Advanced Bioinformatics

Biostatistics & Medical Informatics 776

Computer Sciences 776

Spring 2021

Daifeng Wang

daifeng.wang@wisc.edu

www.biostat.wisc.edu/bmi776/

Agenda Today

- Introductions
- Course information
- Overview of topics

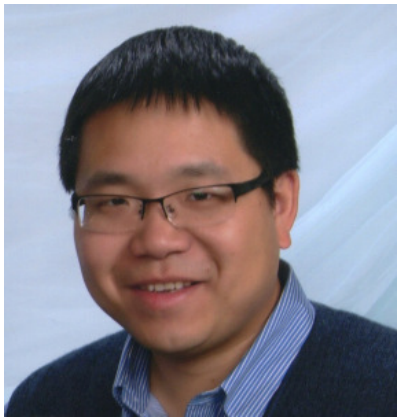
Course Web Site

- www.biostat.wisc.edu/bmi776/
- Syllabus and policies
- Readings
- Tentative schedule
- Lecture slides (draft posted before lecture)
- Announcements
- Homework
- Project information
- Link to Piazza discussion board

Lecture time and location

- Tuesday and Thursday, 1:00-2:15 PM Blackboard Collaborate Ultra Canvas (virtual)
- https://www.biostat.wisc.edu/bmi776/schedule.html

Your Instructor: Daifeng Wang



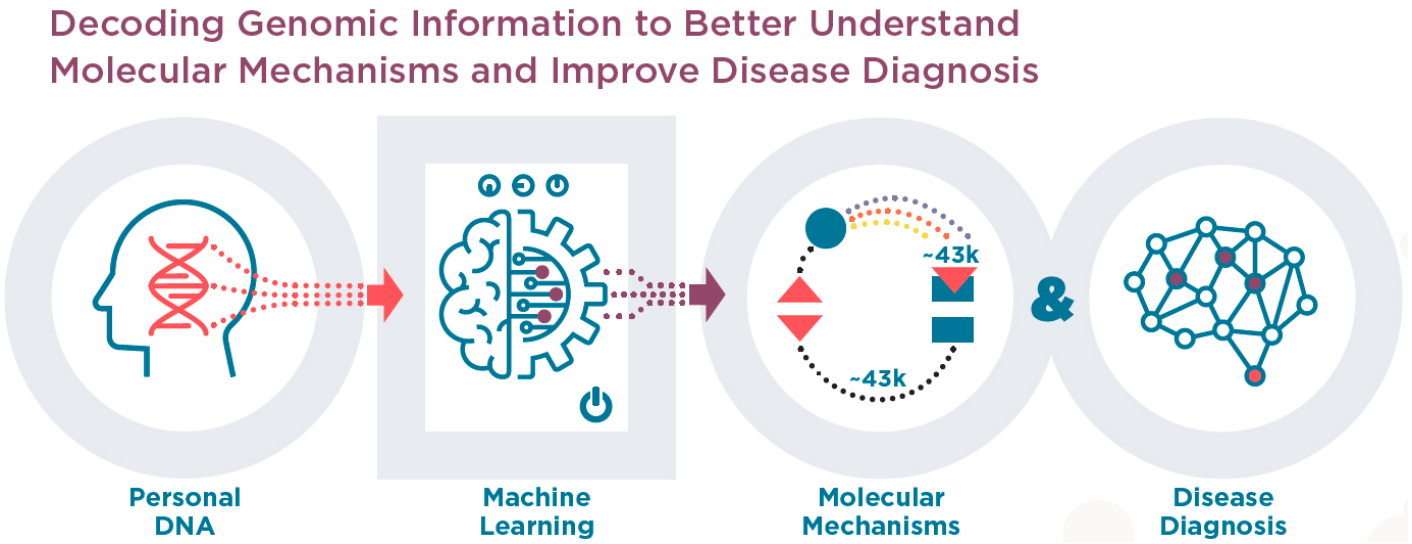
- Email: daifeng.wang@wisc.edu
- Website: https://daifengwanglab.org/
- Office: Waisman Center 517
- Zoom Link for Office Hours: https://uwmadison.zoom.us/j/3743826653
- Office Hours: Tue 2:30-3:30pm, Thu 2:30-3:30pm
- Skype: daifeng_wang

- Assistant Professor in the Department of Biostatistics & Medical Informatics and Investigator in Waisman Center

- Research interests: interpretable machine learning, network biology, functional genomics, comparative genomics, brain diseases, precision medicine

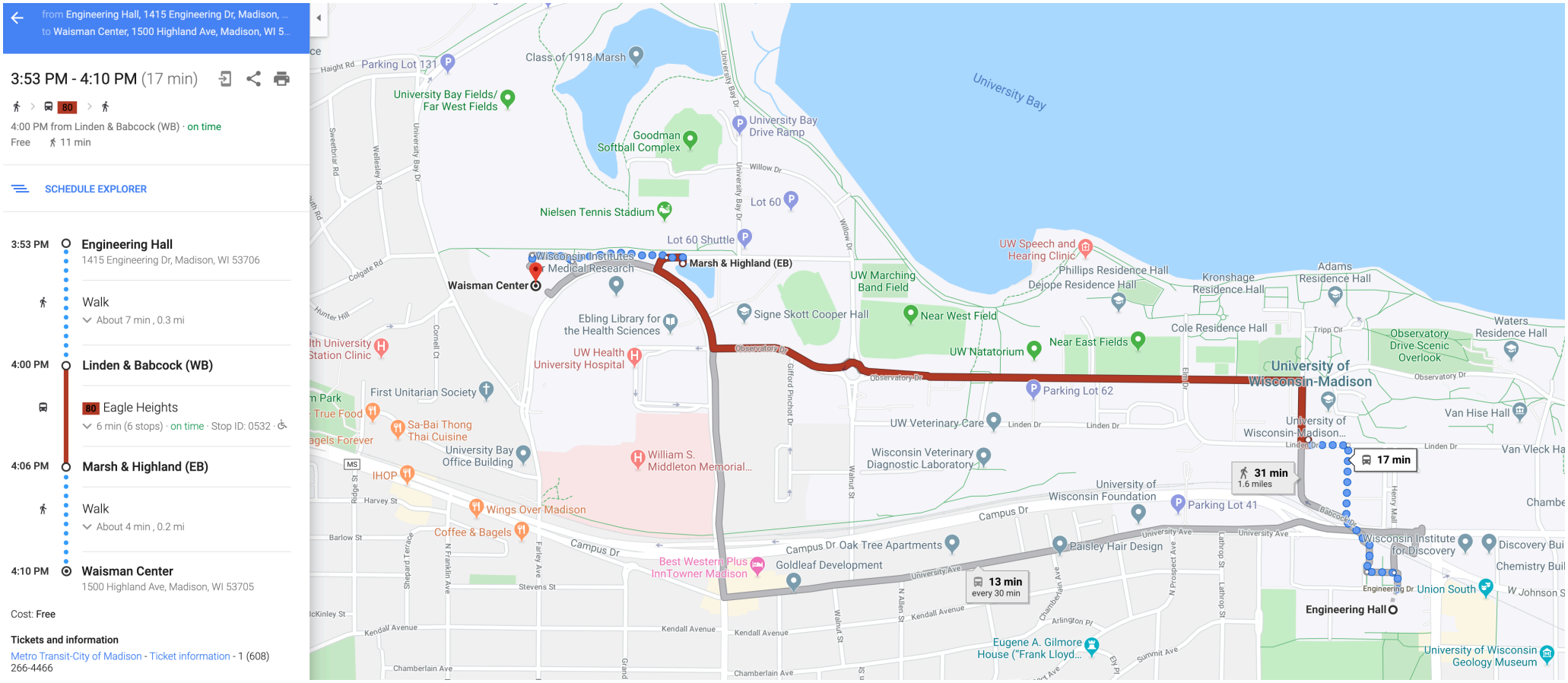
My research in Waisman Center

- Mission of Waisman Center
  - *Advance knowledge about human development, developmental disabilities, and neurodegenerative diseases*
- Goal of my research



https://www.waisman.wisc.edu/2020/01/07/new-researcher-uses-machine-learning-to-decode-genomic-information/

Finding My Office:
517 Waisman Center



- Far away, most west building
- Take No. 80 Bus or Bike/Walk for exercise

Course TA

- Saniya Khullar
  - skhullar2@wisc.edu
  - Skype: saniya0605
  - Office Hours on BBCollaborate Ultra
  - Office Hours:
    - Mondays: 11 am to 12 pm CST
    - Friday: 10 a.m. to 11 a.m. CST
    - Available by appointment as well
  - Graduate student
    - Biomedical Data Science

Office Hours

- Tue 2:30-3:30pm, Thu 2:30-3:30pm
  - https://uwmadison.zoom.us/j/3743826653
- Will begin next week
- Free to schedule an individual meeting
- You are encouraged to visit our office hours!

You

- So that we can all get to know each other better, please tell us your
  - name
  - major or graduate program
  - research interests and/or topics you're especially interested in learning about
  - favorite programming language

Course Requirements

- 4 homework assignments: ~40%
  - Written exercises
  - Programming (Python)
  - Computational experiments (e.g. measure the effect of varying parameter *x* in algorithm *y*)
  - Five late days permitted

- Project: ~30%
- Midterm: ~15%
- Final exam: ~10%
- Class participation: ~5%

Exams

- Midterm: Friday, March 19, 3-hour take-home
- Final: Wednesday May 5, 3-hour take-home

- Please let me know *immediately* if you have a conflict with either of these exam times

Computing Resources for the Class

- Linux servers in Dept. of Biostatistics & Medical Informatics
  - No “lab”, must log in remotely (use WiscVPN)
  - Will create accounts for everyone on course roster
  - Two machines
    mi1.biostat.wisc.edu
    mi2.biostat.wisc.edu
  - HW0 tests your access to these machines
  - Homework must be able to run on these machines

- CS department usually offers Unix orientation sessions at beginning of semester

To Do:

- Please register for the Wisc VPN (and ensure you can login to the Biostat server and access your account: /u/medinfo/handin/bmi776/.
- Please contact the UW-Madison Biostatistics & Medical Informatics Department with any questions.

Programming Assignments

- All programming assignments require Python
  - Project can be in any language
- Have a Python 3 environment on biostat servers
  - Permitted packages on course website
  - Can request others
- HW0 will be Python introduction
- Use Piazza for Python discussion
  - If you know Python, please help answer questions

Project

- Design and implement a new computational method for a task in molecular biology
- Improve an existing method
- Perform an evaluation of several existing methods
- Run on real biological data
- Suggestions will be provided
- Not simply your existing research
- Can email me now to discuss ideas

Participation

- Do the assigned readings before class
- Show up to class
- No one will have the perfect background
  - Ask questions about computational or biological concepts
- Correct me when I am wrong
  - Seriously, it will happen
- Piazza discussion board
  - Questions and answers

Piazza Discussion Board

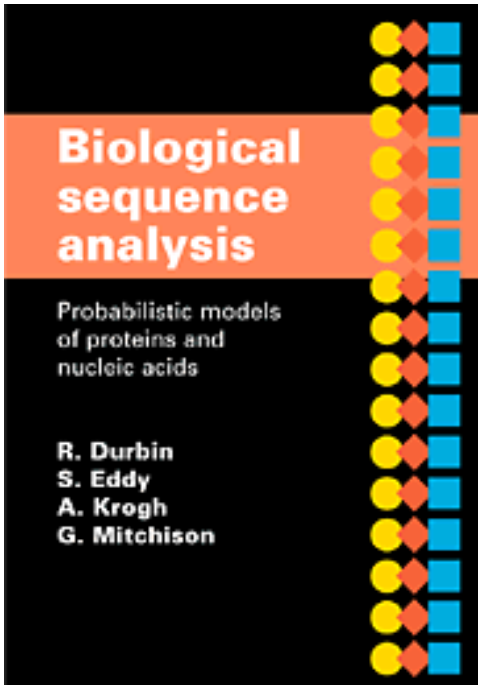
- Instead of a mailing list
- piazza.com/wisc/spring2021/bmics776
- Post your questions to Piazza instead of emailing the instructor or TA
  - Unless it is a private issue or project-related
- Answer your classmates' questions
- Announcements will also be posted to Piazza
- Supplementary material for lecture topics

Course Readings

- Mostly articles from the primary literature
- Must be using a campus IP address to download some of the articles (can use WiscVPN from off campus)

Recommended textbook

- *Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids*. R. Durbin, S. Eddy, A. Krogh, and G. Mitchison. Cambridge University Press, 1998.

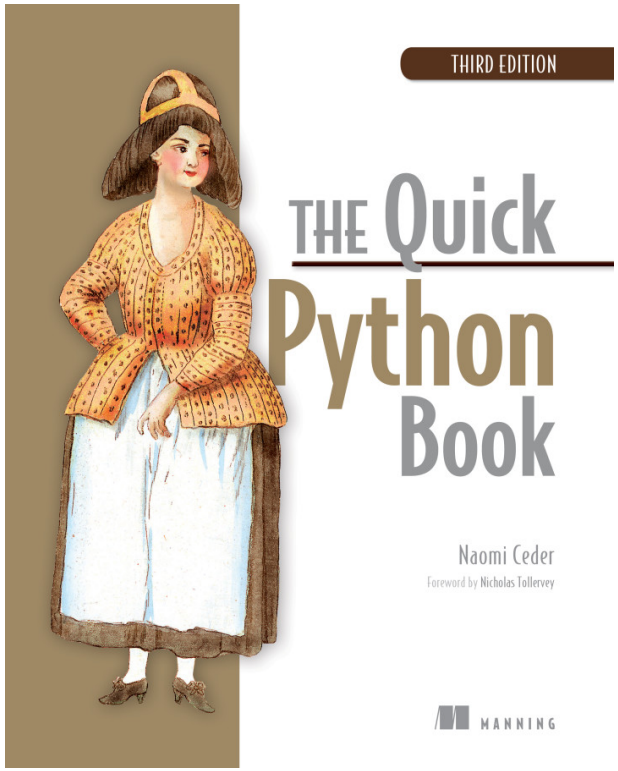


Recommended online reading

- Translational Bioinformatics
  - https://collections.plos.org/translational-bioinformatics

Python references

- https://docs.python.org
- If you want a book:
  - Python 3 for programmers
- Many other good books and online resources



https://www.manning.com/books/the-quick-python-book-third-edition

Prerequisites

- BMI/CS 576 or equivalent
- Knowledge of basic biology and methods from that course will be assumed
- May want to go over the material on the 576 website to refresh
- http://www.biostat.wisc.edu/bmi576/

What you should get out of this course

- An understanding of some of the major problems in computational biology and bioinformatics
- Familiarity with the techniques for addressing these problems
  - Computational, statistical, machine learning
- How to think about different data types
- At the end you should be able to
  - Read the bioinformatics literature
  - Apply the methods you have learned to other problems both within and outside of bioinformatics
  - Write a short bioinformatics research paper

Major Topics to be Covered (the algorithms perspective)

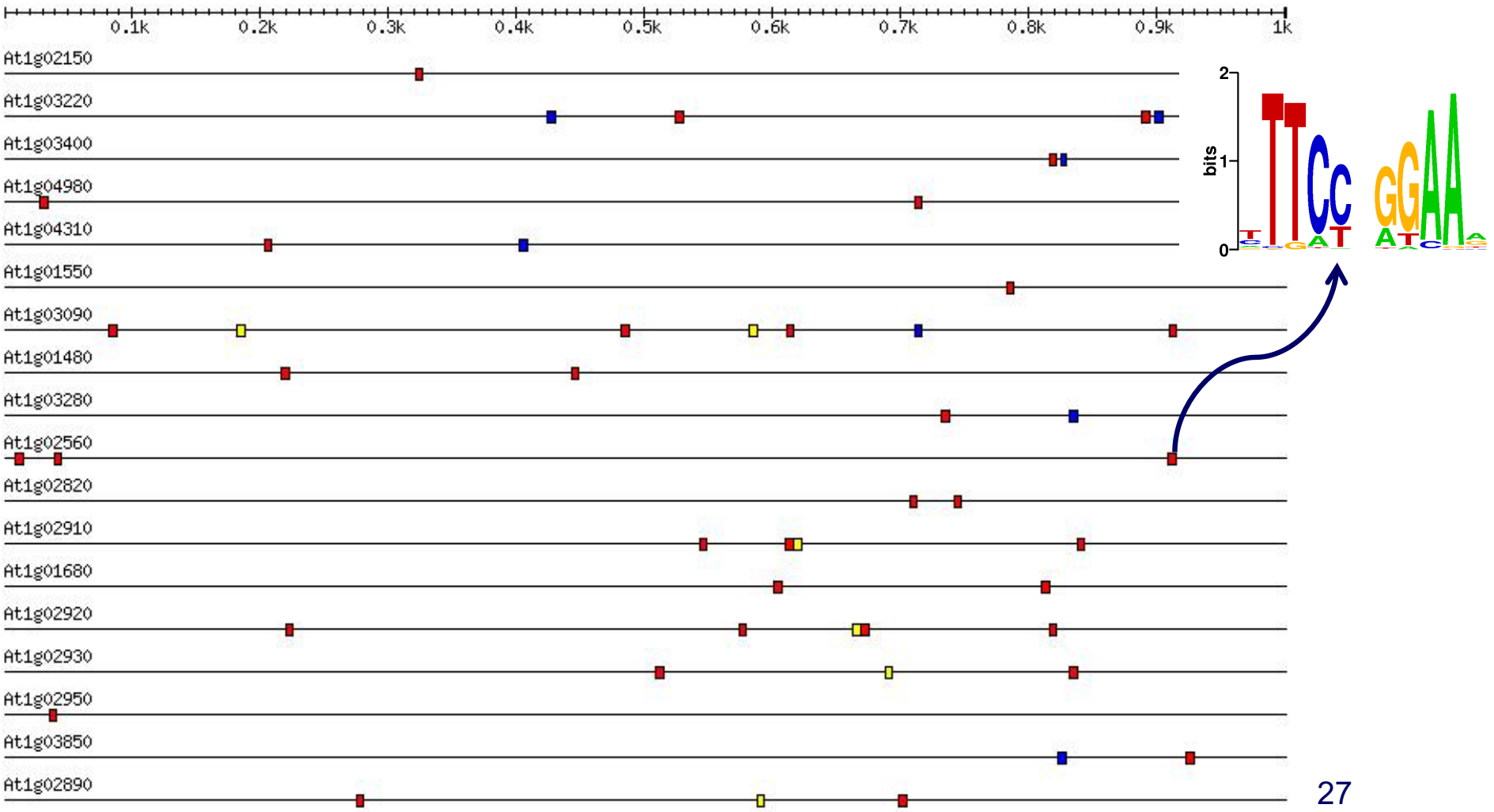
- Expectation Maximization
- Gibbs sampling
- Mutual information
- Network flow algorithms
- Stochastic context free grammars
- Multiple hypothesis testing correction
- Deep learning (e.g., Convolutional neural networks)
- Linear programming
- Tries and suffix trees
- Markov random fields

Major Topics to be Covered (the task perspective)

- Modeling of motifs and *cis*-regulatory modules
- Identification of transcription factor binding sites
- Transcriptome quantification
- Transcriptome assembly
- RNA sequence and structure modeling
- Regulatory information in epigenomic data
- Genotype analysis and association studies
- Network biology
- Single-cell genomics
- Machine learning analysis

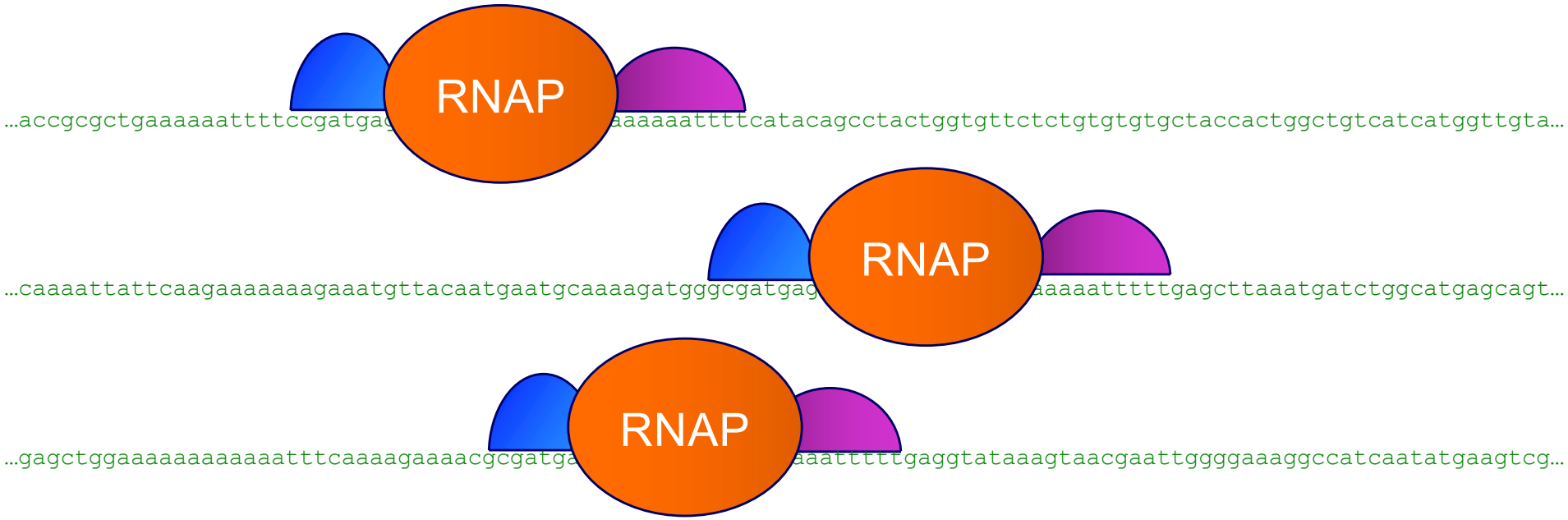
Motif Modeling

What sequence motif do these promoter regions have in common?



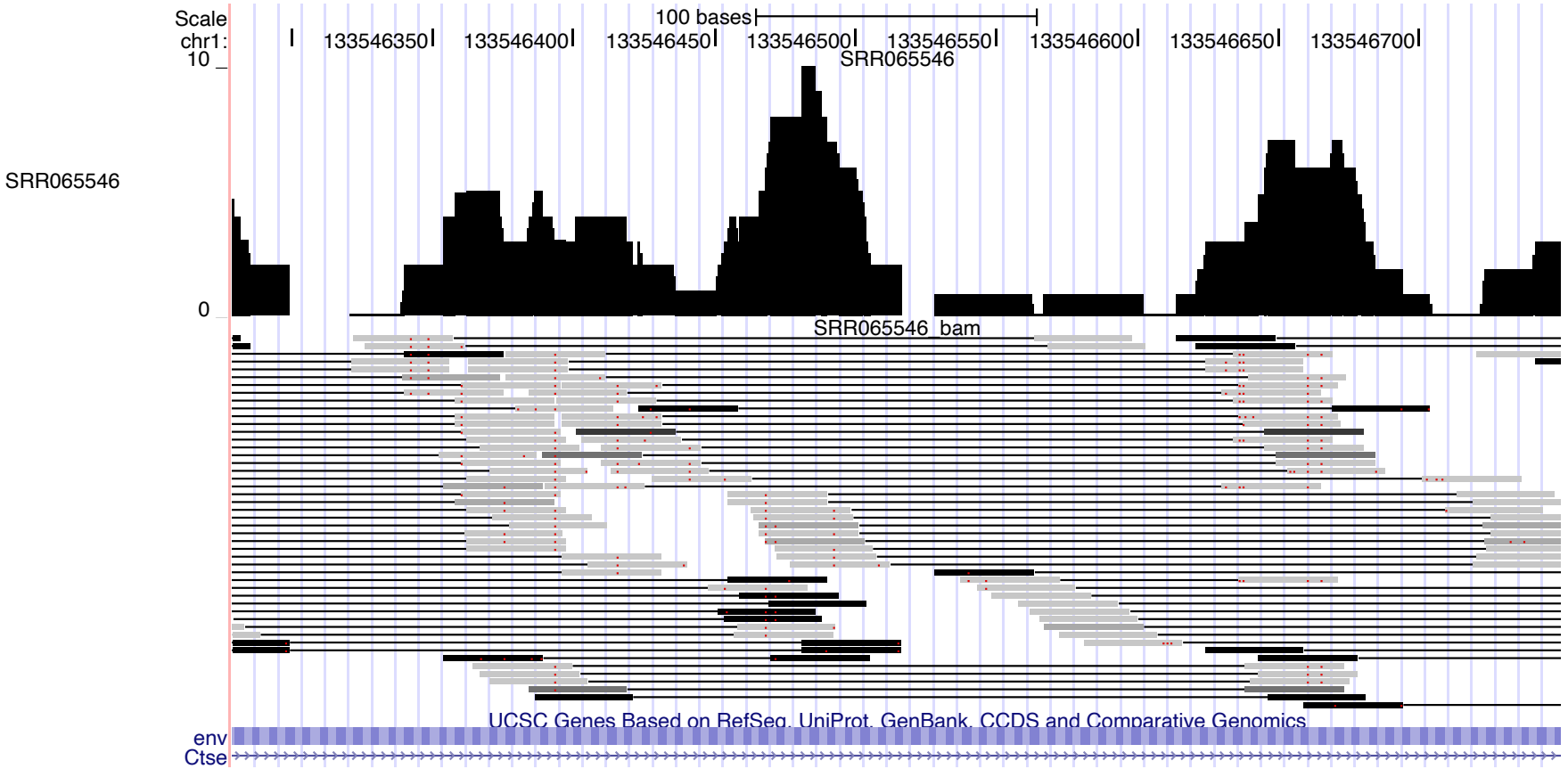
cis-Regulatory Modules

What configuration of sequence motifs do these promoter regions have in common?

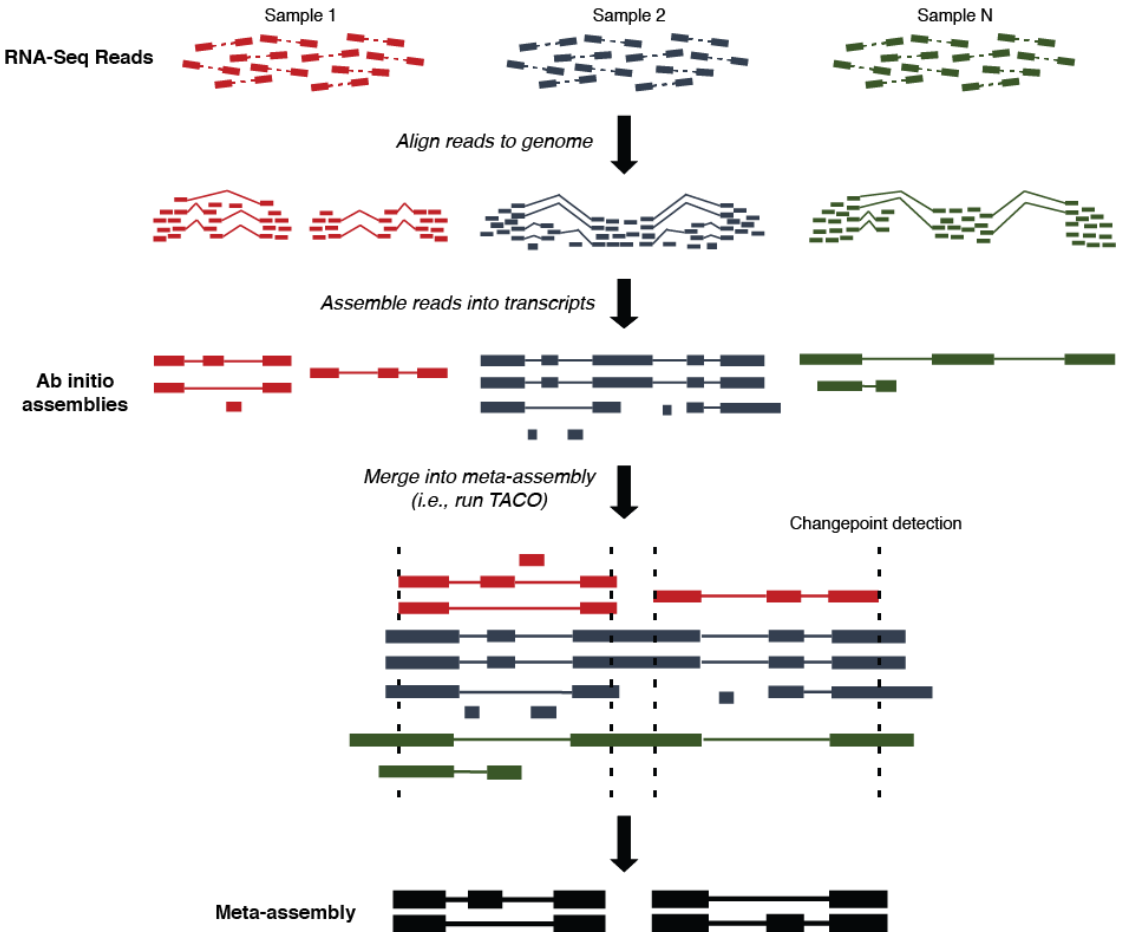


Transcriptome Analysis with RNA-Seq

What genes are expressed and at what levels?



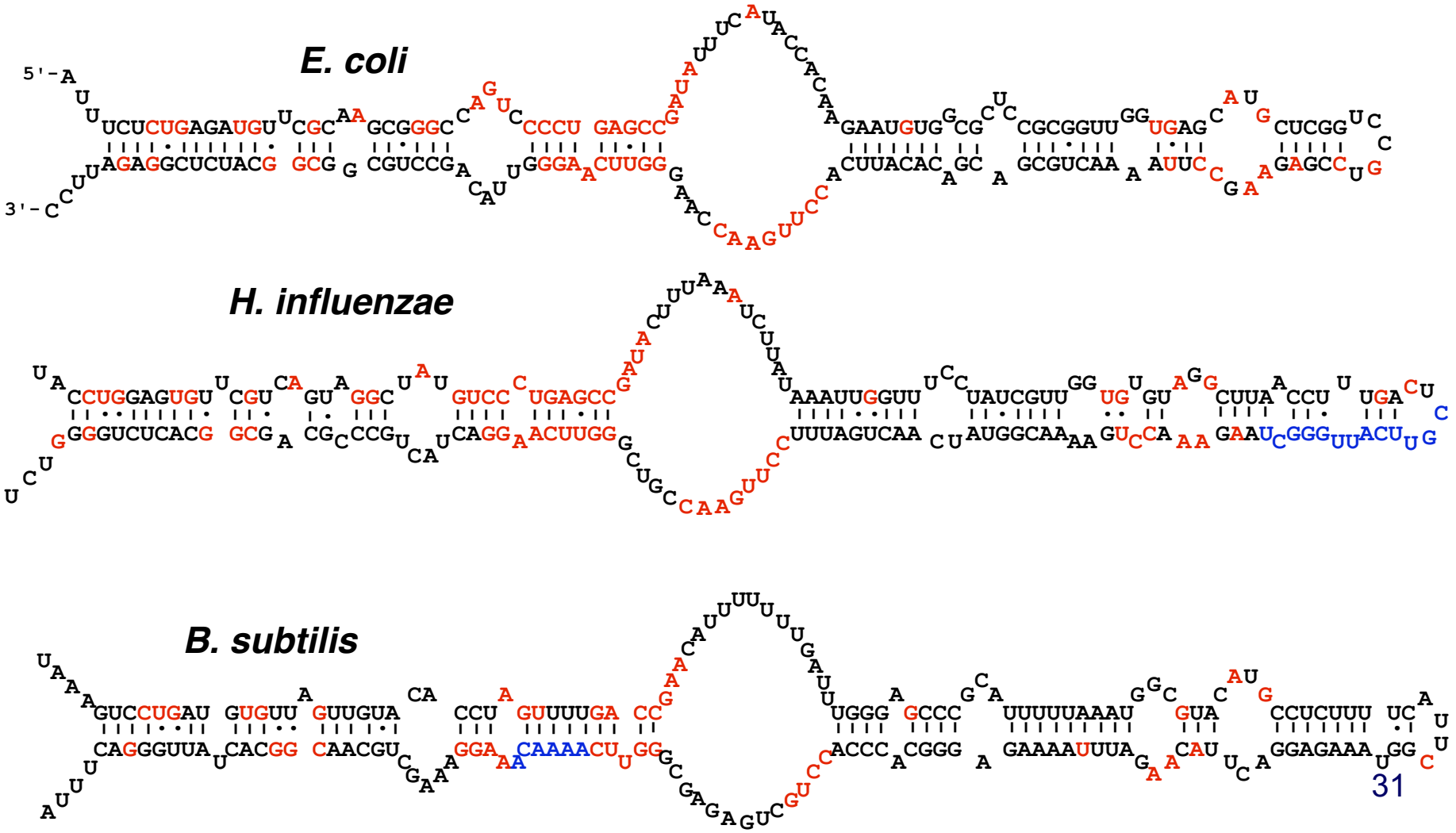
Transcriptome assembly



https://tacorna.github.io/

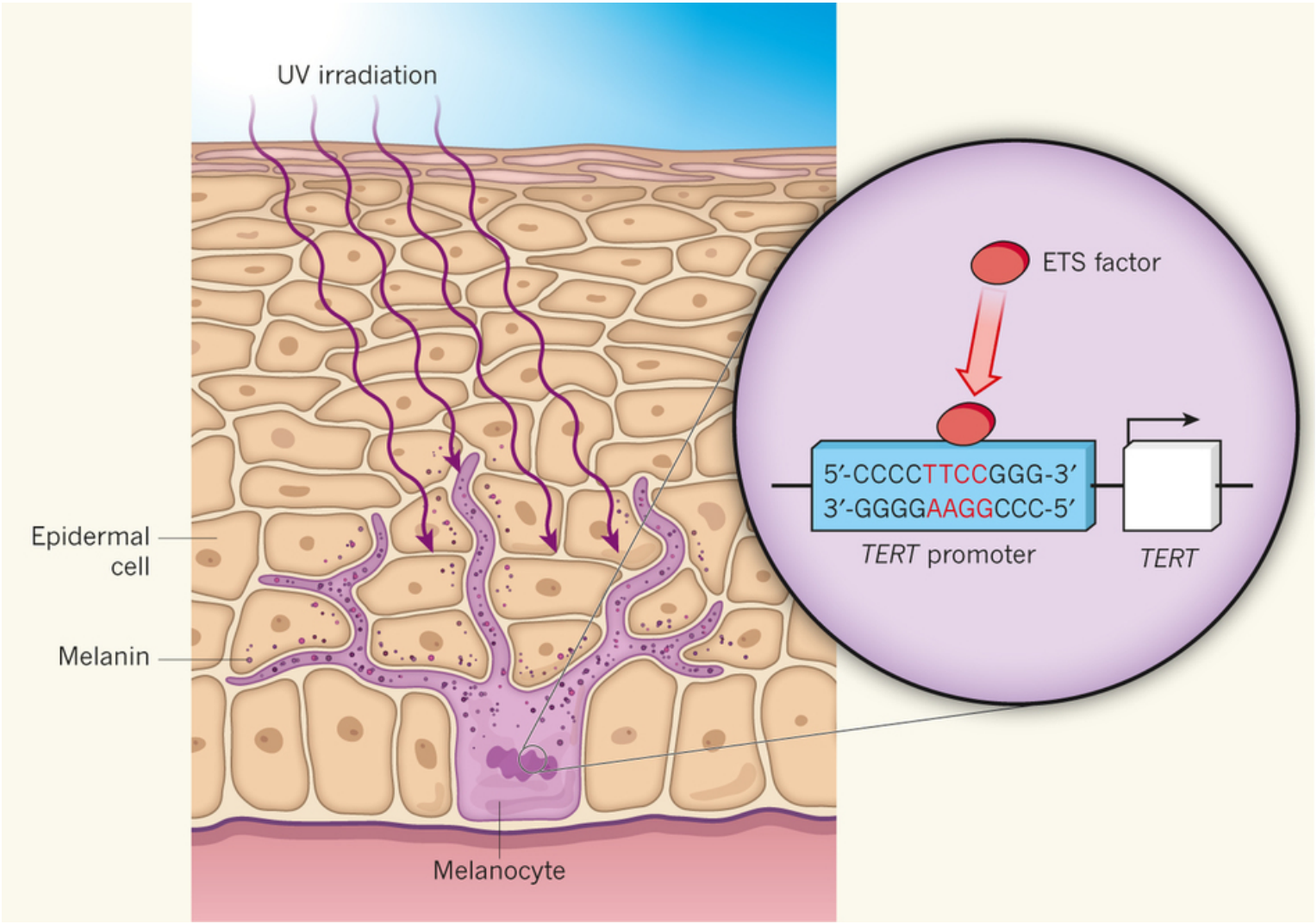
RNA Sequence and Structure Modeling

How can we identify sequences that encode this RNA structure?



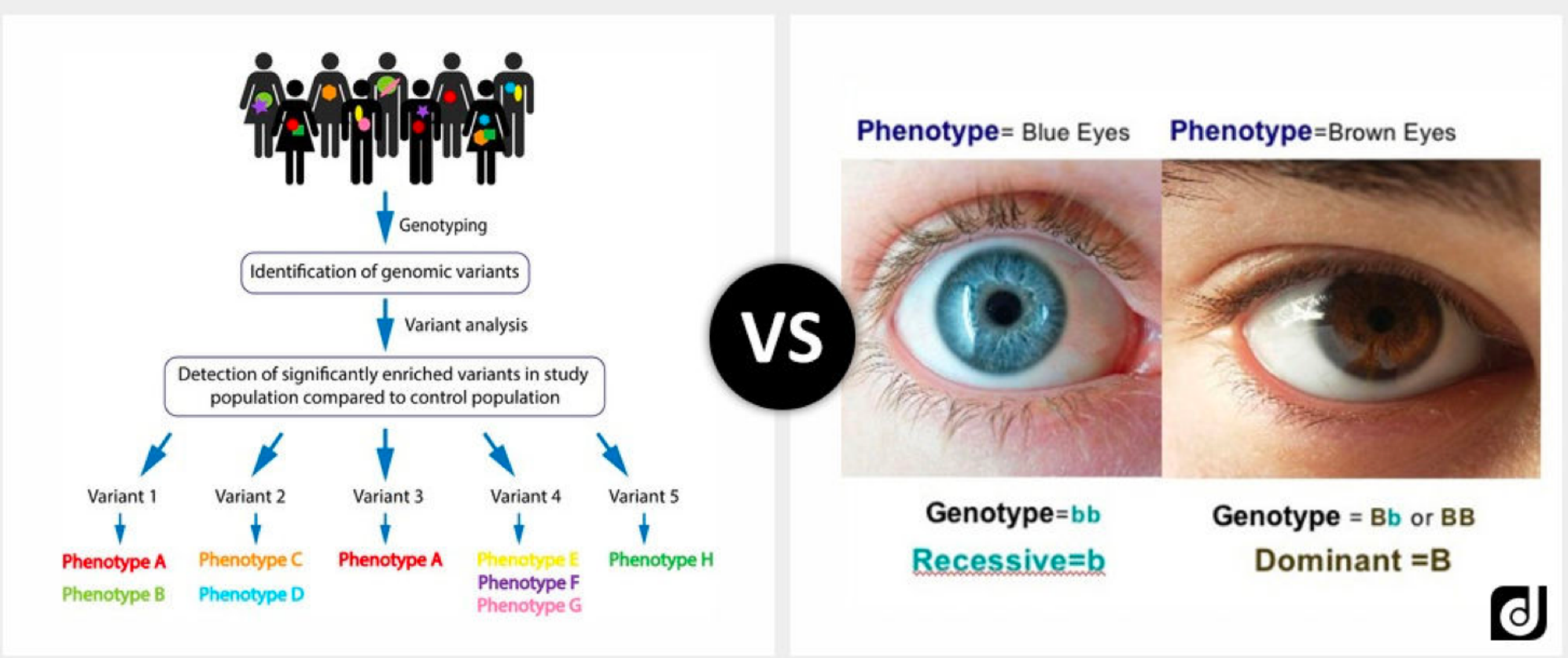
Noncoding Genetic Variants

How do genetic variants outside protein coding regions impact phenotypes?



Patton and Harrington, *Nature*, 2013

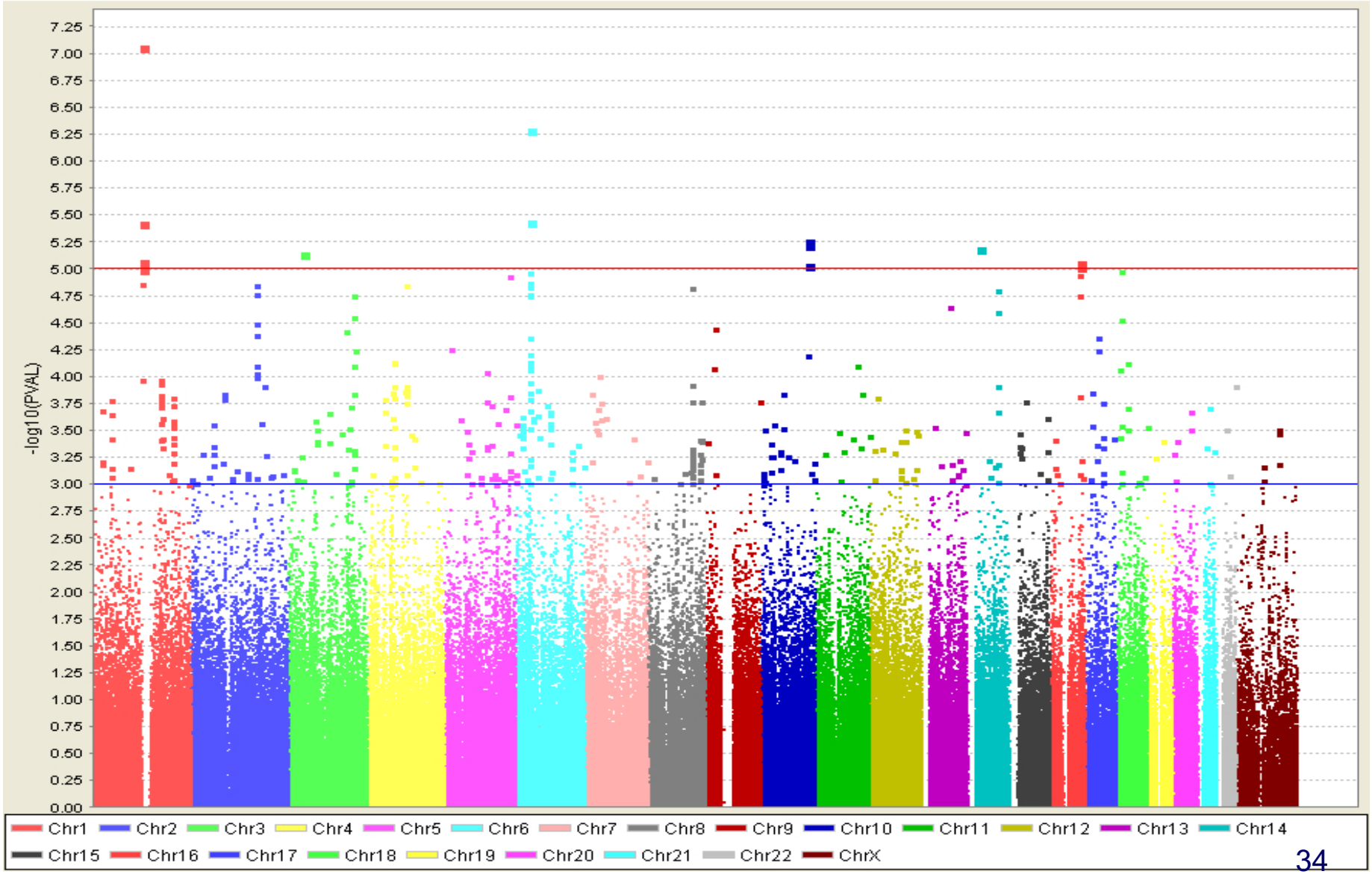
Genotype to Phenotype



Genotype vs. Phenotype

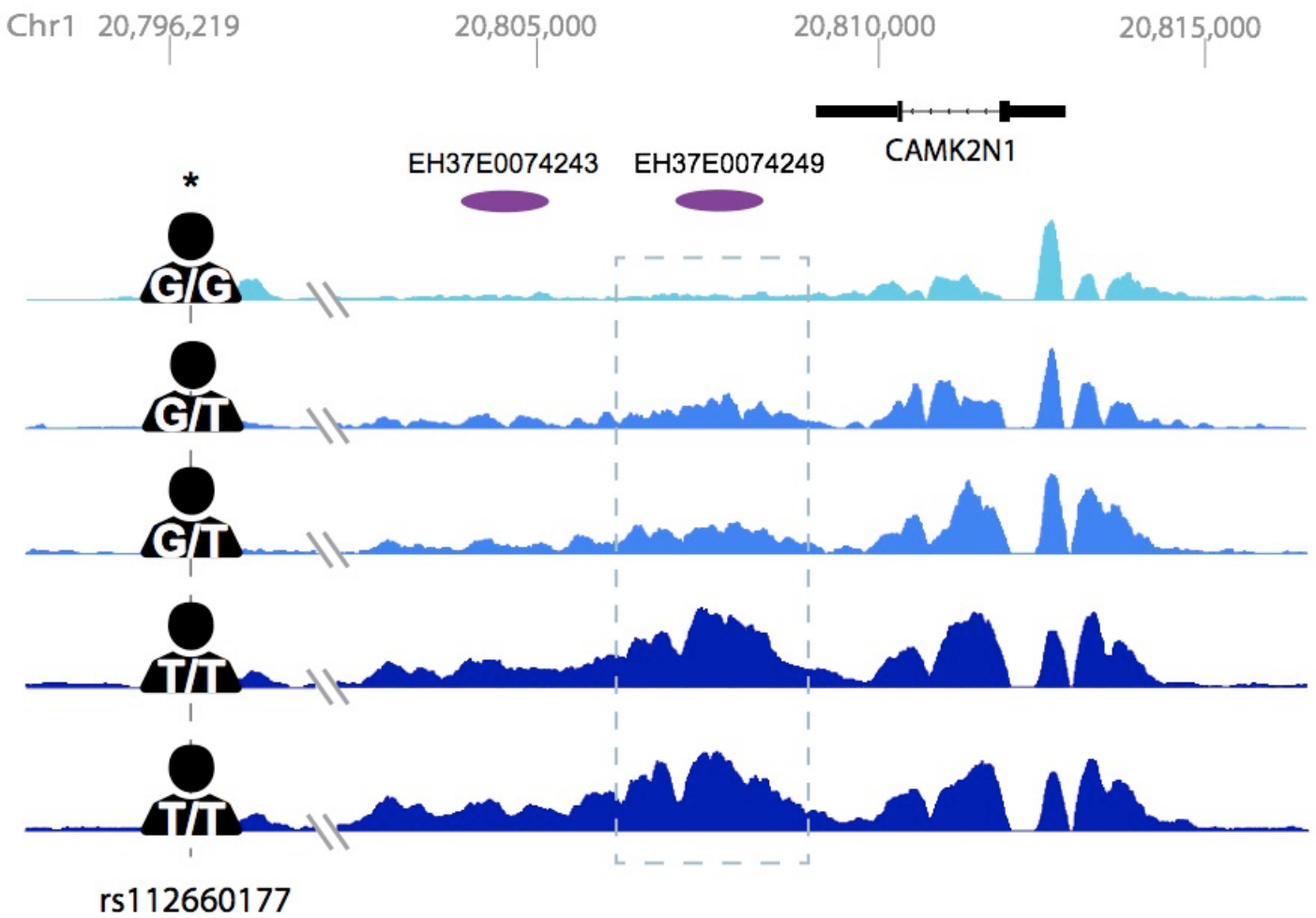
Genome-wide Association Studies

Which genes are involved in diabetes?



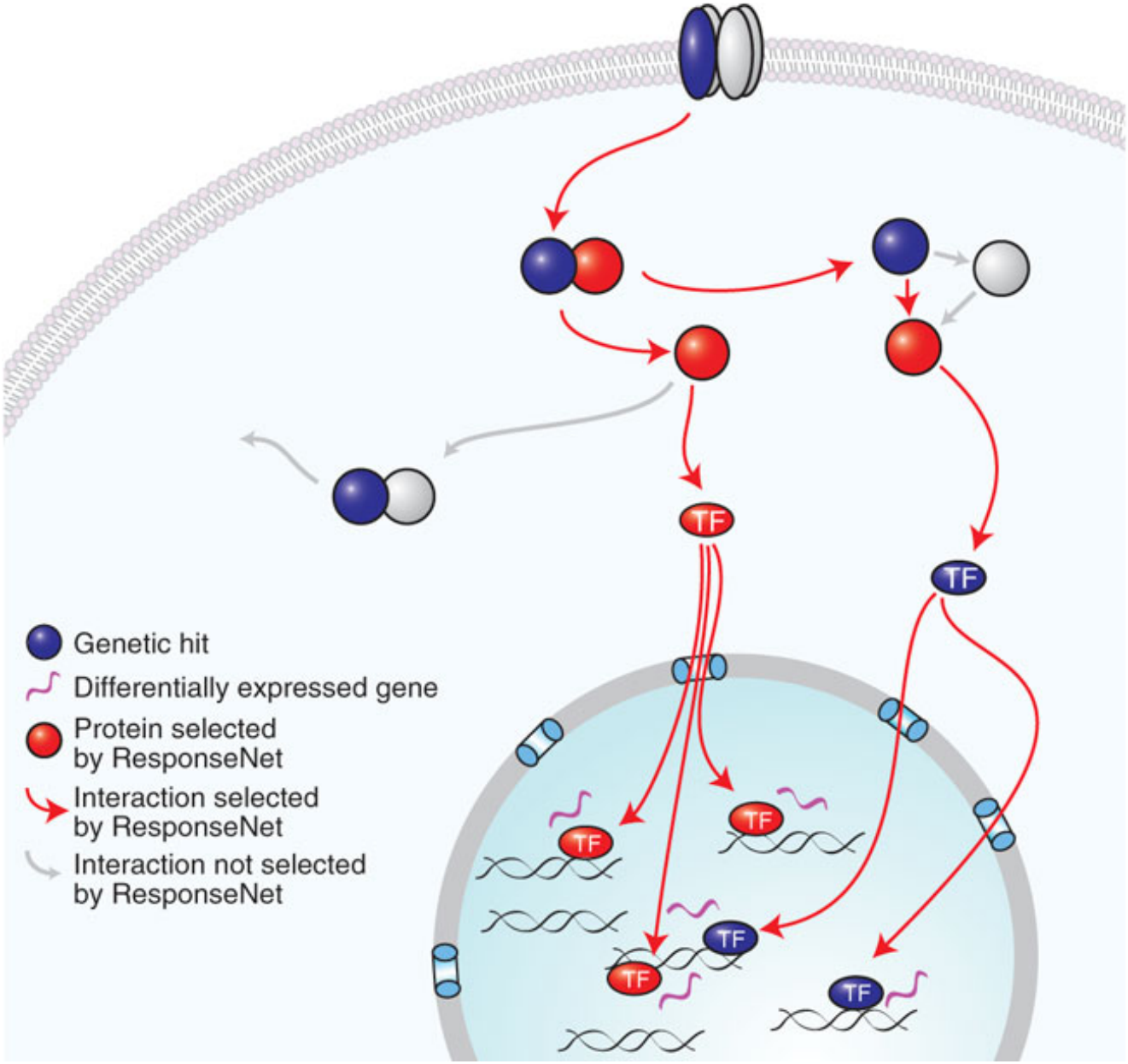
Type 2 diabetes association P values by chromosome (386,731 markers). The x-axis is the genomic position by chromosome 1-22 and X (by color), and the y-axis is the negative base 10 logarithm of the P value.

Quantitative Trait Locus (QTL) analysis



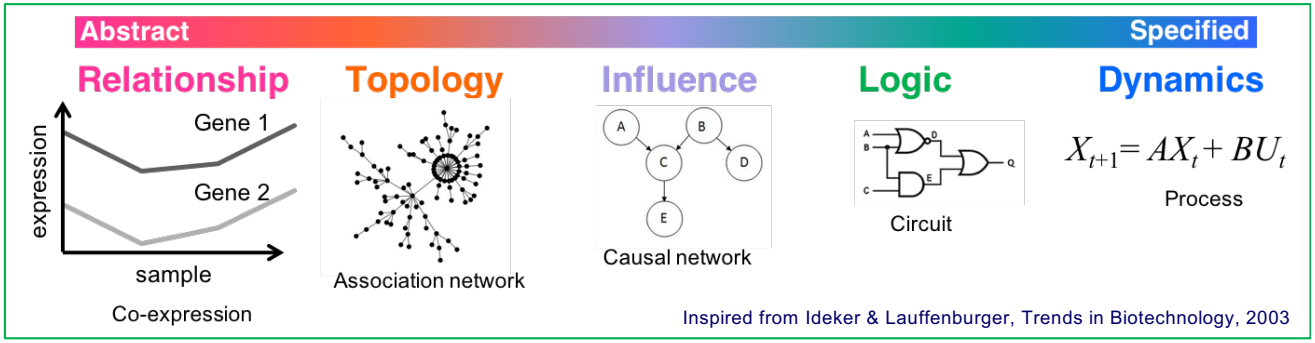
Network biology

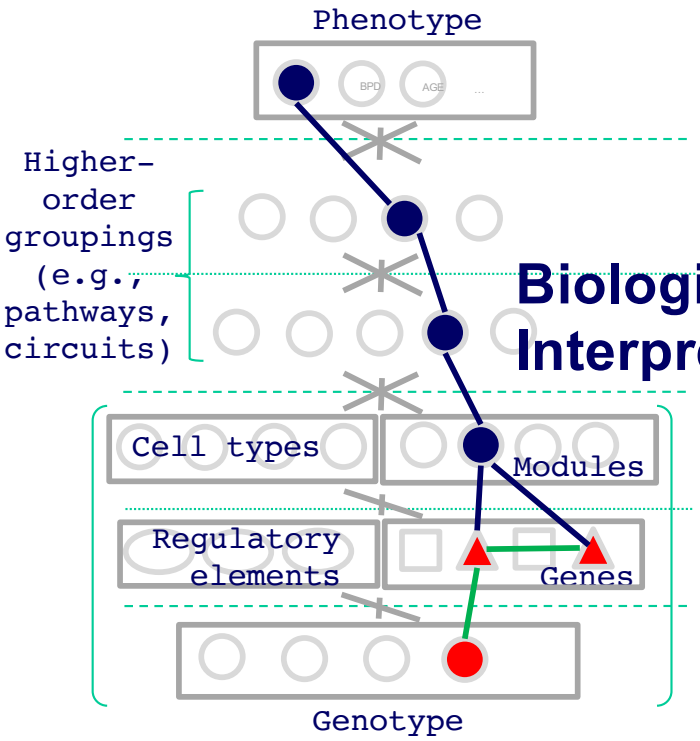
How do proteins coordinate to transmit information?



Yeger-Lotem et al., *Nature Genetics,* 2009

Machine learning and integrative analysis



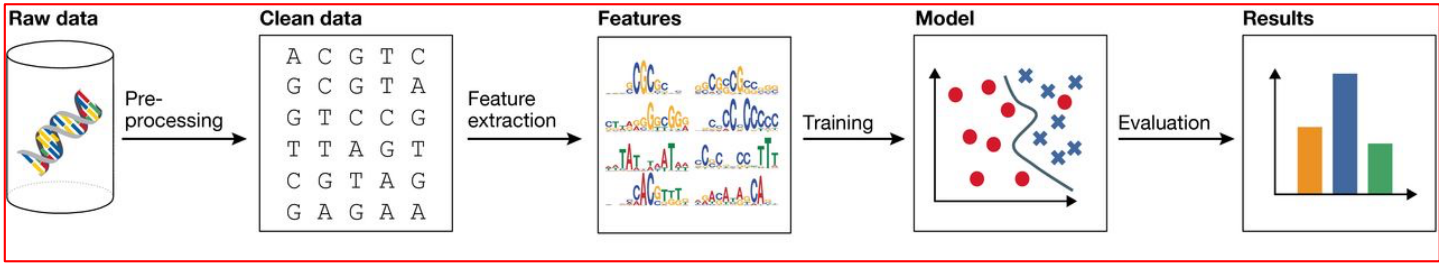


Biological Interpretation

Interactions between elements (e.g., co-expression, regulation)

Integrative & Predictive model (e.g., deep neural network)

Genomic elements (e.g., GWAS, differentially expressed genes)



Christof Angermueller et al. Mol Syst Biol 2016;12:878

Other Topics

- Many topics we aren't covering
  - Protein structure prediction
  - Protein function annotation
  - Metagenomics
  - Metabolomics
  - Graph genomes
  - Mass spectrometry
  - Text mining
  - Others?

Reading Groups

- Computational Systems Biology Reading Group
  - http://lists.discovery.wisc.edu/mailman/listinfo/compsysbiojc
- AI Reading Group
  - http://lists.cs.wisc.edu/mailman/listinfo/airg
- ComBEE Python Study Group
  - https://combee-uw-madison.github.io/studyGroup/
- Many relevant seminars on campus