Visualizing Co-occurrence of Events in Populations of Viral Genome Sequences

Alper Sarikaya[1], Michael Correll[2], Jorge M. Dinis[1],
David H. O'Connor[1,3], and Michael Gleicher[1]

[1] University of Wisconsin-Madison

[2] University of Washington

[3] Wisconsin National Primate Center

http://graphics.cs.wisc.edu/Vis/CoocurViewer/

@yelperalp

http://cs.wisc.edu/~sarikaya/

Outline

Biological Background
bound our design space and exploration

Displaying occurrence relationships (in biology)
similar visual metaphors and related workflow techniques

MatrixViewer
exploring design decisions in the first iteration, learning from analyst confusion

CooccurViewer
analyst-guided exploration of ‘interesting’ co-occurrences

Case Study, Future Work
application to virology workflow, application to other data domains

Variation in RNA viruses

RNA viruses are very error prone in replication

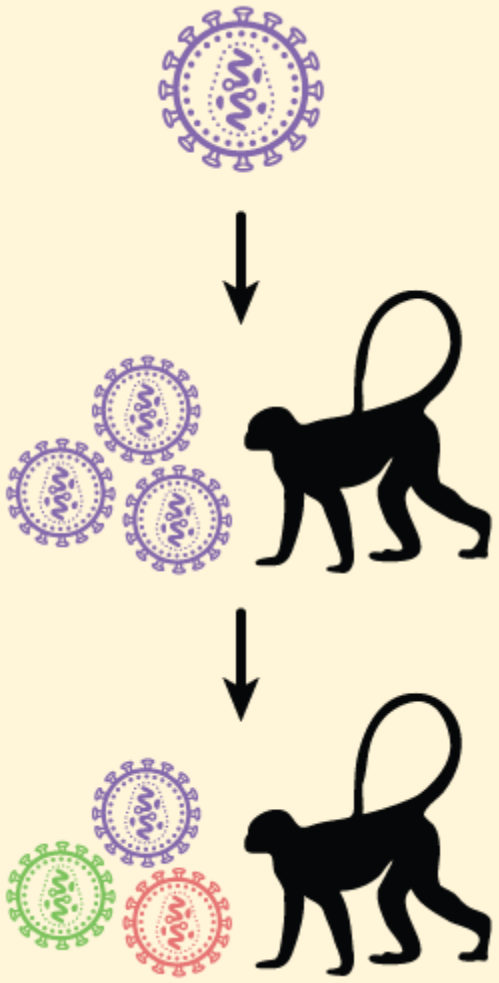
lacks the error-checking of double-stranded DNA

Viruses accumulate variation to help its survival

known as "viral fitness," this can identify how a virus can adapt to new challenges from immune response

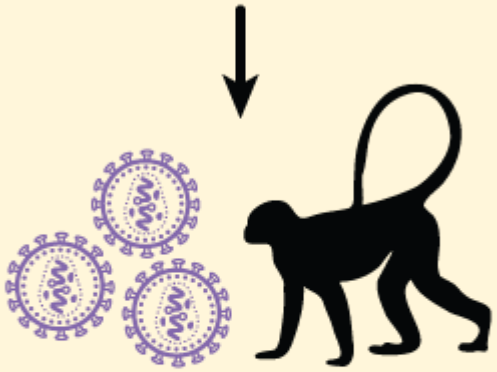
Influenza, H1N1, Zika are hard to eliminate

these RNA viruses all have a wide swath of variation, and therapies for these viruses attack essential viral function

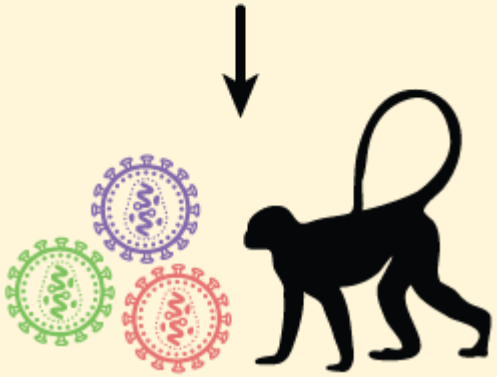


Timeline of RNA virus infection

Original virus



Infection



Population of viral genomes

(lots of variants!)

The Analysis Goal

The virologists goal

Discover where functional shifts are occurring
driven by virologist intuition coupled with previous work

What we support in this work

Identify ‘co-occurrences’ of mutations in genome
epistasis can identify functional shifts that are preferred in the given environment

Another potential solution (though tech needed)

Identify groups of like-behaving subpopulations
understand how mutated viruses conserve vital functionality in order to target therapies

The Analysis Goal

The virologists goal

Discover where functional shifts are occurring

driven by virologist intuition coupled with previous work

What we support in this work

Identify ‘co-occurrences’ of mutations in genome

epistasis can identify functional shifts that are preferred in the given environment

Another potential solution (though tech needed)

Identify groups of like-behaving subpopulations

understand how mutated viruses conserve vital functionality in order to target therapies

The Analysis Goal

The virologists goal

Discover where functional shifts are occurring

driven by virologist intuition coupled with previous work

What we support in this work

Identify ‘co-occurrences’ of mutations in genome

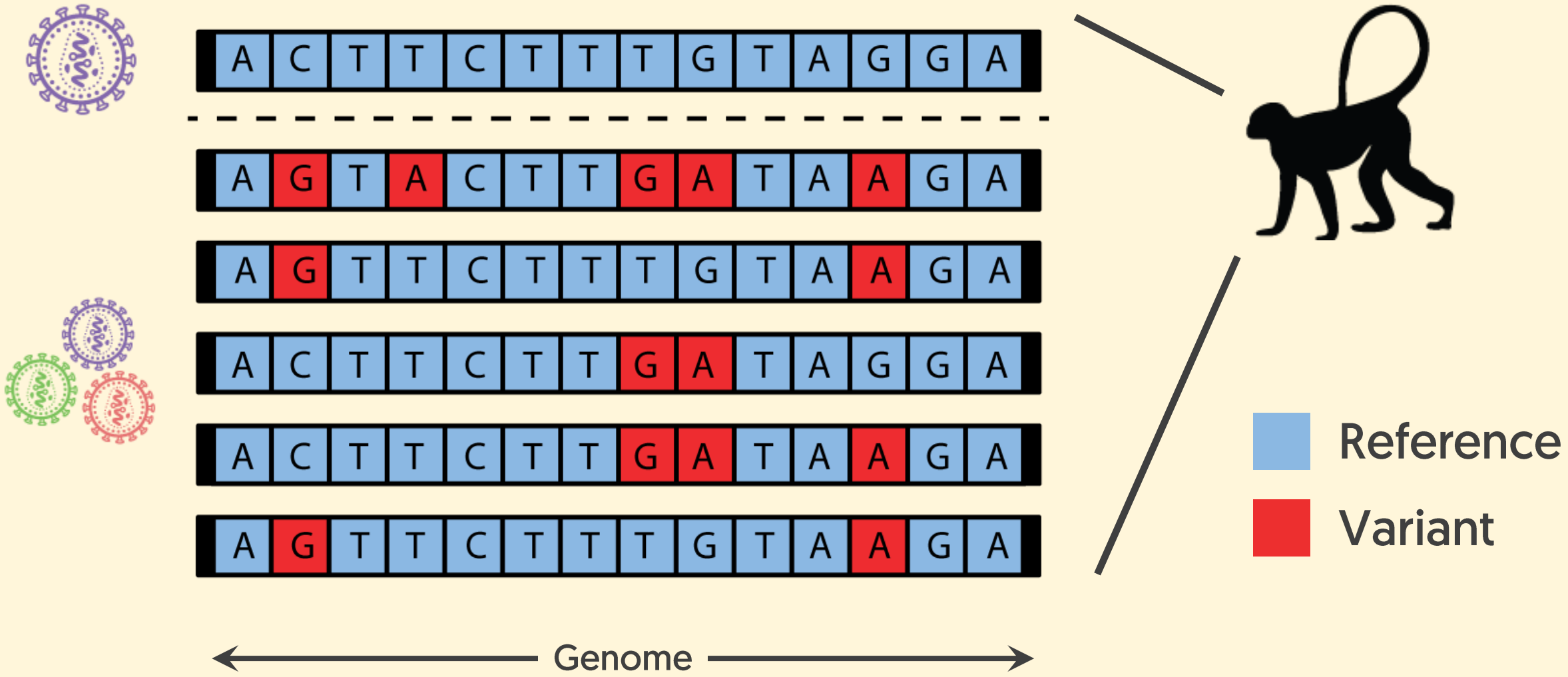
epistasis can identify functional shifts that are preferred in the given environment

Another potential solution (though tech needed)

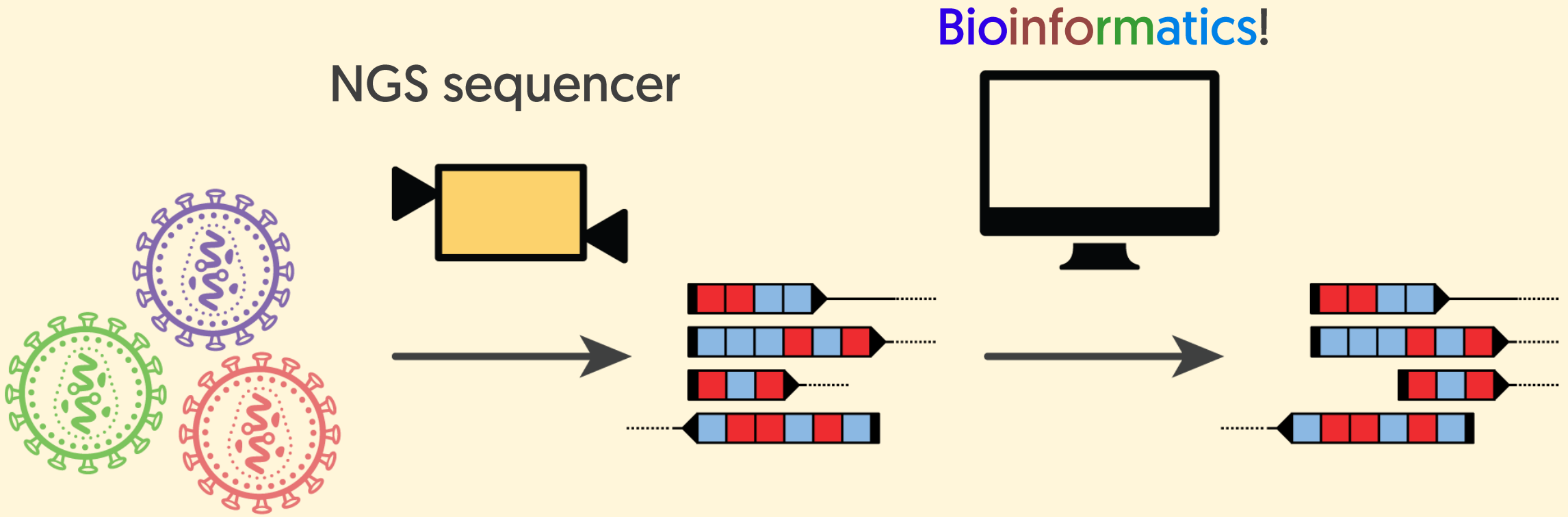
Identify groups of like-behaving subpopulations

understand how mutated viruses conserve vital functionality in order to target therapies

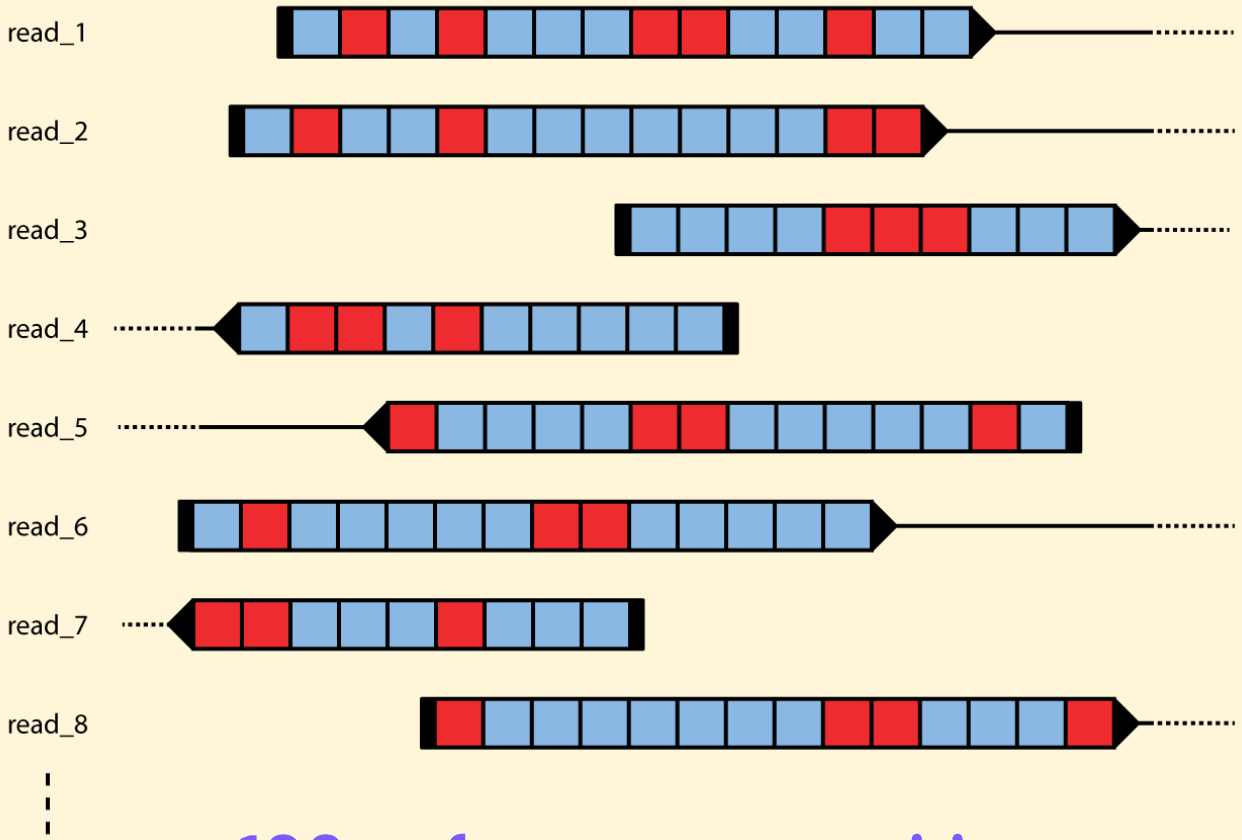
Population of Viral Genomes



Obtaining the Data



Aligned Genome Reads



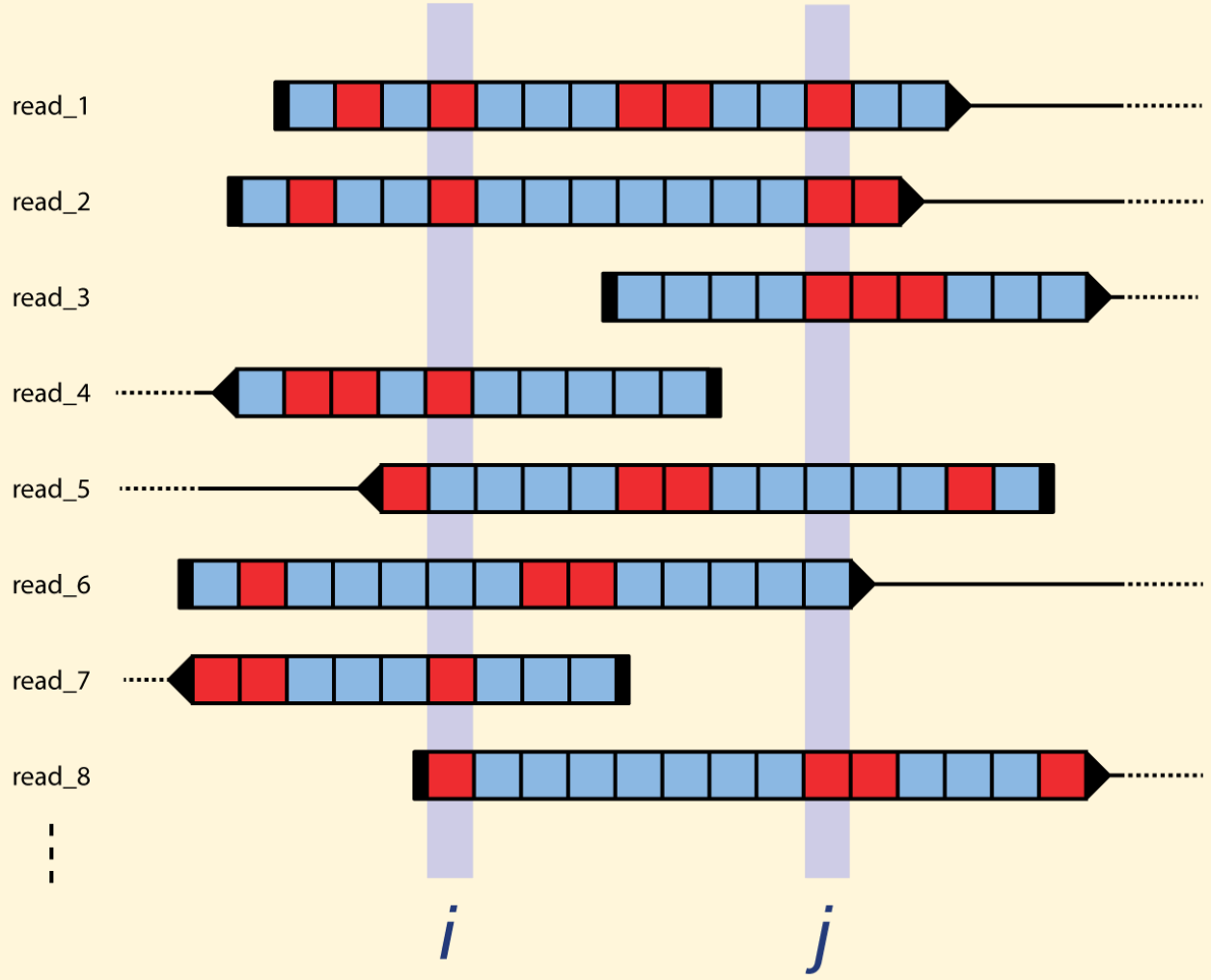
100,000s of genomic fragments

100s of genome positions

Aligned Genome Reads

Identify pairs of positions
where mutations co-occur
identify epistasis, indicating a functionality shift

Analysis requires
a maximum of sifting through
(# positions)^2 correlations



Outline

Biological Background
bound our design space and exploration

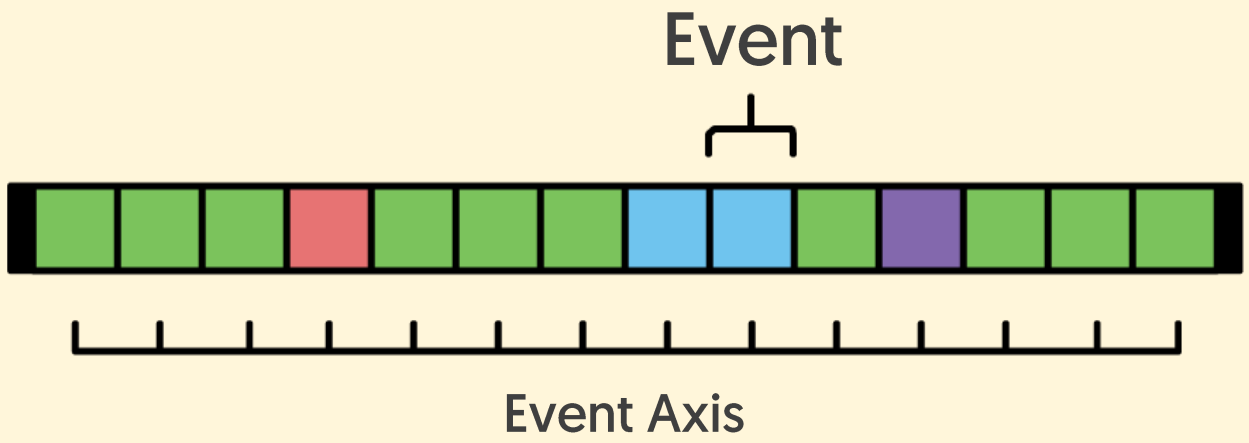
Displaying occurrence relationships (in biology)
similar visual metaphors and related workflow techniques

MatrixViewer
exploring design decisions in the first iteration, learning from analyst confusion

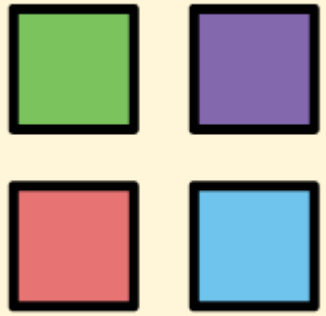
CooccurViewer
analyst-guided exploration of ‘interesting’ co-occurrences

Case Study, Future Work
application to virology workflow, application to other data domains

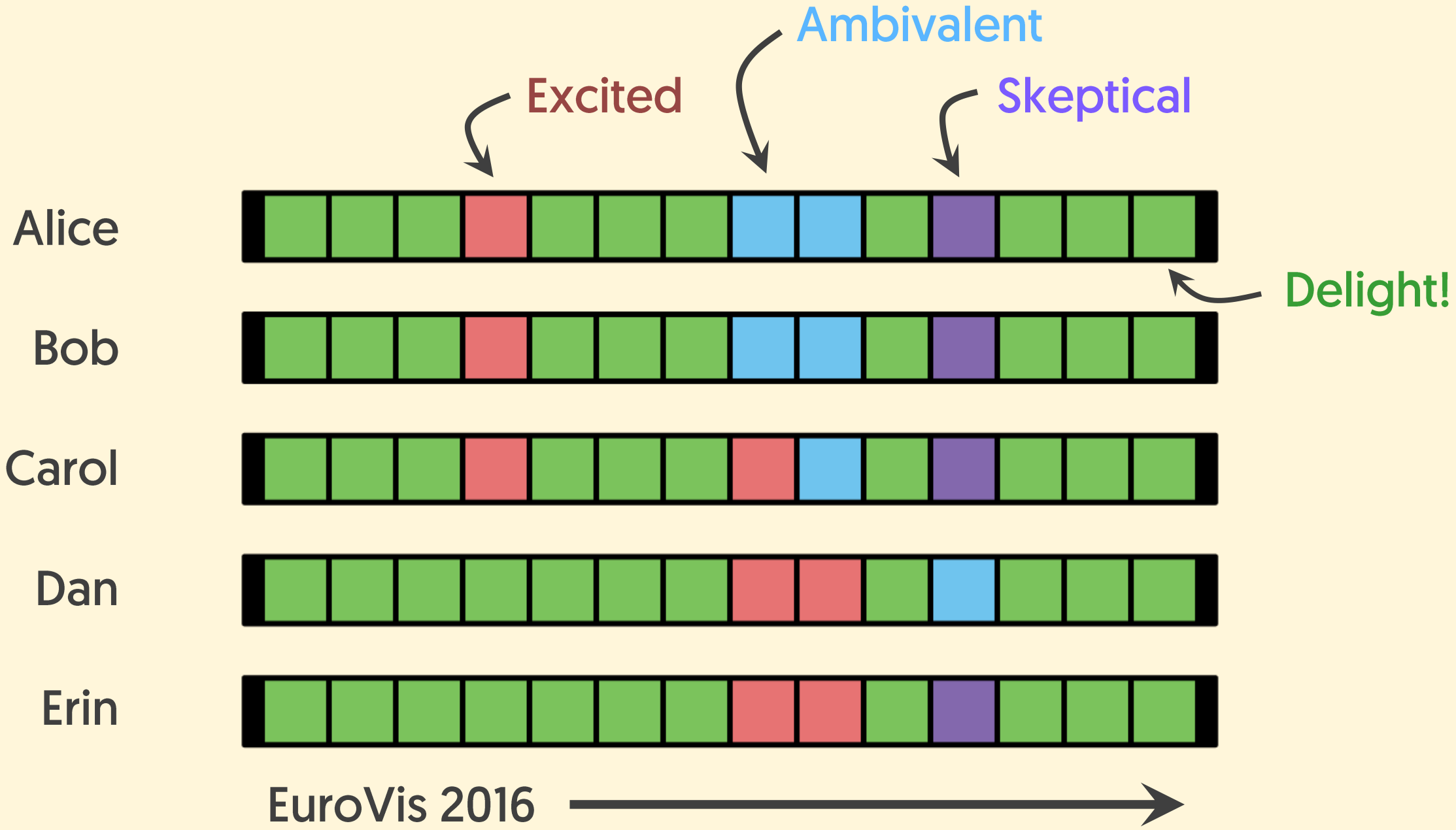
Problem Abstraction

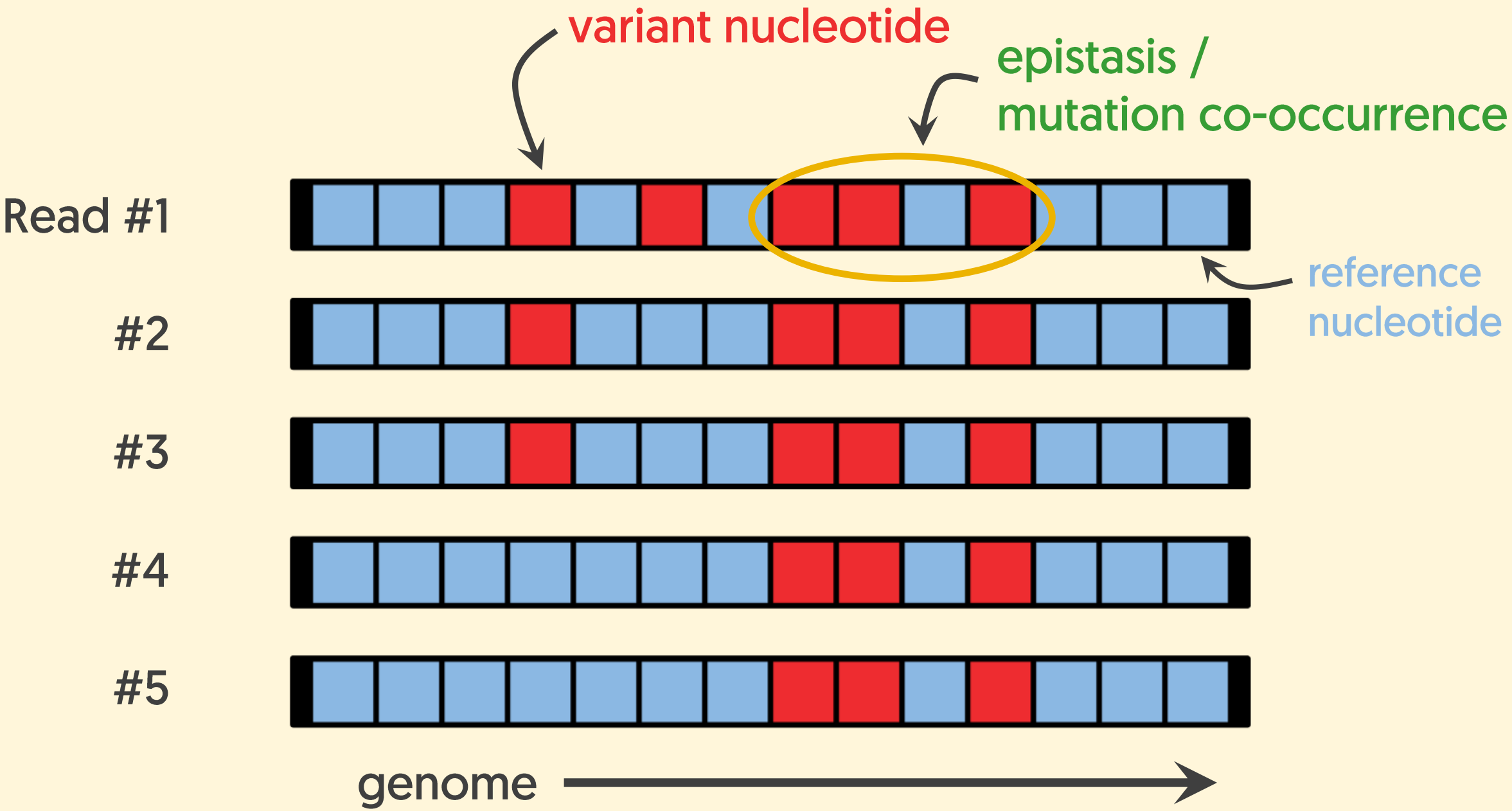


Observer

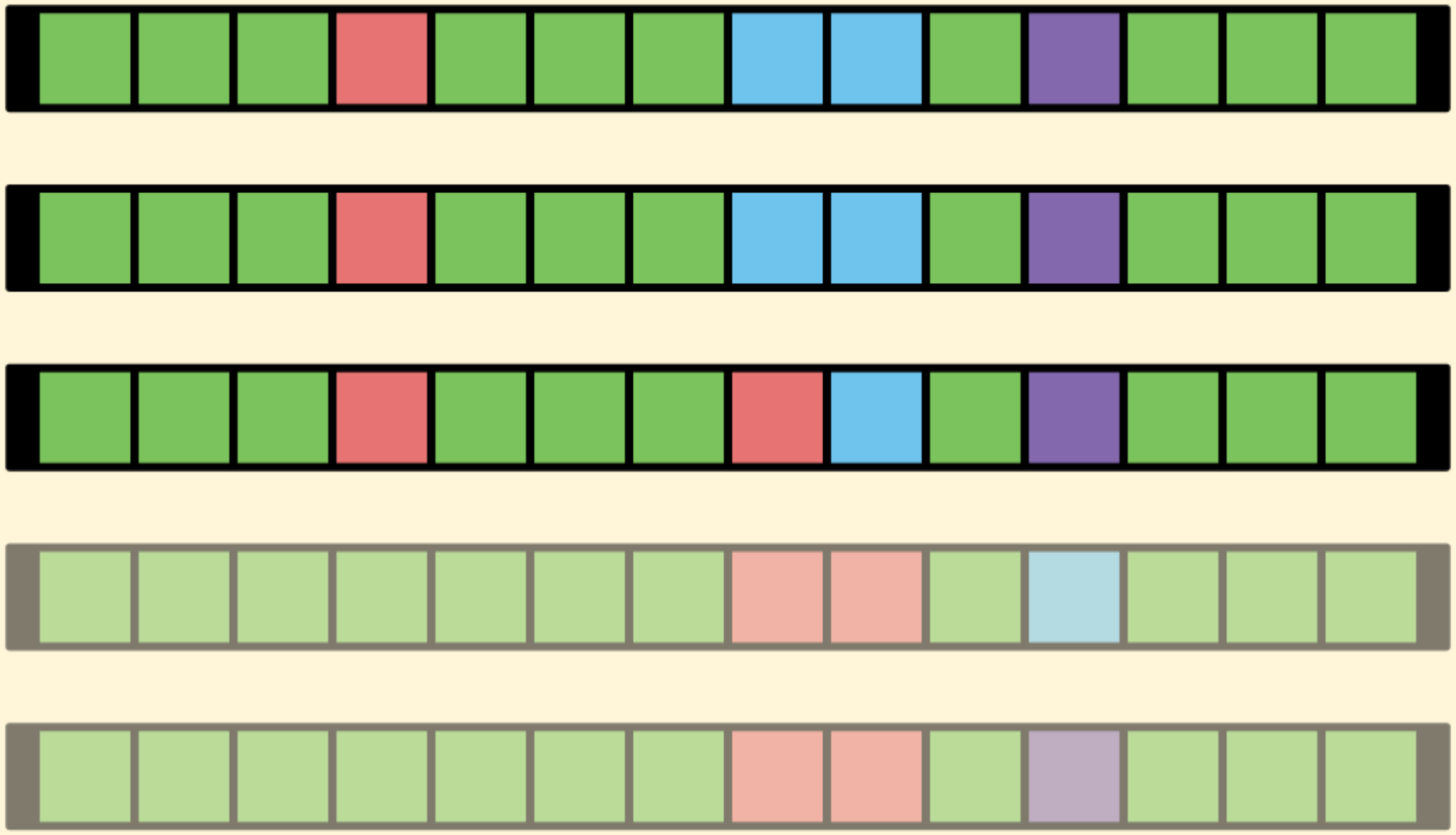


Observations

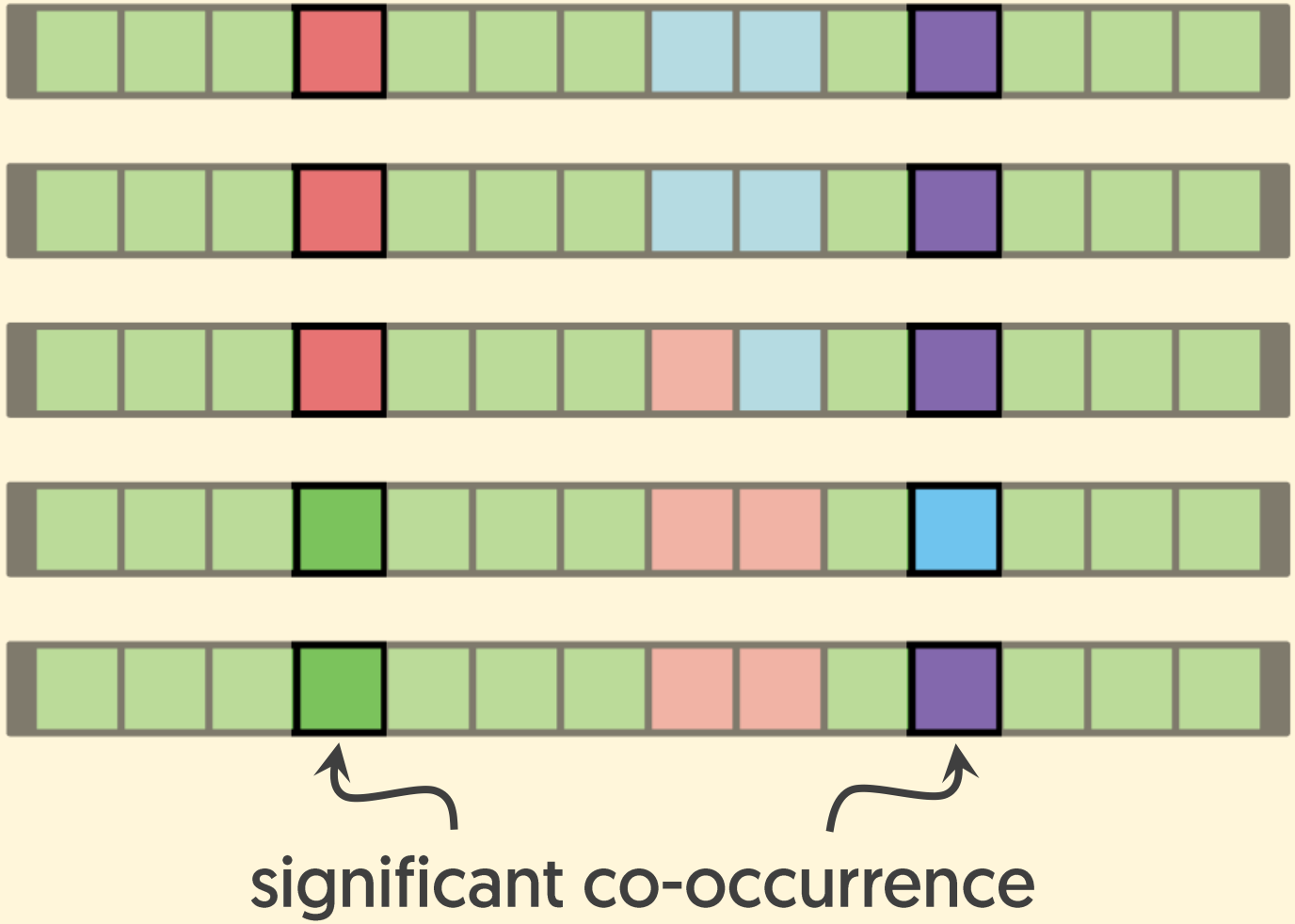

Excited
Ambivalent
Skeptical
Alice
Bob
Carol
Dan
Erin
Delight!
EuroVis 2016


variant nucleotide
epistasis /
mutation co-occurrence
Read #1
#2
#3
#4
#5
reference
nucleotide
genome

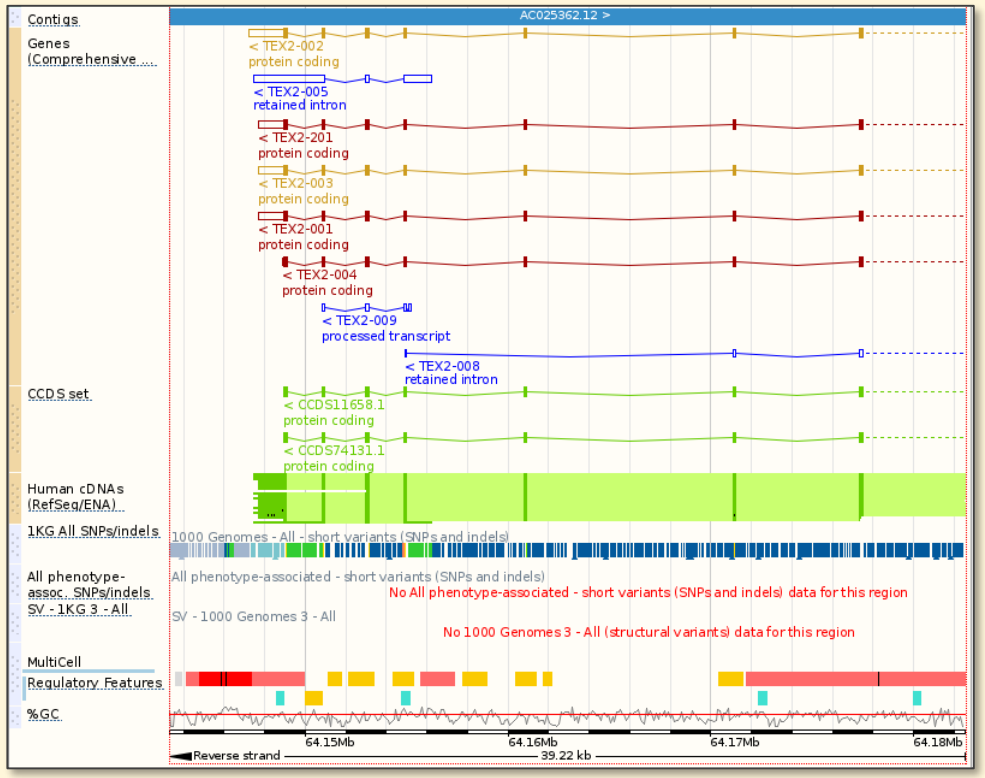
Abstraction: grouping



Abstraction: interesting events



Related Work: Genome Browsers

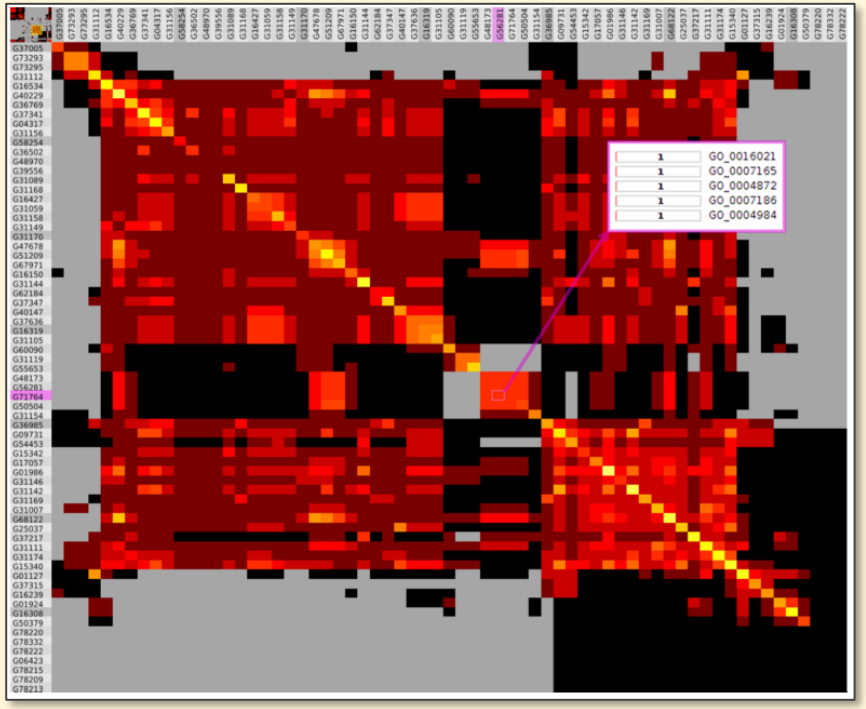


ensemble Genome Browser

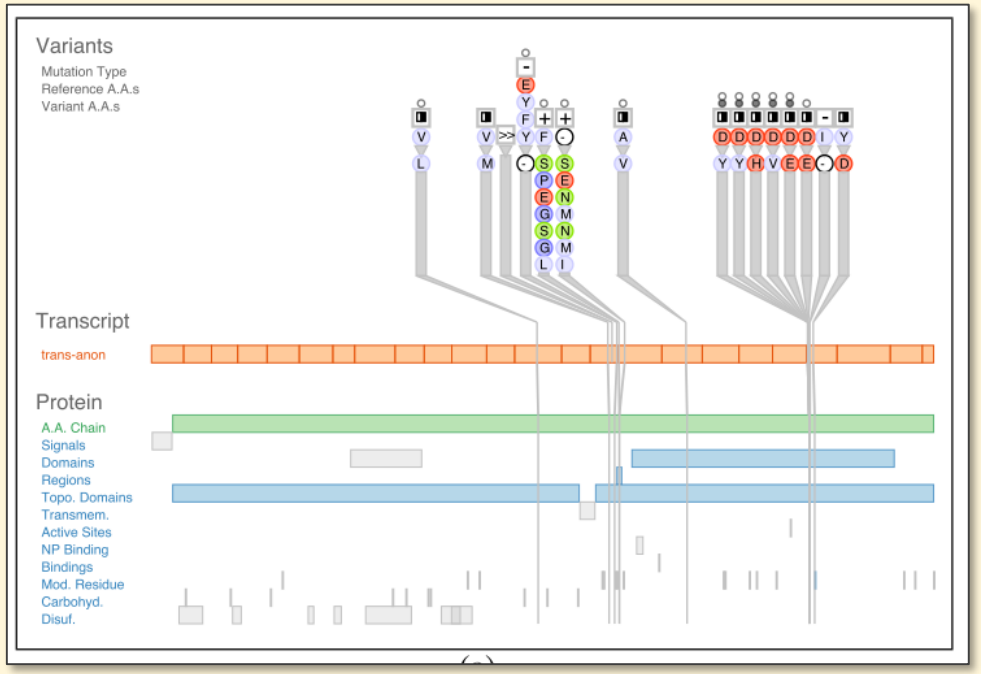
UCSC Genome Browser

Visualization of Correlation

See Diaz, et al [2002] for more on graph construction of correlation. [doi]



van Brakel, et al. COMBat: Visualizing Co-occurrence of Annotation Terms. BioVis 2011. [doi]



Ferstay, et al. Variant View: Visualizing Sequence Variants in their Gene Context. VIS 2013. [doi]

Visualization of Correlation

Correll, et al. LayerCake: A Tool for the Visual Comparison of Viral Deep Sequencing Data. Bioinformatics, 2015. [doi]

Outline

Biological Background
bound our design space and exploration

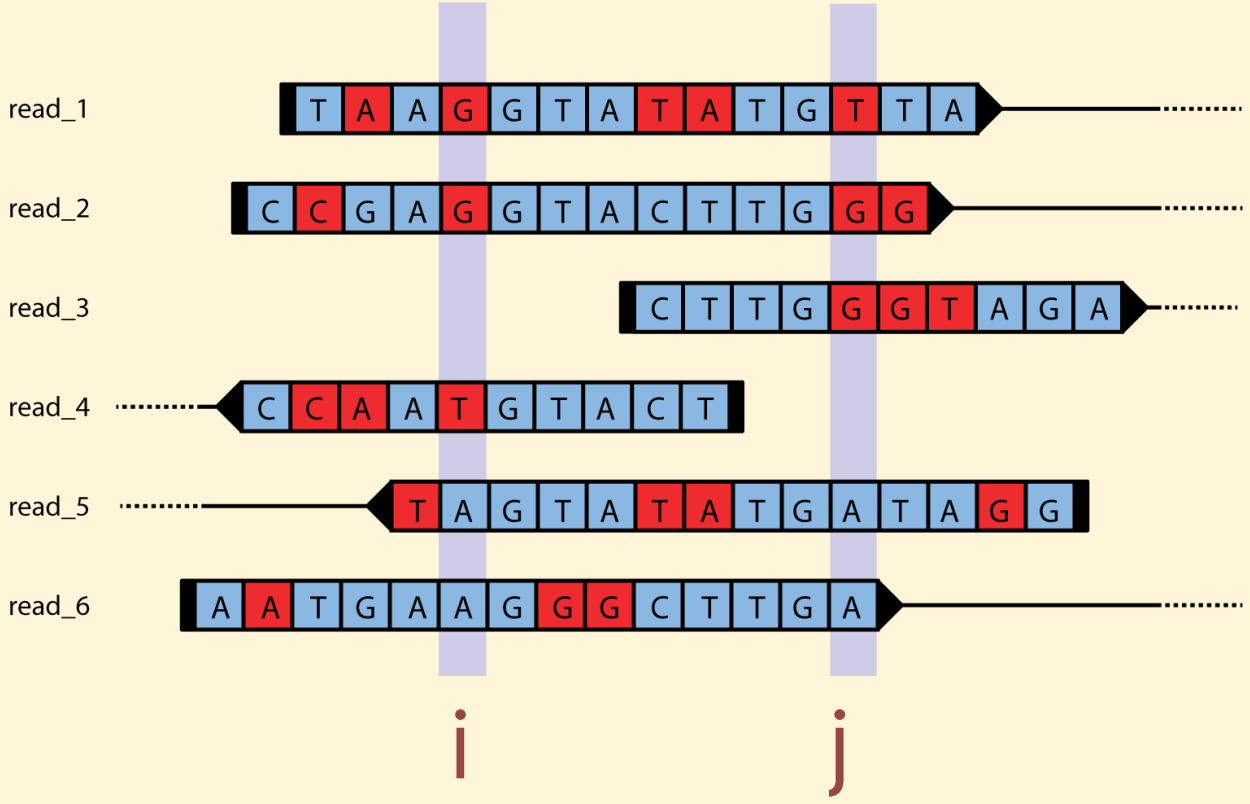
Displaying occurrence relationships (in biology)
similar visual metaphors and related workflow techniques

MatrixViewer
exploring design decisions in the first iteration, learning from analyst confusion

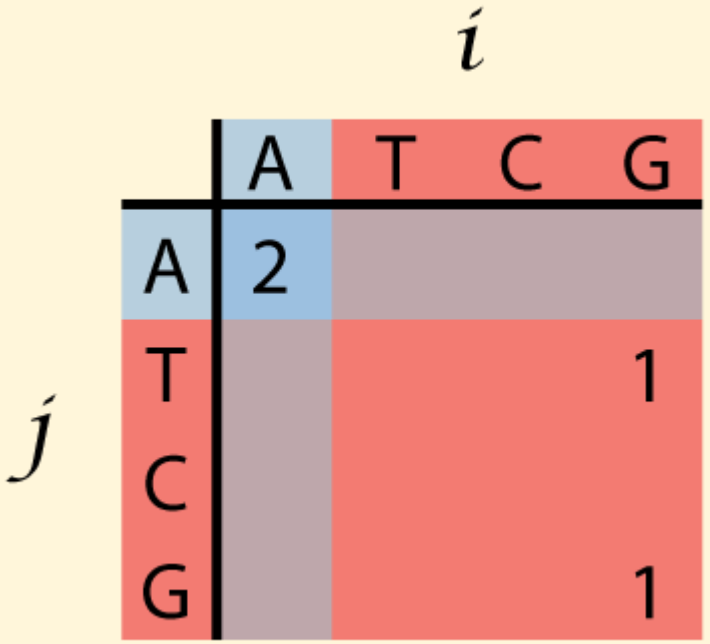
CooccurViewer
analyst-guided exploration of ‘interesting’ co-occurrences

Case Study, Future Work
application to virology workflow, application to other data domains

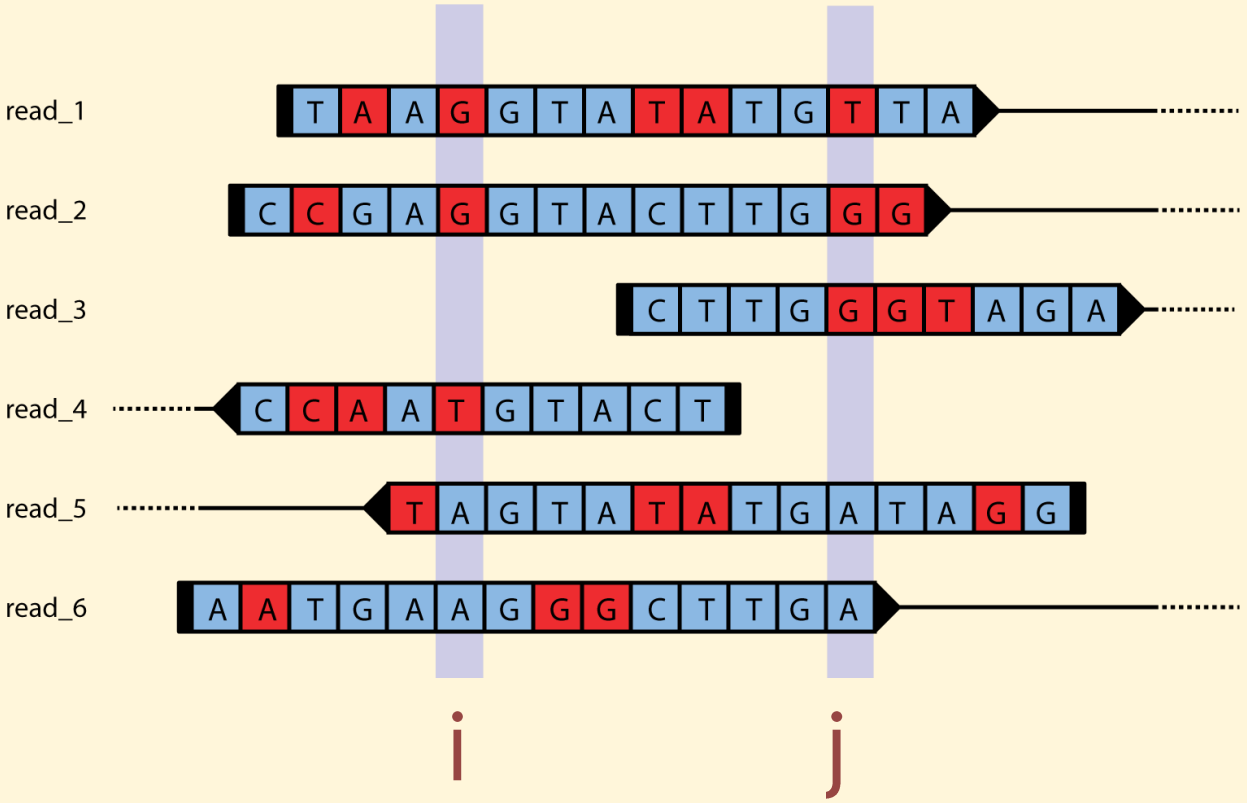
Visualizing Pairwise Correlation

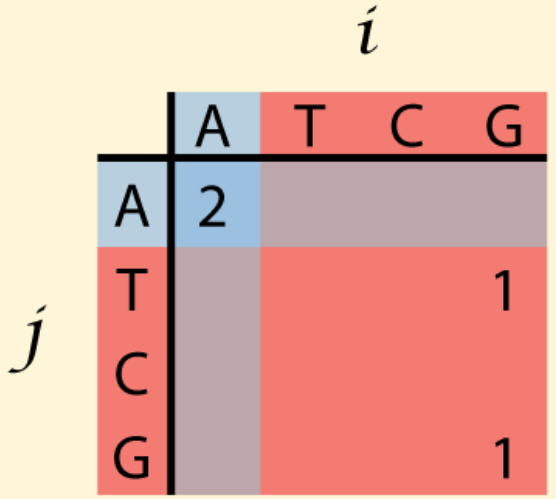


Collect counts of bases (A, C, T, G) for each pair of positions



Visualizing Pairwise Correlation



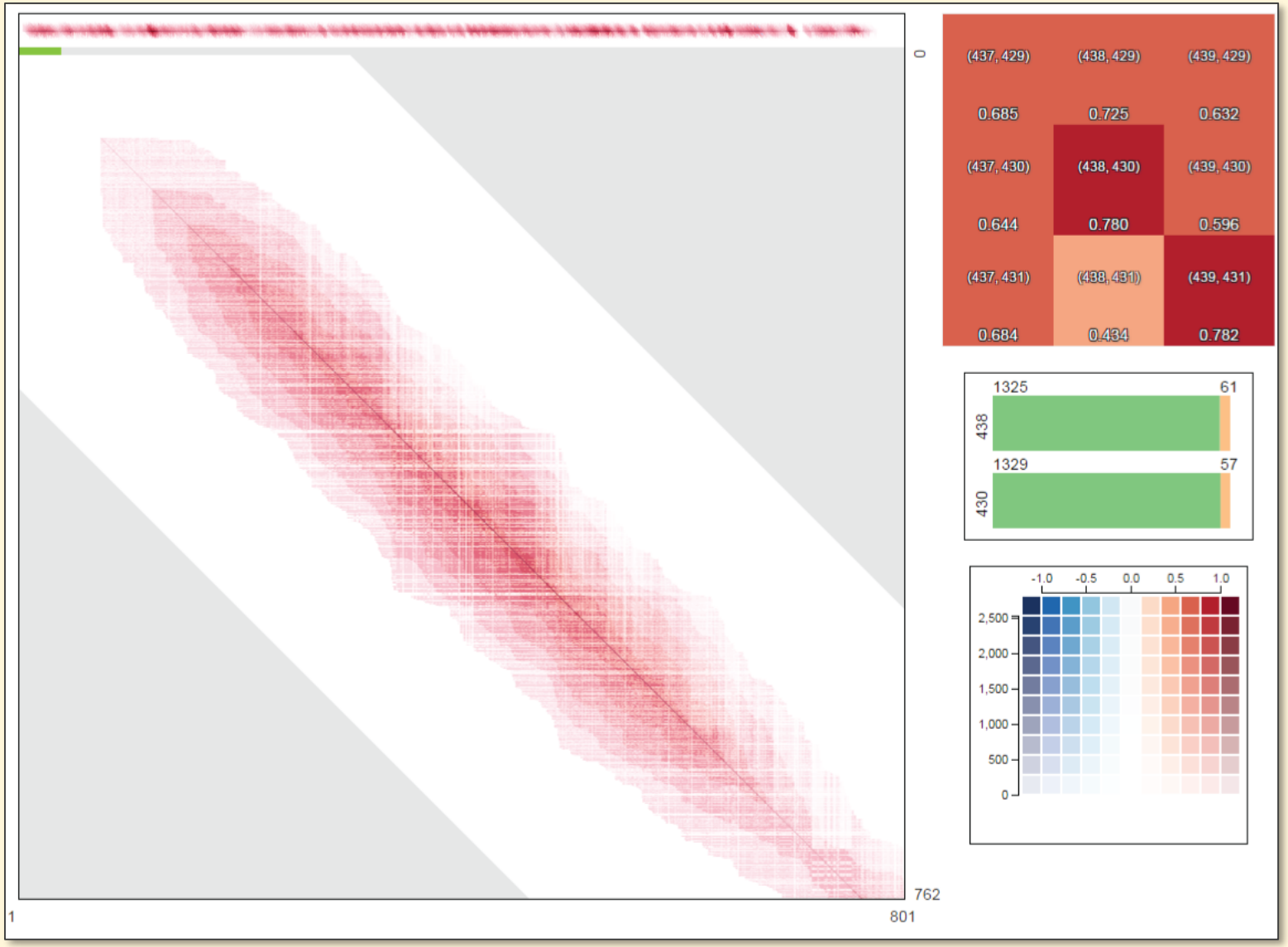


Compute co-occurrence strength between every pair of genomic positions

$$M_{i,j\_} = \Pr(j\_ | i\_) - \Pr(j\_ | i\_+)$$

Overview

Super-zoom



Pairwise genomic space

Key

Show co-occurrences in full pairwise genomic space, in a web browser

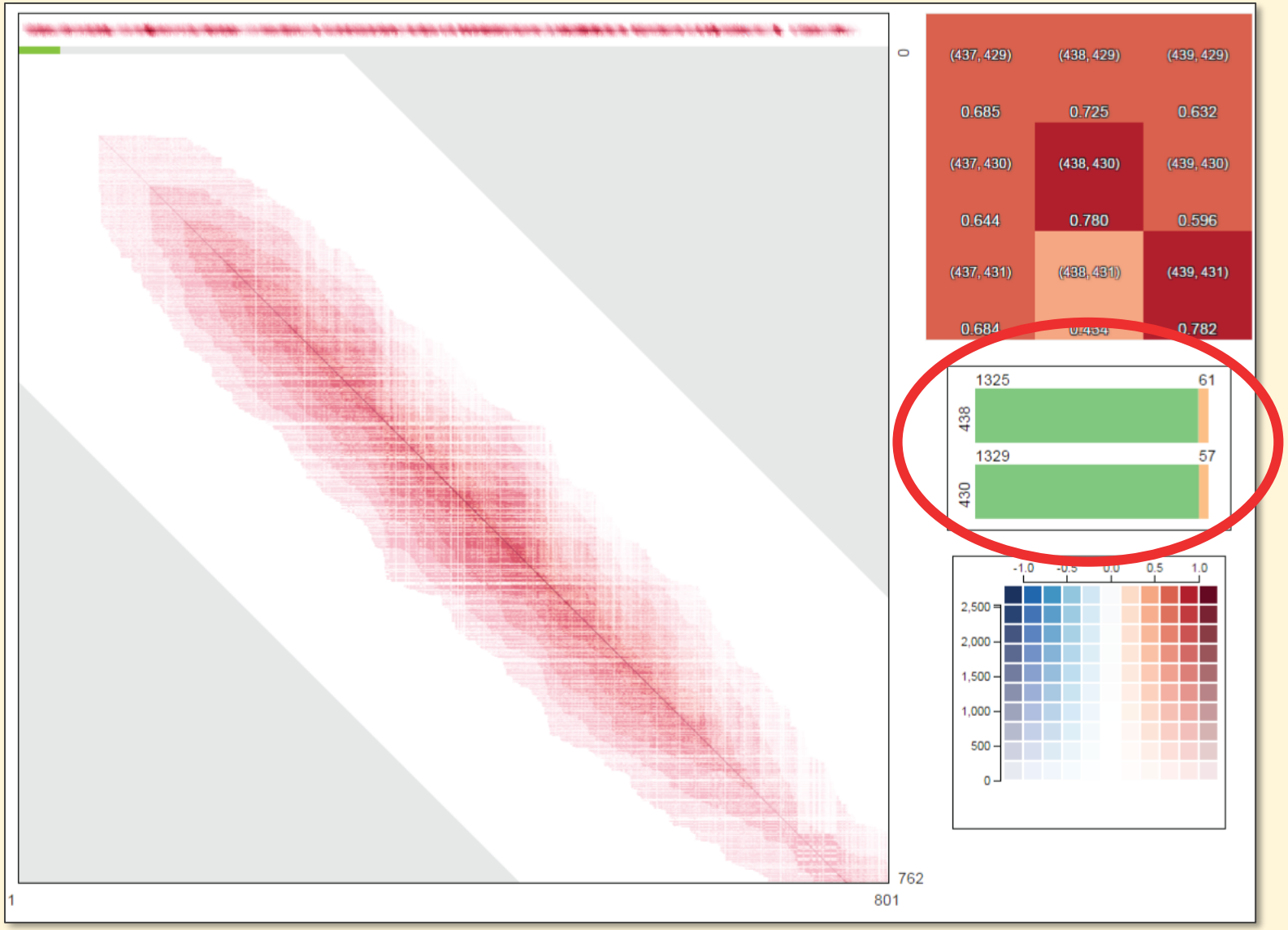
Scale up to 20,000 x 20,000

about 280k correlations considered

boost with WebGL and binary files

Color shows the co-occurrence strength

$$M_{i,j\_} = \Pr(j\_ | i\_) - \Pr(j\_ | i+)$$



Show co-occurrences in full pairwise genomic space, in a web browser

Scale up to 20,000 x 20,000

about 280k correlations considered

boost with WebGL and binary files

Color shows the co-occurrence strength

$$M_{i,j\_} = \Pr(j\_ | i\_) - \Pr(j\_ | i+)$$

Too much data to sift through

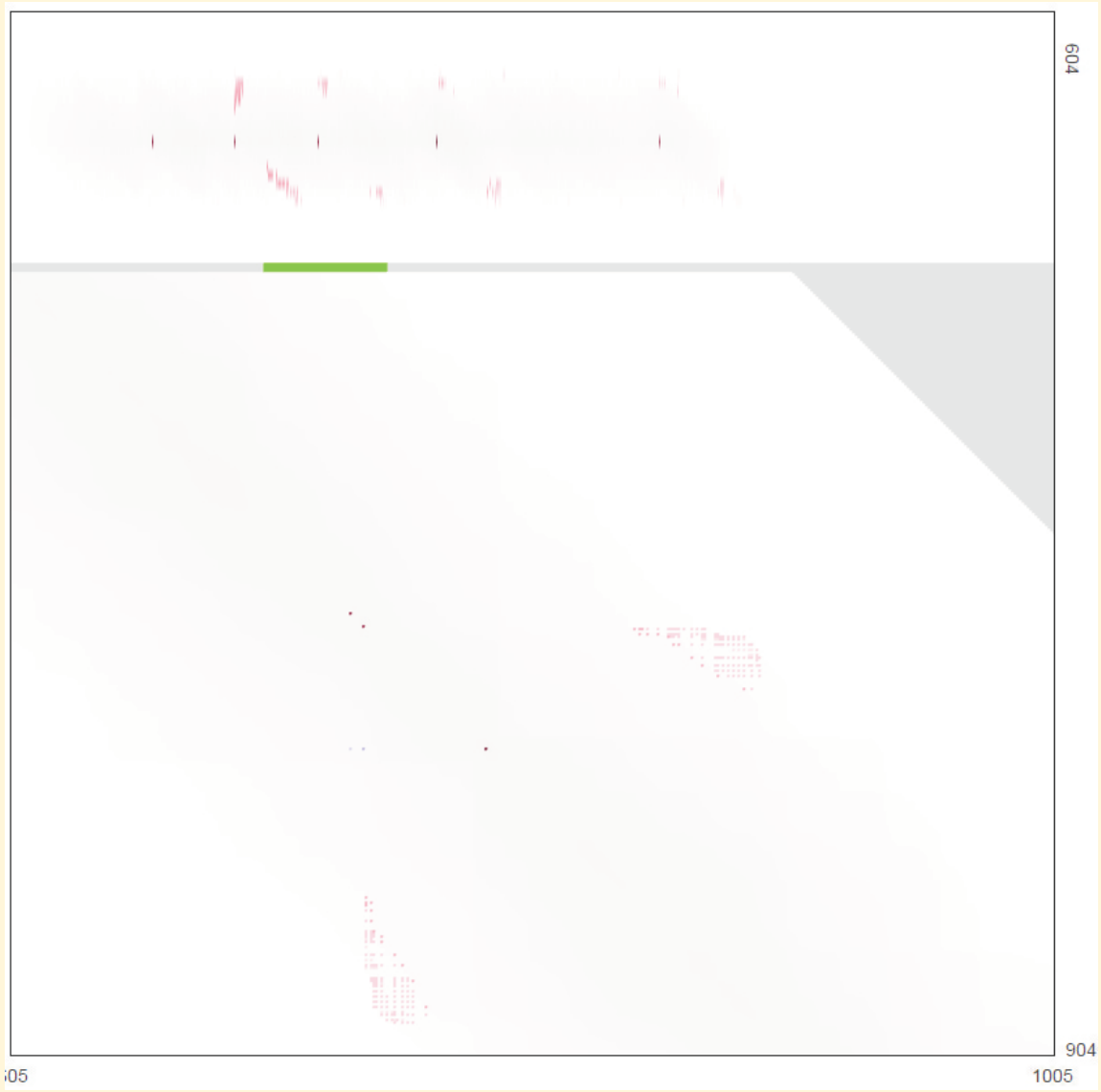
need to find the needle in the haystack by displaying the full space

Alignment errors produce false positives

only showing pairwise co-occurrences with 5% mutations makes matrix very sparse

Difficult to get an overview

Changing visualization parameters can have minute changes, easily missed by analyst



Learning from First Steps

Always present data in genomic sequence order

match mental model of the virologist, allows for rapid spatial identification

Display annotations alongside genome

annotations can provide valuable wayfinding with previous results and reading frames (nucleic bases to proteins)

Scaffold to navigate space of all pairwise correlation

support the analyst in discovering the most “interesting” co-occurrences

Support identifying synonymy

due to degeneracy in transcription, a change in the genome may not translate to a change in derived protein

Outline

Biological Background
bound our design space and exploration

Displaying occurrence relationships (in biology)
similar visual metaphors and related workflow techniques

MatrixViewer
exploring design decisions in the first iteration, learning from analyst confusion

CooccurViewer
analyst-guided exploration of ‘interesting’ co-occurrences

Case Study, Future Work
application to virology workflow, application to other data domains

Interest Metrics

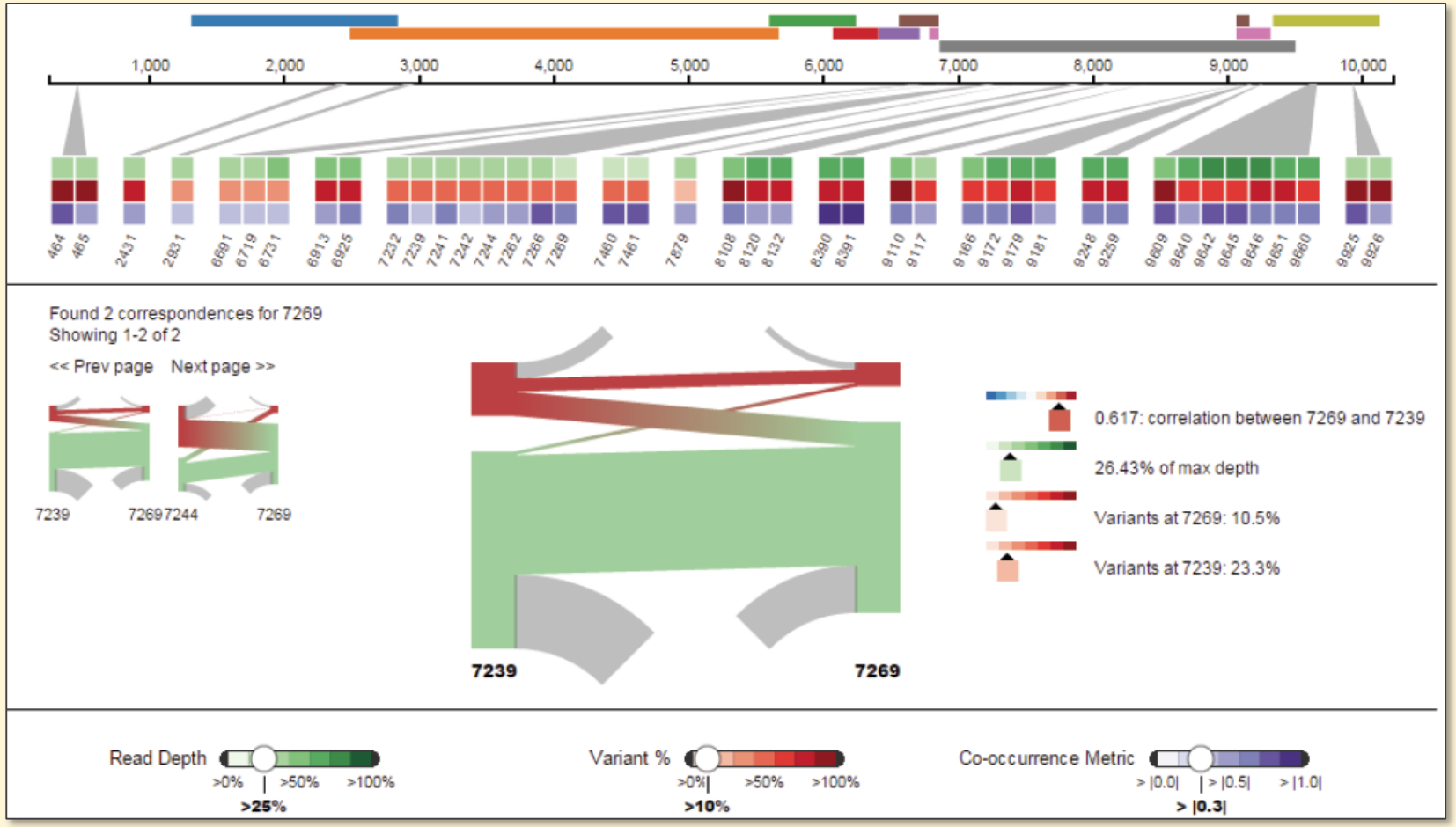
Coverage (read depth)
is there enough data to be meaningful?

Variation (mutations)
only showing pairwise co-occurrences with 5% mutations makes matrix very sparse

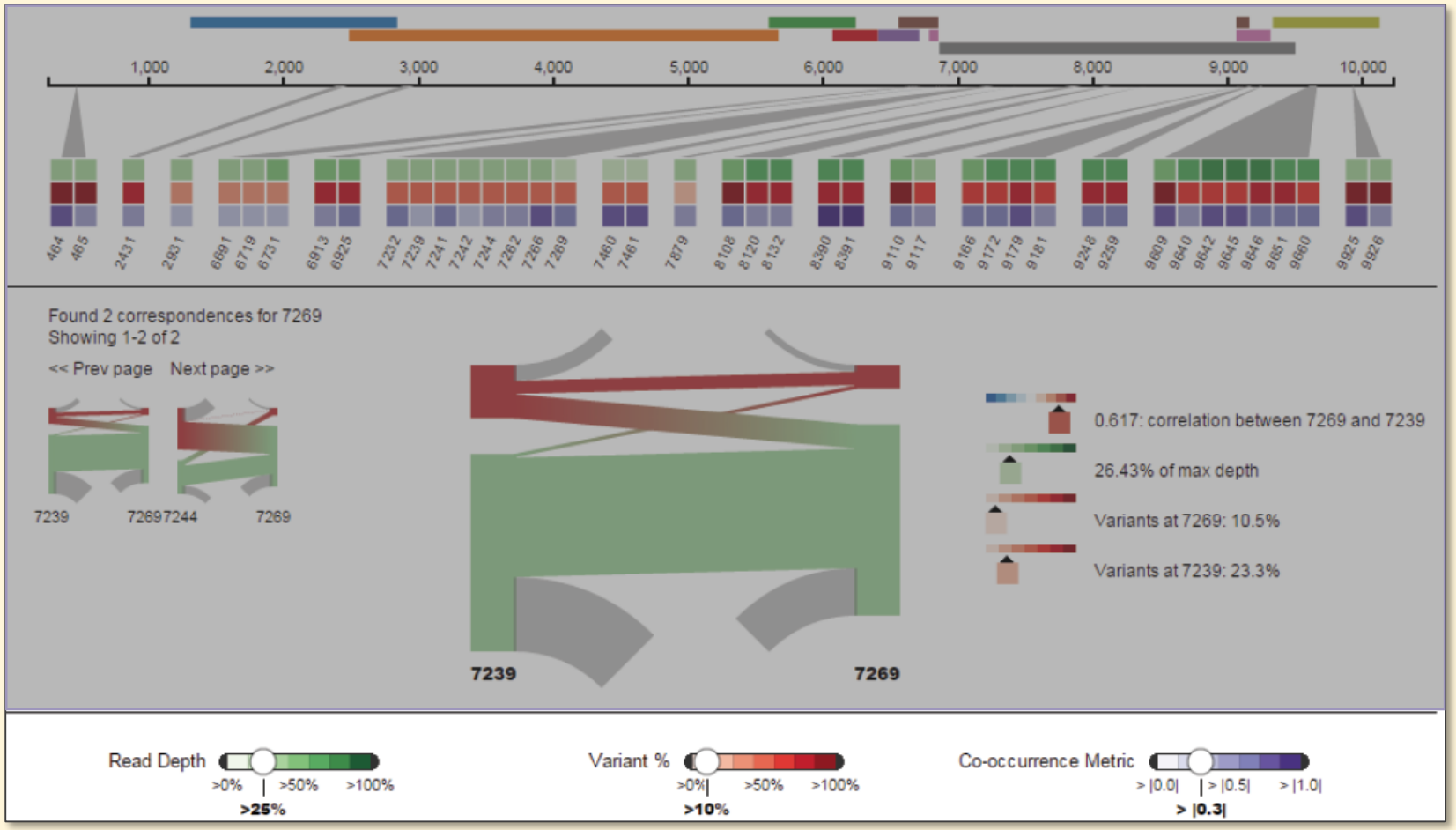
$$V_{i\_} = \Pr(i\_)$$

Co-occurrence strength
measure of interesting correlation,
signed positive or negative correlation

$$M_{i,j\_} = \Pr(j\_ | i\_) - \Pr(j\_ | i_+)$$

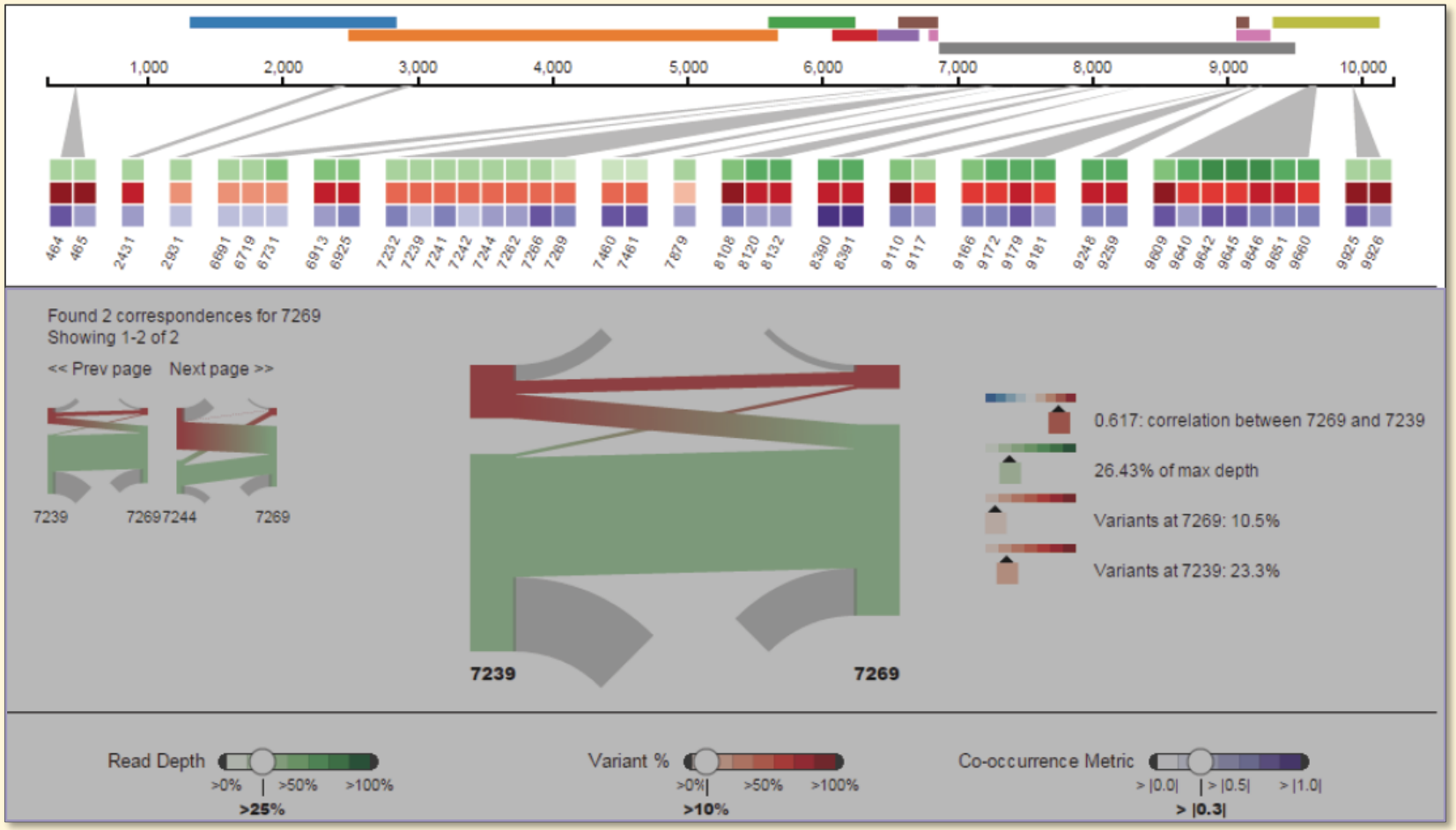


http://graphics.cs.wisc.edu/Vis/CooccurViewer



User-controlled metrics

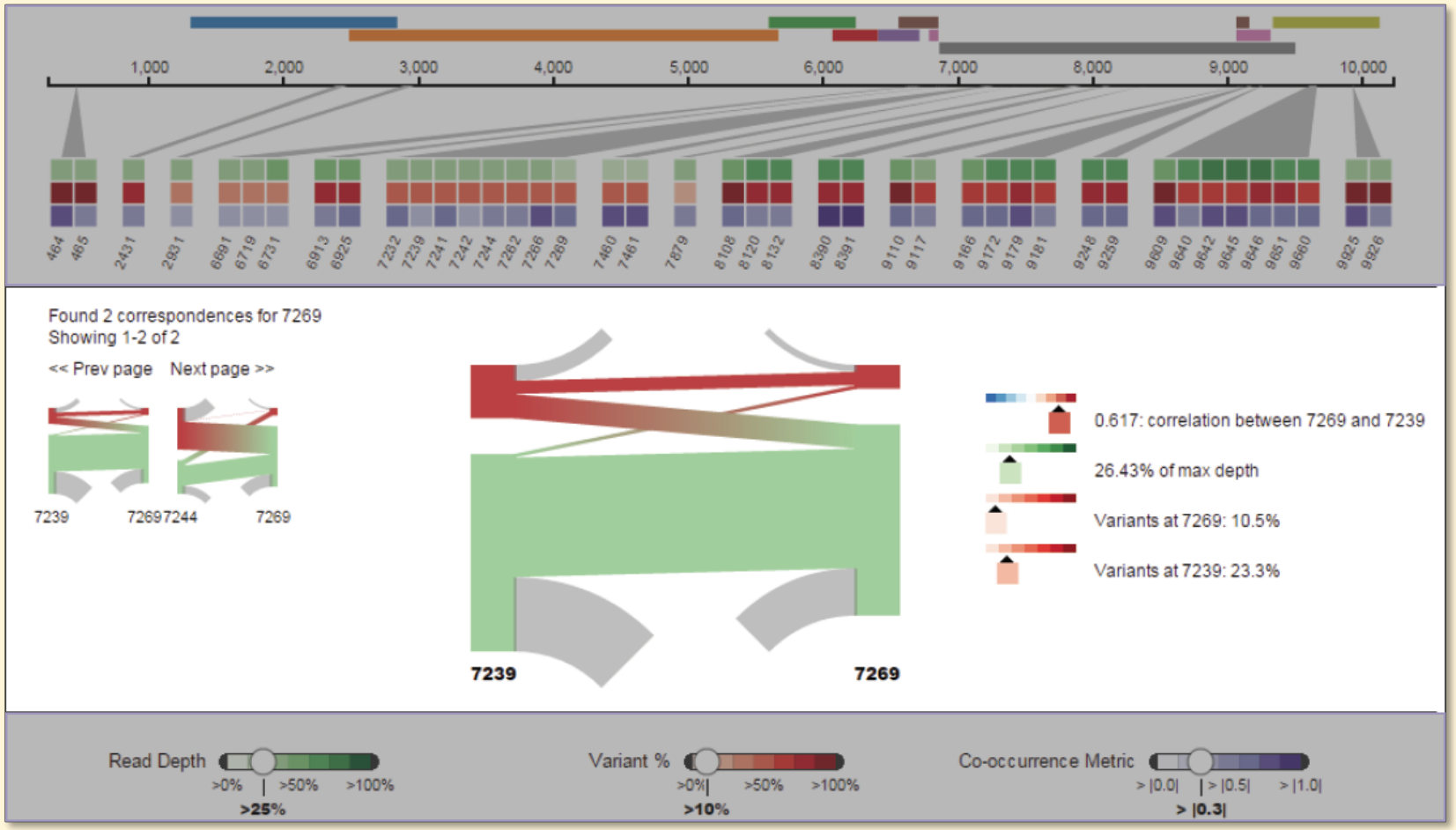
http://graphics.cs.wisc.edu/Vis/CooccurViewer



Annotations

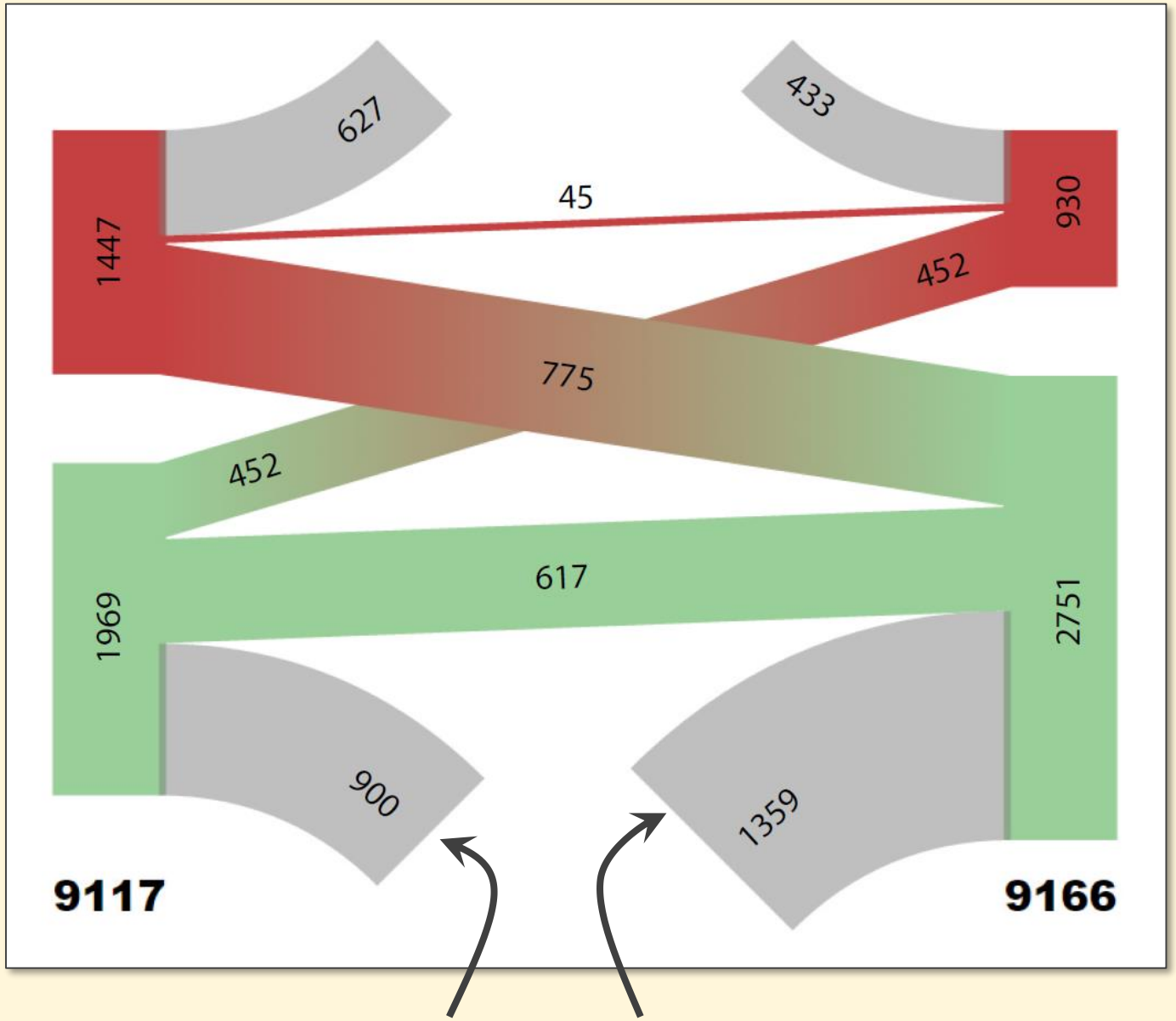
Positions with significant co-occurrences

http://graphics.cs.wisc.edu/Vis/CooccurViewer

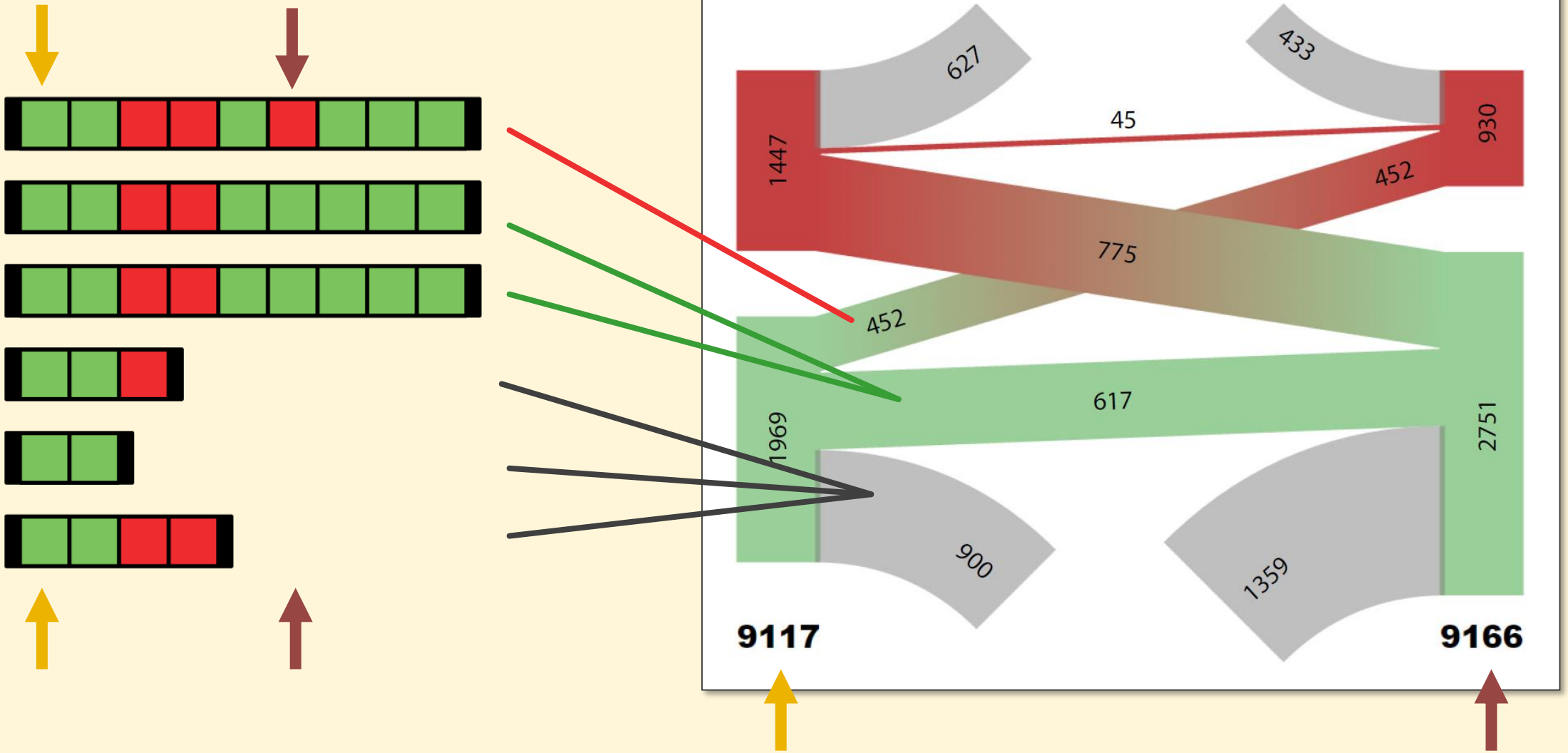


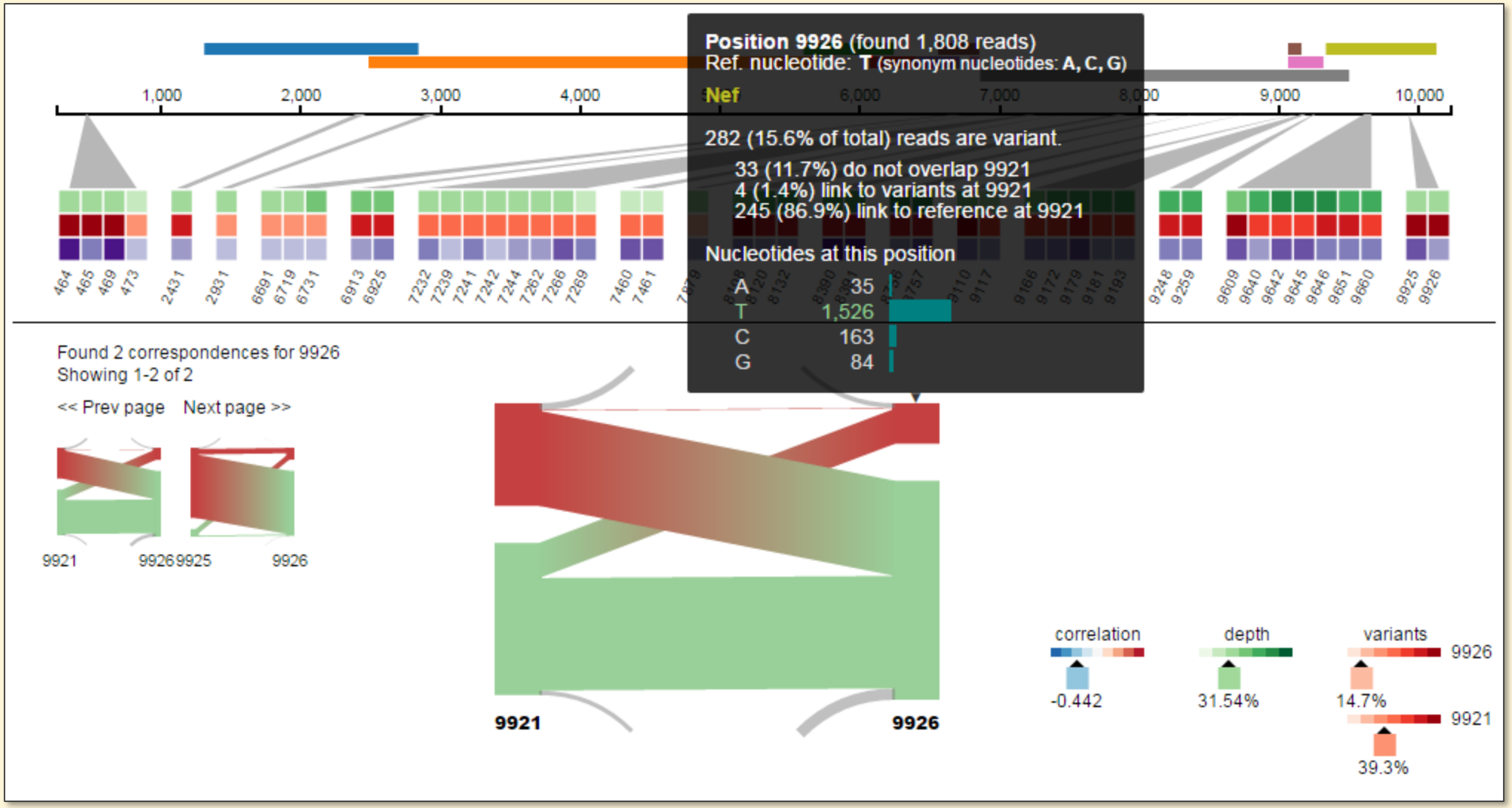
Pairwise co-occurrences with a particular position

http://graphics.cs.wisc.edu/Vis/CooccurViewer



Reads that do not overlap with the paired position


627
433
45
1447
930
452
775
452
617
1969
2751
900
1359
9117
9166


Position 9926 (found 1,808 reads)
Ref. nucleotide: T (synonym nucleotides: A, C, G)
Nef
1,000
2,000
3,000
4,000
6,000
7,000
8,000
9,000
10,000
282 (15.6% of total) reads are variant.
33 (11.7%) do not overlap 9921
4 (1.4%) link to variants at 9921
245 (86.9%) link to reference at 9921
Nucleotides at this position
A 35
T 1,526
C 163
G 84
Found 2 correspondences for 9926
Showing 1-2 of 2
<< Prev page
Next page >>
9921
9926
9925
9926
9921
9926
correlation
-0.442
depth
31.54%
variants
9926
14.7%
9921
39.3%

Outline

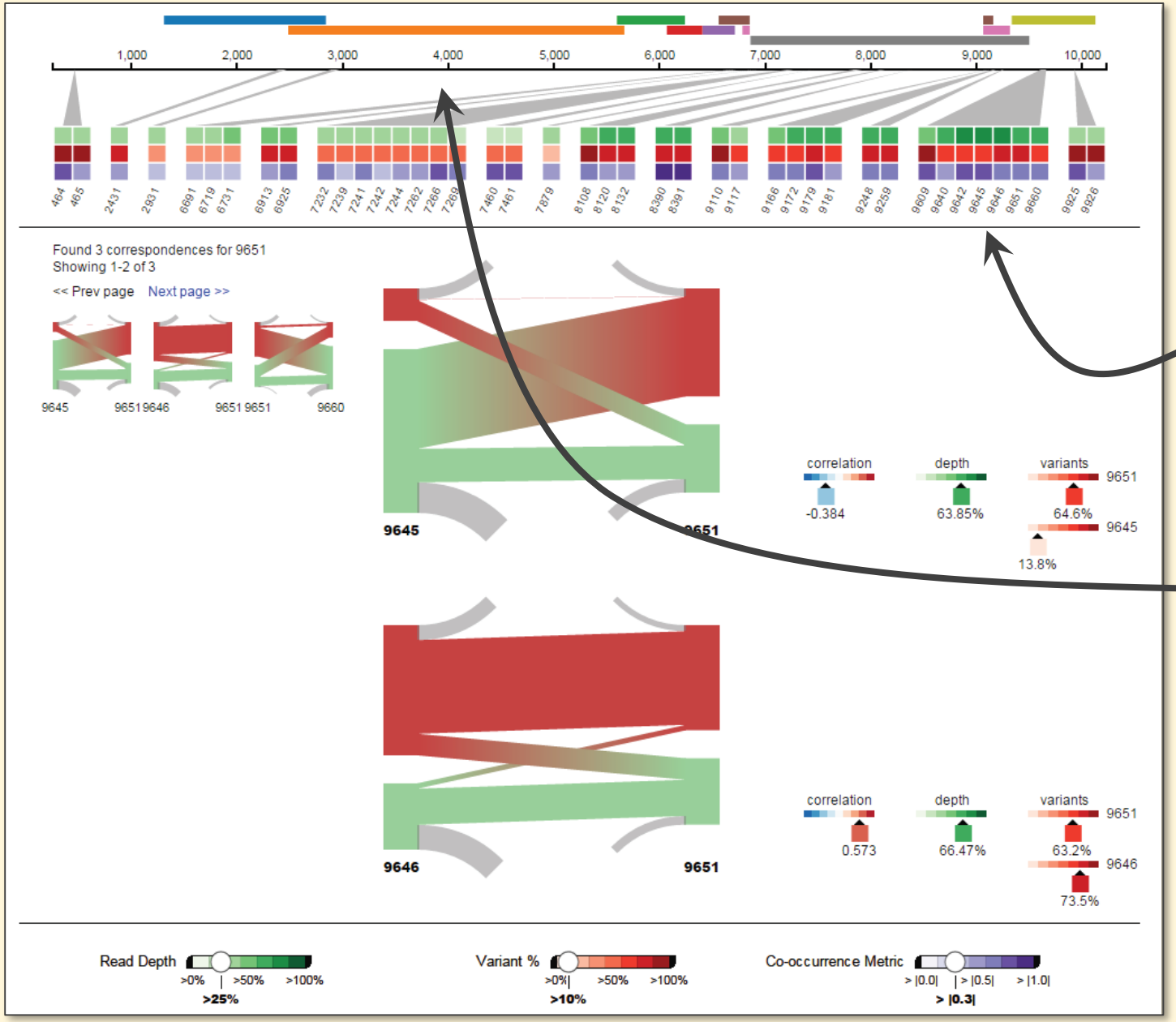
Biological Background
bound our design space and exploration

Displaying occurrence relationships (in biology)
similar visual metaphors and related workflow techniques

MatrixViewer
exploring design decisions in the first iteration, learning from analyst confusion

CooccurViewer
analyst-guided exploration of ‘interesting’ co-occurrences

Case Study, Future Work
application to virology workflow, application to other data domains



Sample of **SIV**:
simian equivalent of HIV

Large cluster of correlated mutations in Nef protein to evade T cell recognition

Nearly no co-occurrences in structural proteins Gal & Pol

Scale: 238k reads (24-151 bp each), genome is 9,973 bp; 2.78M pairwise comparisons

Discussion

Use analyst-controlled metrics to focus exploration

requires iteration to identify the key metrics interesting co-occurrences

Displaying the full space does not necessarily empower analysts

design must enable the analyst to quickly target their analysis to the critical relationships

Providing usable context and scaffolding

display of annotations and common genomic axis maintain virologists' mental map of the viral genome

Future Work

Support comparison between multiple samples, and multi-step co-occurrence

requires iteration to identify the key triggers, appropriate summarization

Data aggregation and filtering techniques to support larger data sizes

filter and aggregate data using WebGL (e.g. **imMens**), compress data

Application to other event-driven sequences

findings within this work can drive exploration of other domains, such as medical event data, event log data, etc.

Acknowledgments

@yelperalp

http://cs.wisc.edu/~sarikaya/

Funding from the NIH and NSF

we graciously acknowledge the support of NSF IIS-1162037 and
NIH award 5R01AI077376-07

Feedback from colleagues, virologists, and reviewers

for lifting this design study to benefit both the domain and vis communities

Code and working demo available online!

web: http://graphics.cs.wisc.edu/Vis/CoocurViewer/

github: http://github.com/uwgraphics/CooccurViewer/