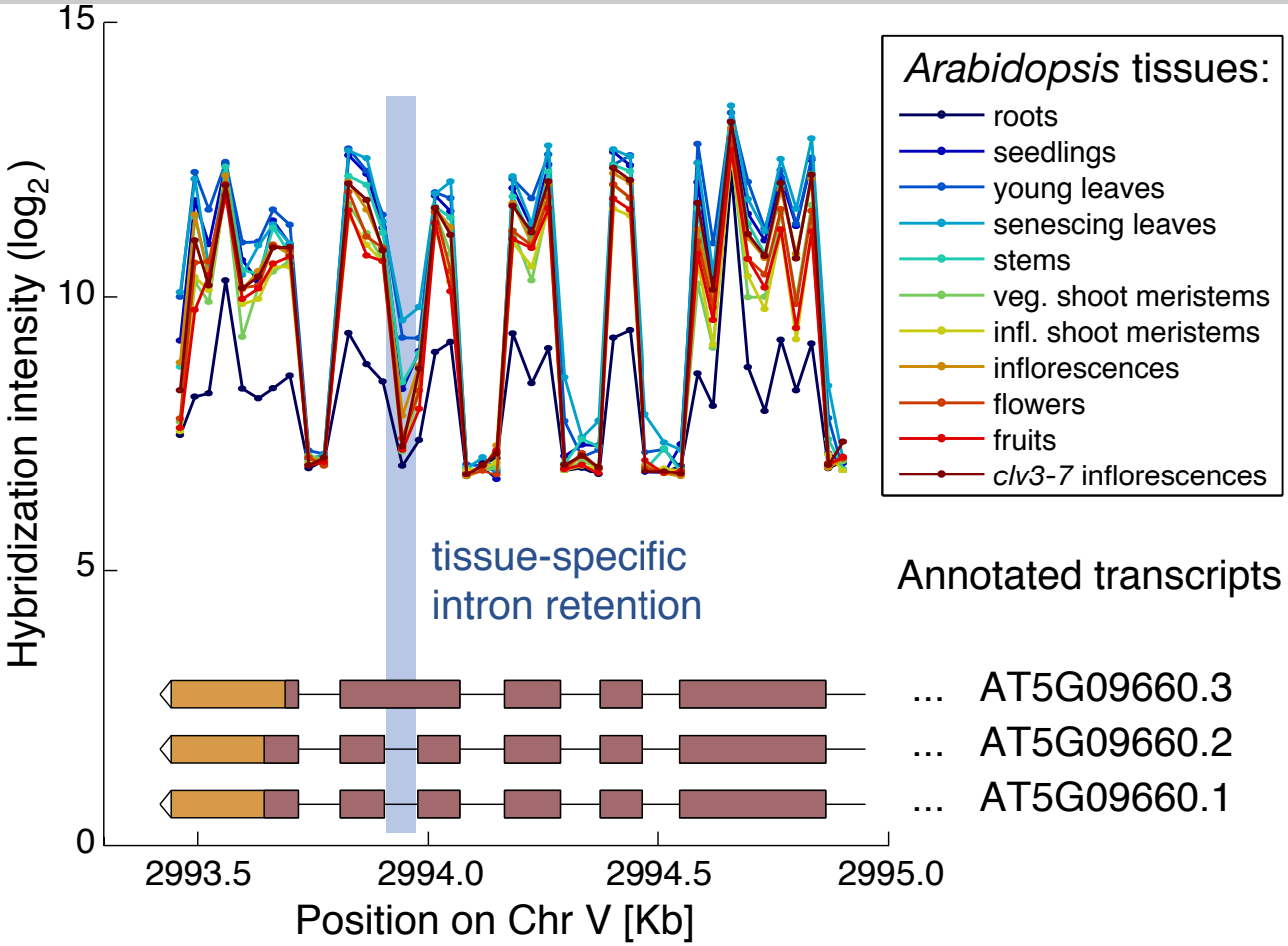
Alternatively Spliced Genes



Goal: Identify exon/intron segments that show different intensities than *other exons/introns* in at least one analyzed sample.

[Eichner et al., 2009, in prep.]

Differentially Spliced Genes



Goal: Identify exon/intron segments that are *differentially* spliced in the analyzed samples. [Eichner et al., 2009, in prep.]

Genome-wide Analyses of Alternative Splicing

- *A. thaliana* transcriptomes in 11 different tissues, 5 different abiotic stresses, RNA processing mutants (3 replicates)
- 1^{st} exon/intron-resolution analysis in plants [Laubinger et al., 2008b]

- Identified ≈7,000 cases of intron retentions (est. FDR=14%)
- Many of them show differential splicing [Eichner et al., 2009, in prep.]

- Profiling cap-binding/miRNA processing mutants (CBP80/CBP20)

$\Rightarrow$ Influence splicing efficiency

$\Rightarrow$ 1^{st} intron often retained [Laubinger et al., 2008a]

Other analyses: under stresses & in small RNA biogenesis mutants

[Zeller et al., 2009, Laubinger et al., 2009, submitted]

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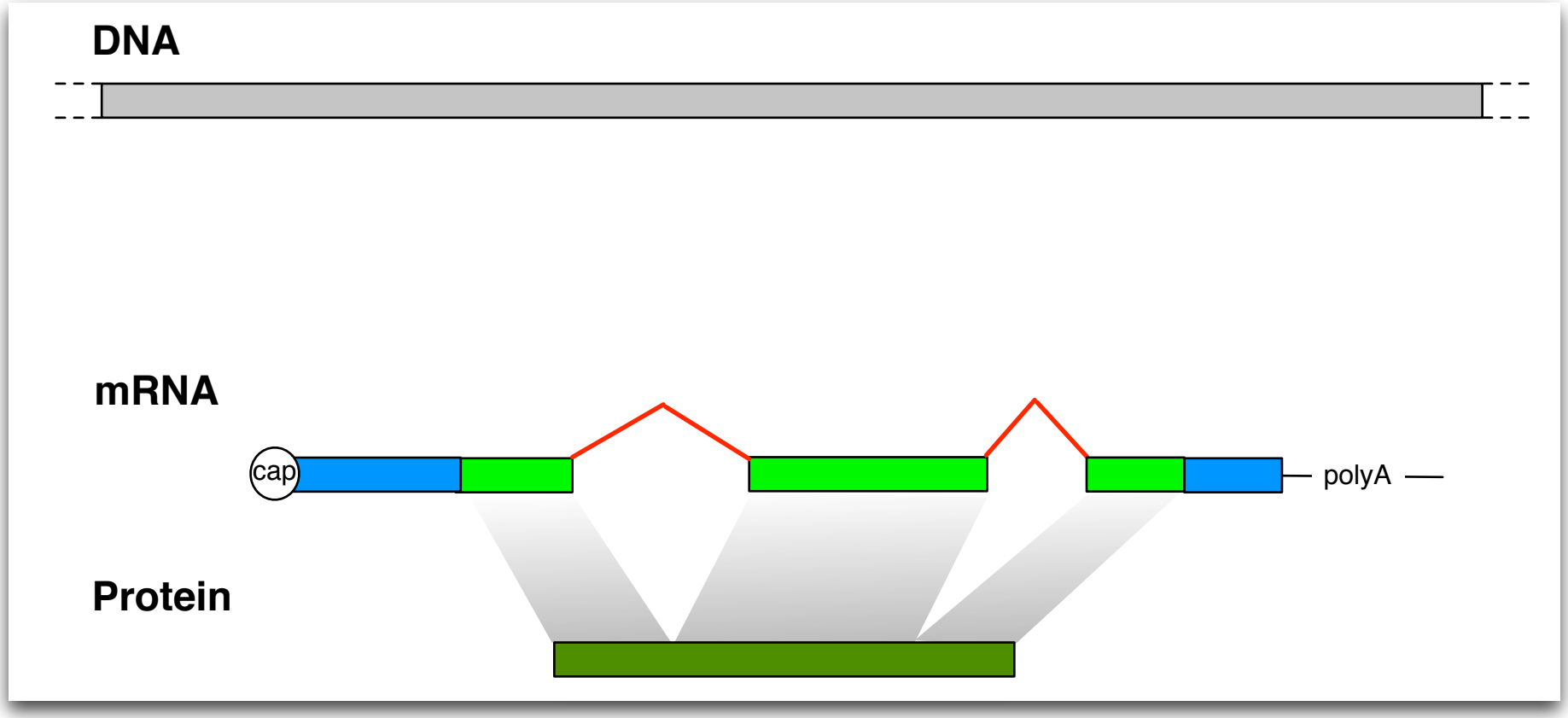
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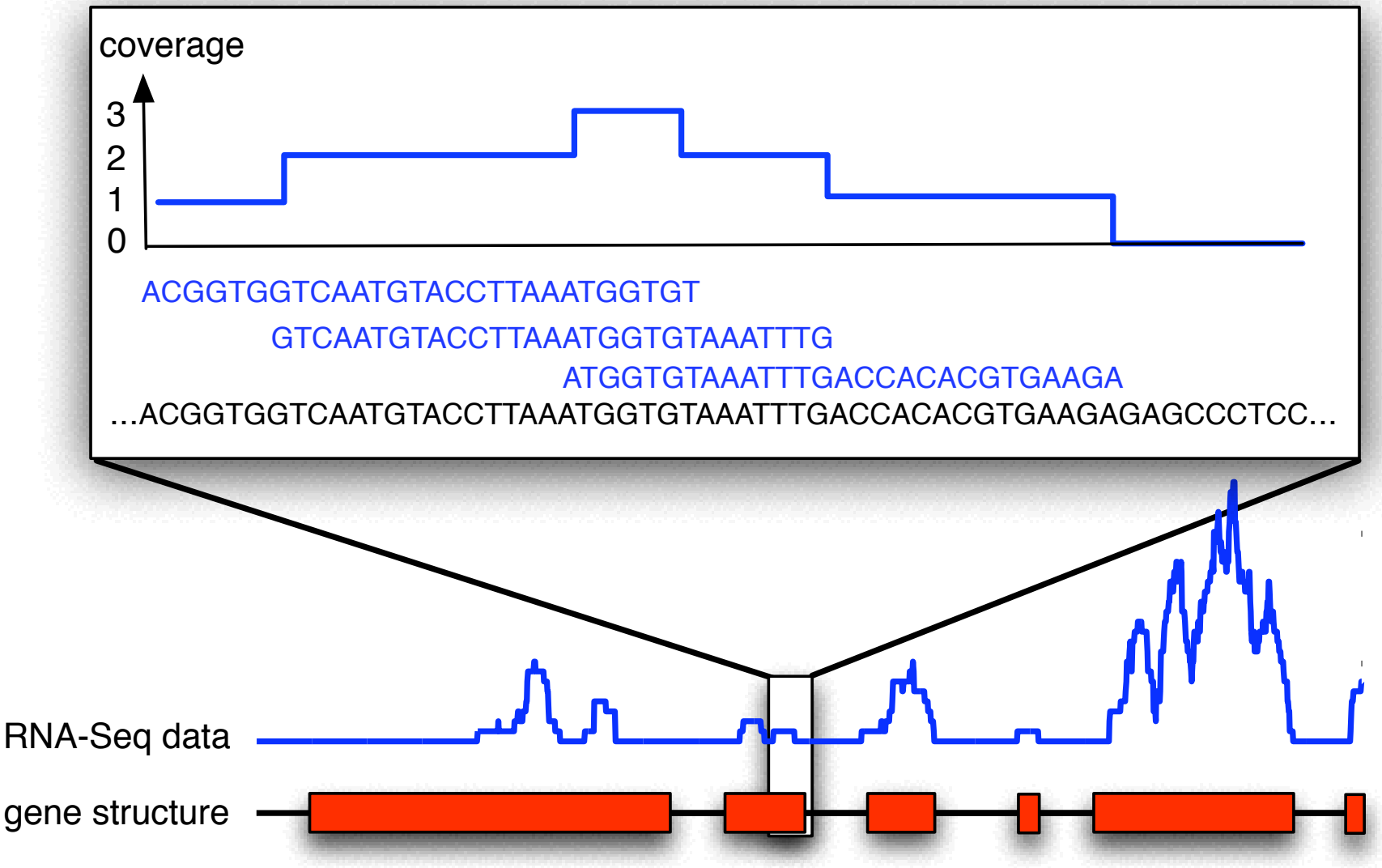
From Transcriptome to Products



Directly measure the transcriptome

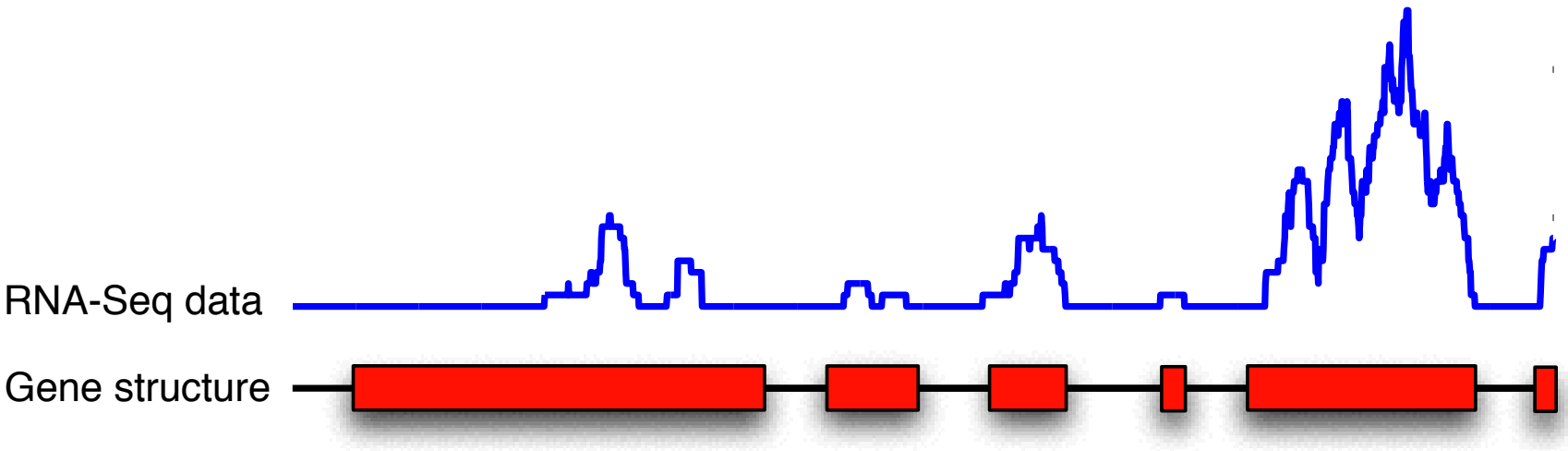
- Whole genome tiling arrays
- **Transcriptome sequencing** (Sanger or Next Generation Sequencing)

Next Generation Sequencing



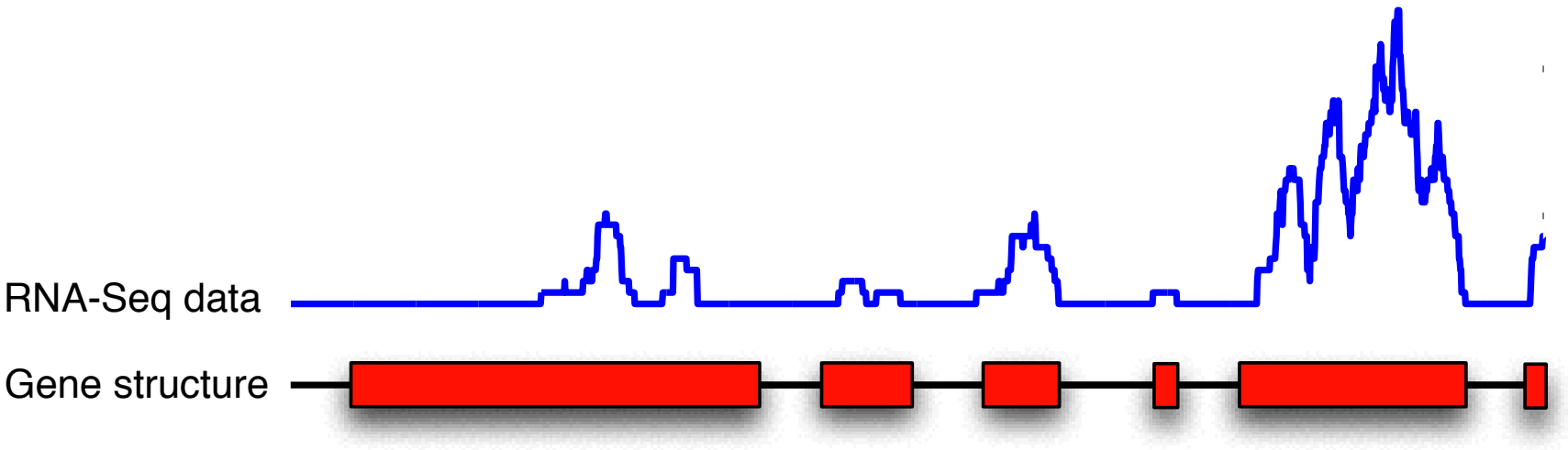
Next Generation Sequencing

```
...GCAAACCAGTGACCTGACTACTACGTCGTAACGTACACGGTAGCT....CCGTAGAATTGACTGTGTTG...
   GCAAACCAGTGACCTGACTACTACGTCGTAACGTAC
```

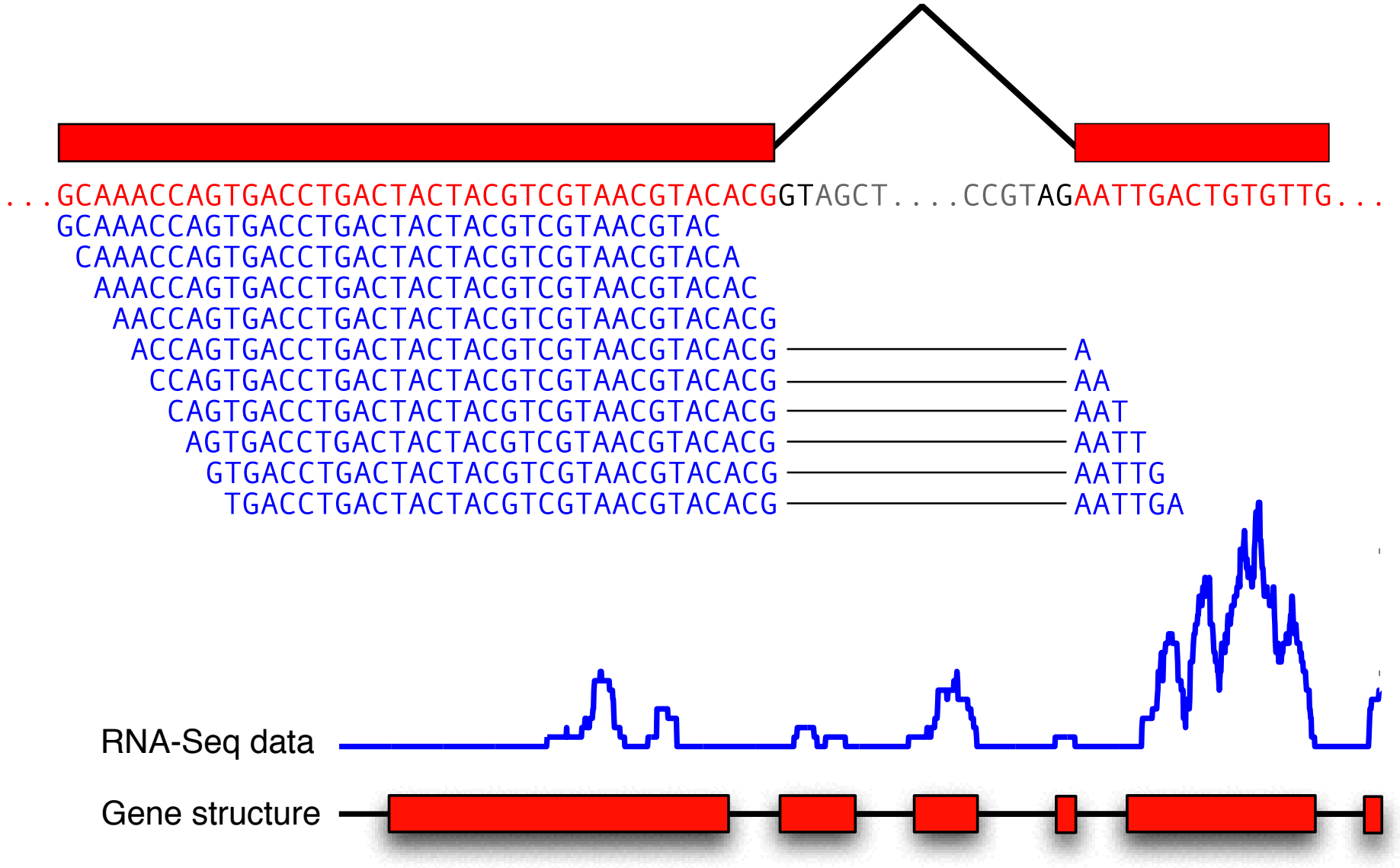


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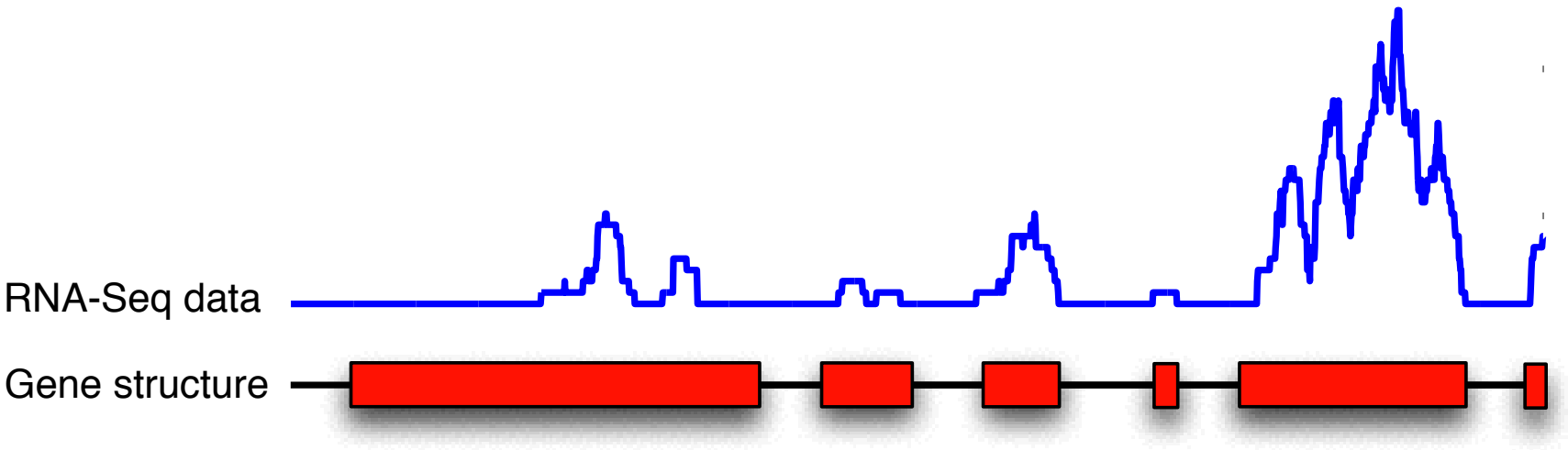


Next Generation Sequencing

RNA-seq reads for *A. thaliana* (collaboration with Dept. Weigel)

- 38nt reads from Illumina Genome Analyzer (polyA enriched)
- Read mapping using **ShoRe** [Ossowski et al., 2008]
- Spliced alignments using **QPalma** [De Bona et al., 2008]

  $\Rightarrow$ Considerably improved alignment accuracy

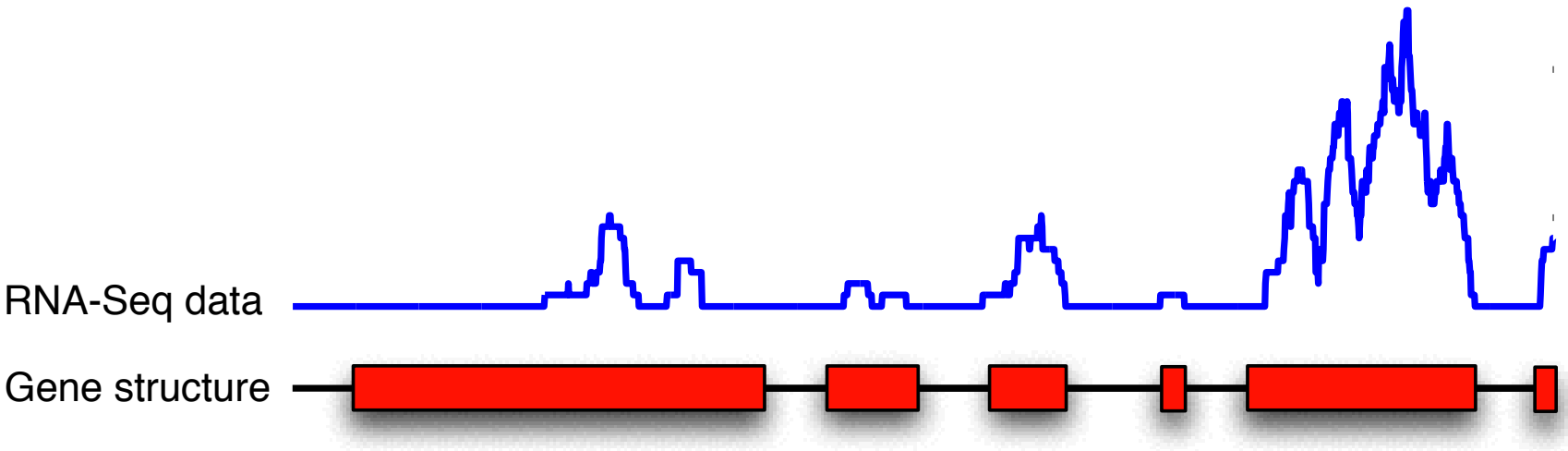


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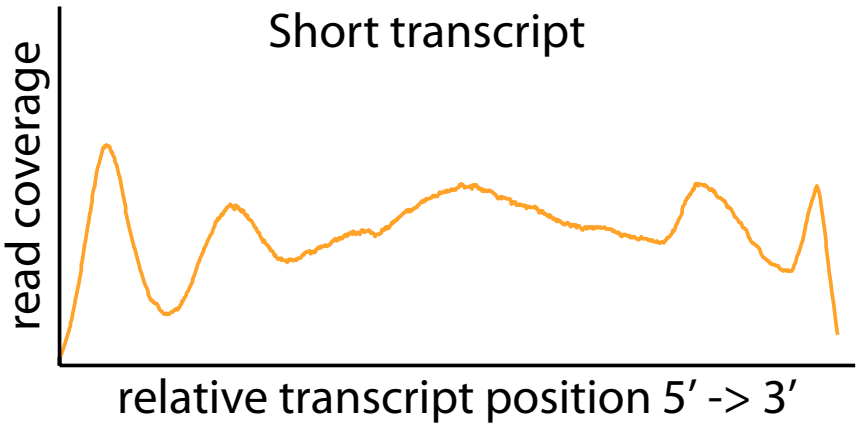
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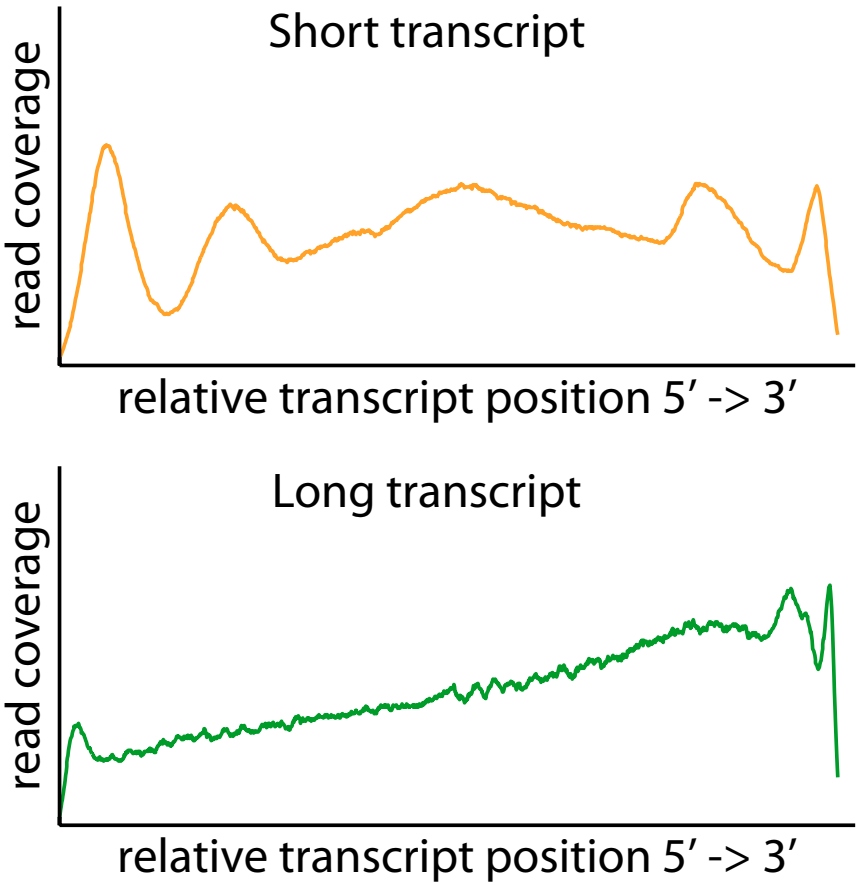


Transcript Quantification

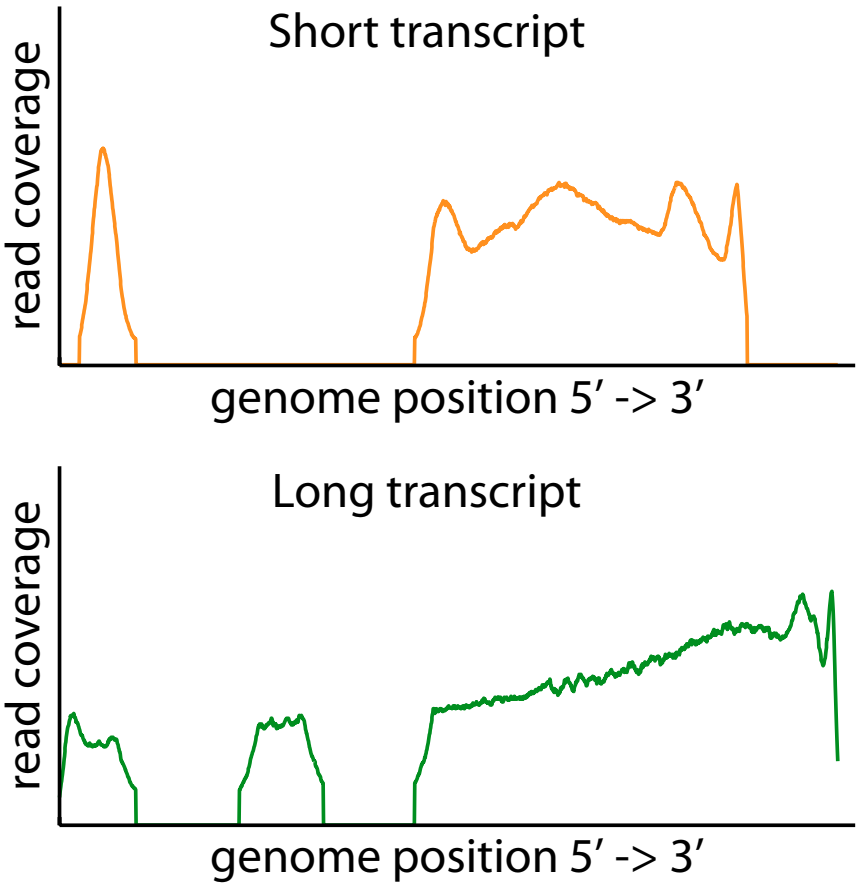




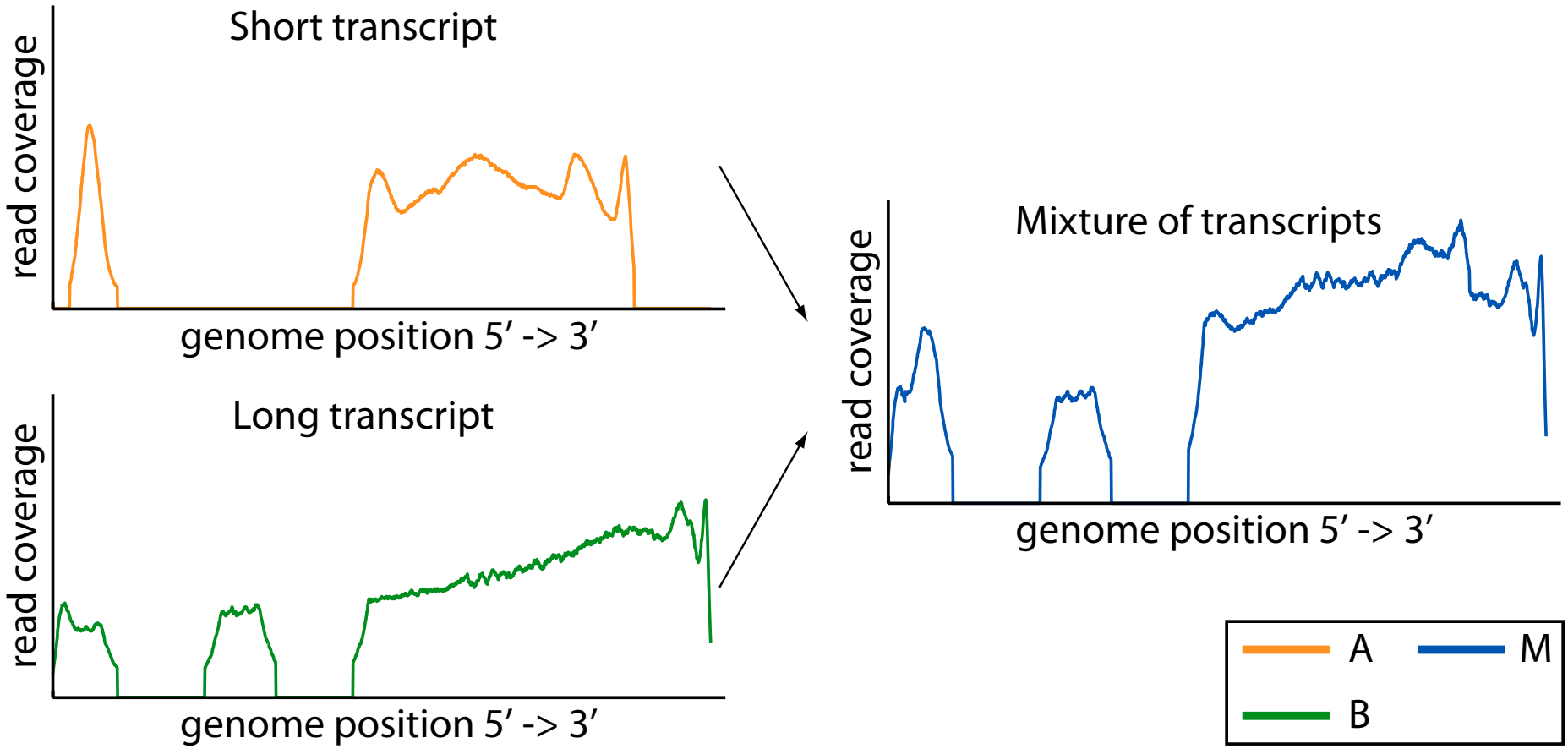
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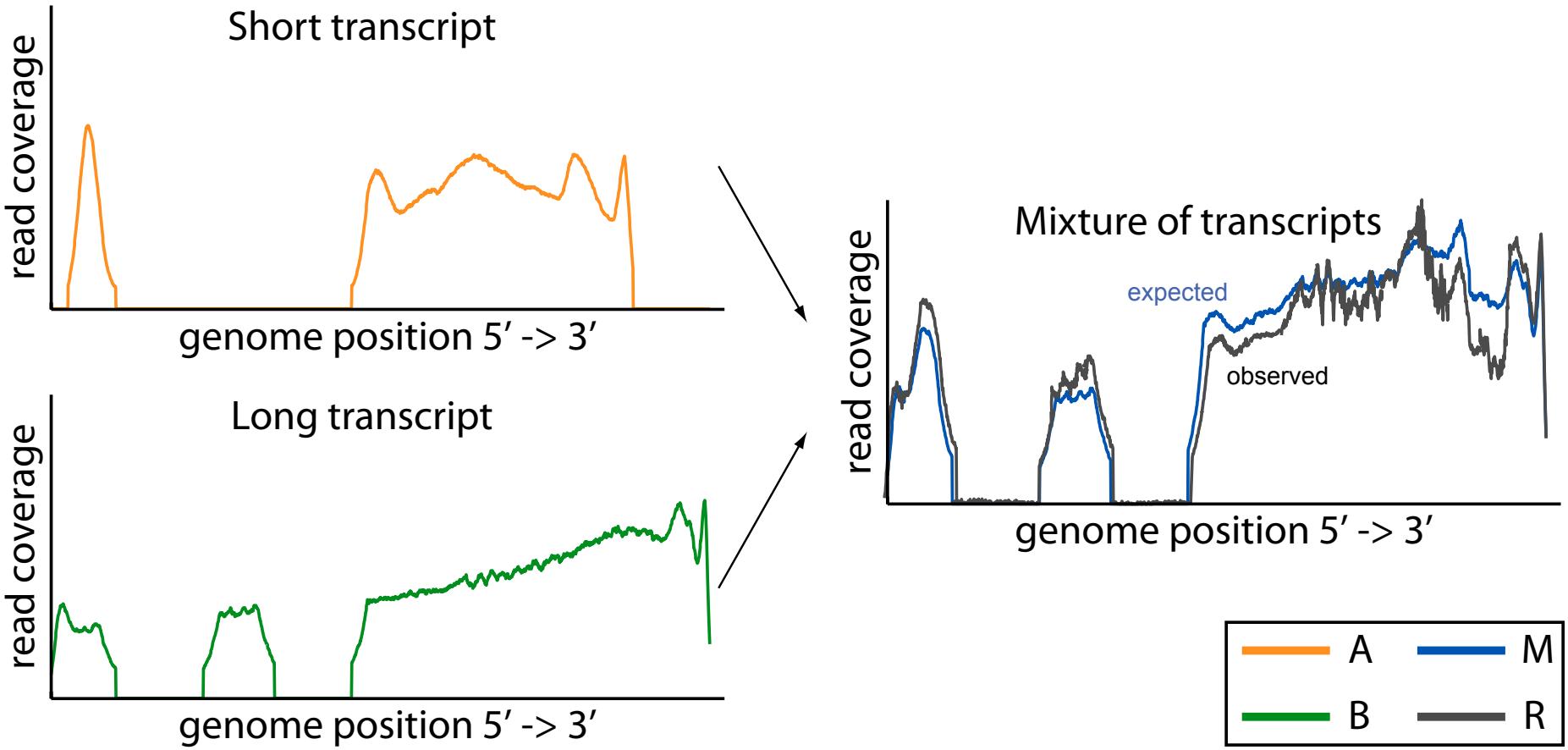
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$$M_i = w_A A_i + w_B B_i \quad \Rightarrow \quad \text{Determine plausible unmixing}$$

[Bohnert et al., 2009, in prep.]

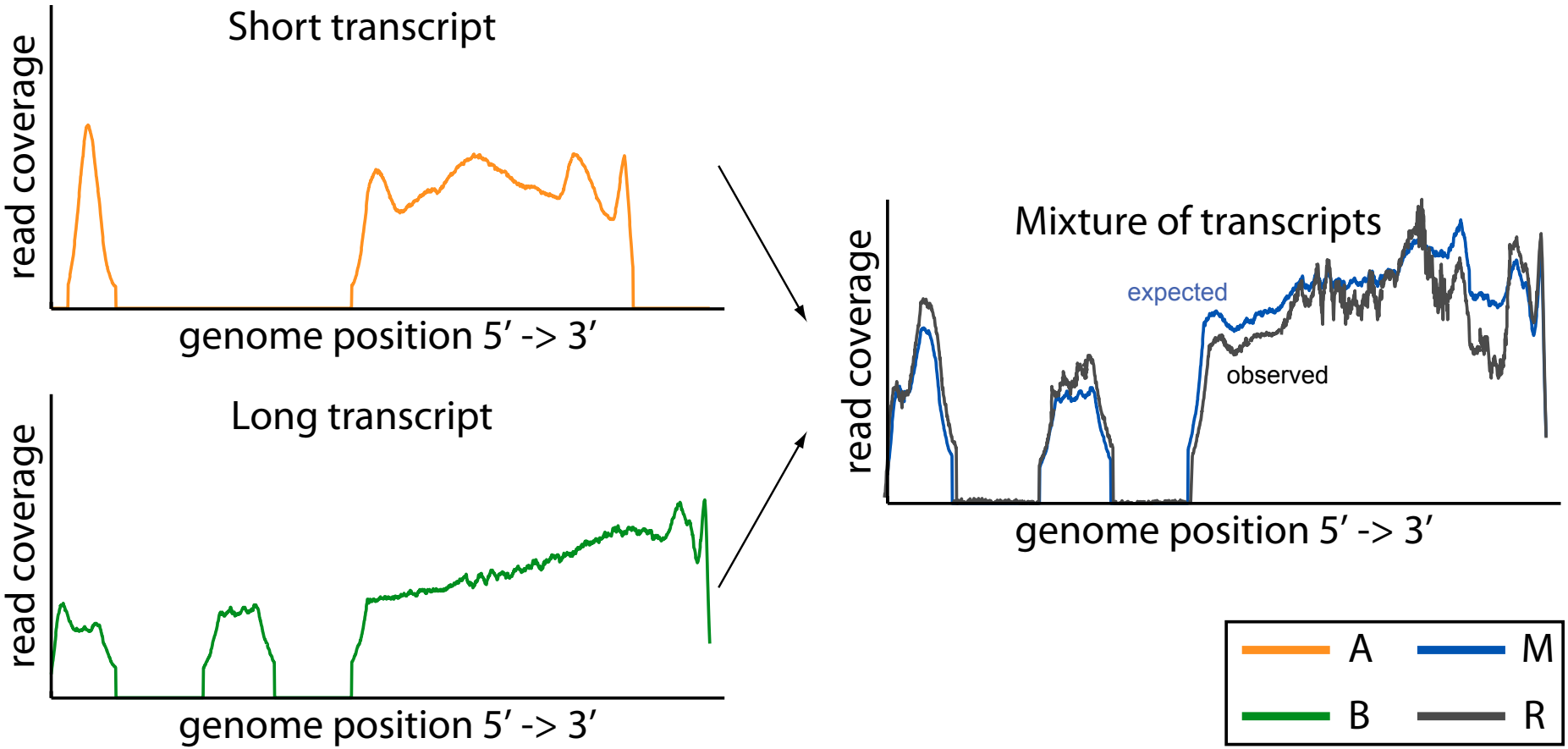
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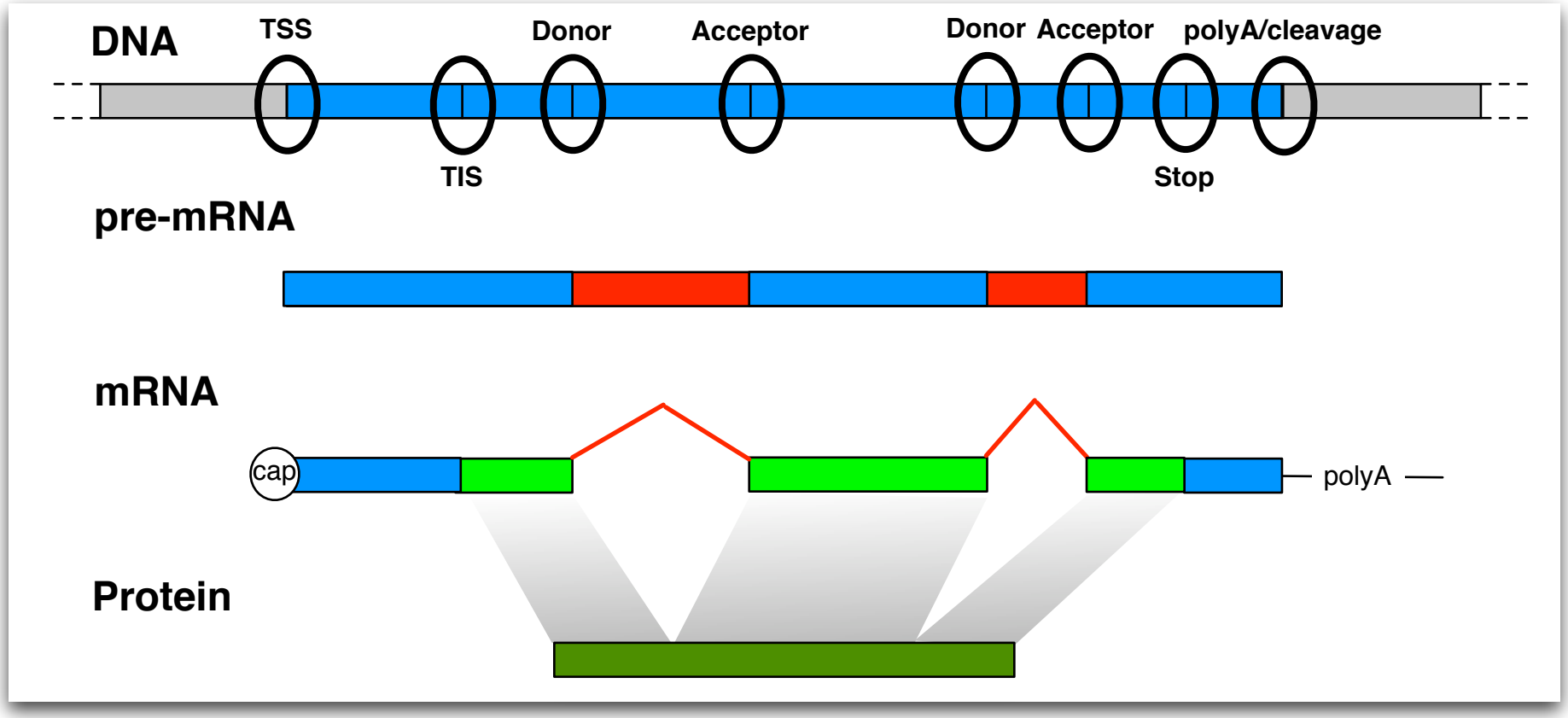
Transcript Quantification



Goals:

1. Determine abundances of (alternative) transcripts
2. *De novo* identify yet unknown transcripts [in preparation]

Gene Finding + Transcriptome Measurements



Combination

- Higher accuracy
- Condition/tissue specific predictions

Gene Finding + Transcriptome Measurements

Idea: Use transcriptome measurements to enhance recognition of exonic regions.

Results for A. thaliana: (Comparison with known gene models)

1. mGene (*ab initio*) . . .
   transcript level performance: **mean(SN, SP) = 73.0%**
2. . . . with tiling arrays (11 tissues)
   transcript level performance: **mean(SN, SP) = 81.6%**
3. . . . with mRNA-seq (1 tissue)
   transcript level performance: **mean(SN, SP) = 81.4%**
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Conclusions

- Methods for characterizing transcriptomes
  - in different organisms
  - under different conditions (development/environment)
- Gene finding methods
  - Improved accuracy due to novel inference methods
  - Limitations: no alternative transcripts or expression information
- Analysis of transcriptome measurements
  - Identification of alternative and differential transcripts
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