The Genomics Task Force, GTrack, and Galaxy warping

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Overview

- The Genomics Task Force
  - statistical analysis of genomic tracks, employing:

The Genomic
HyperBrowser

- GTrack
  - generic file format for all types of genomic tracks
- Warping the Galaxy
  - Example: custom web tool definition framework

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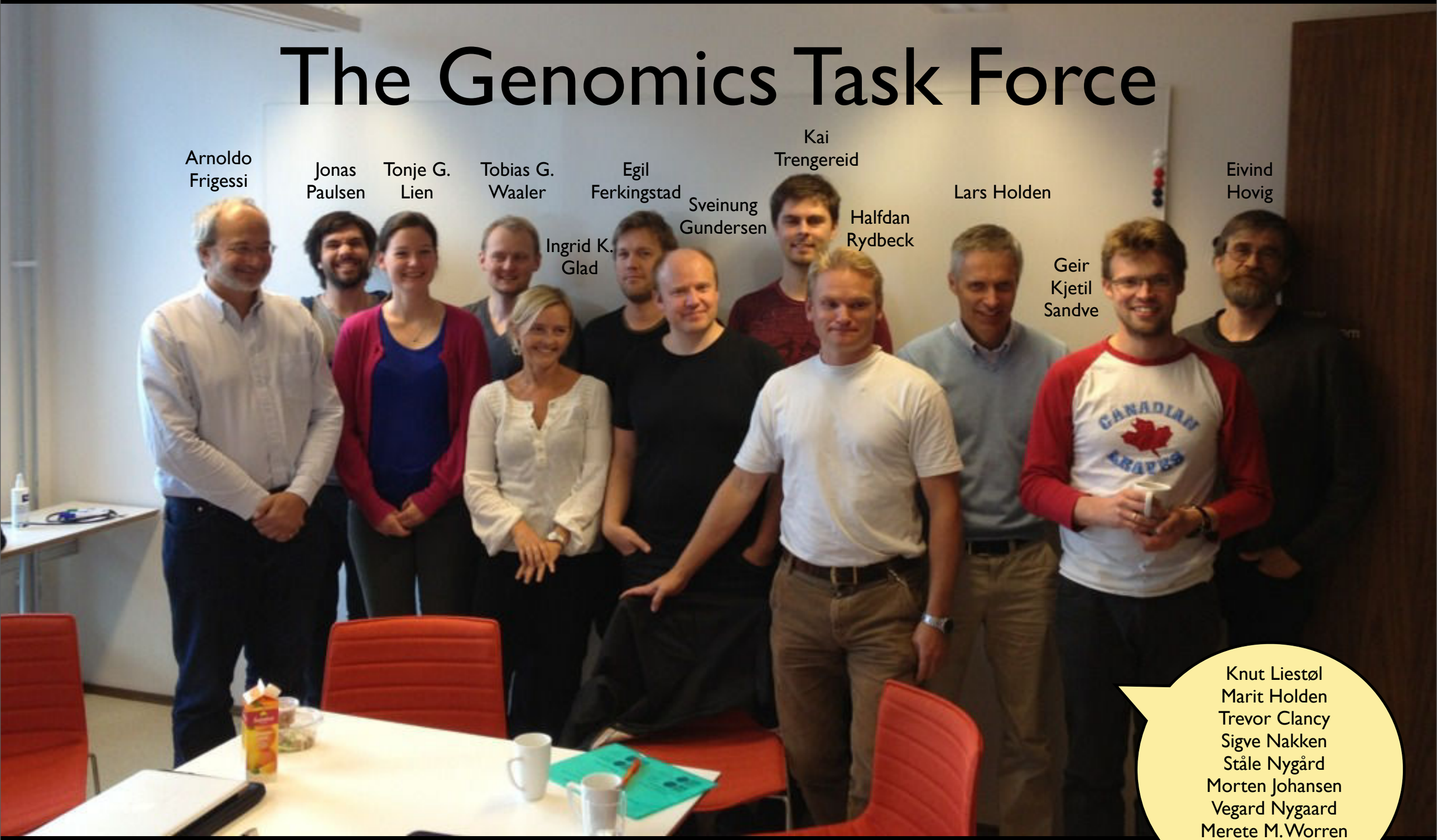
The Genomics Task Force



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Marit Holden
Trevor Clancy
Sigve Nakken
Ståle Nygård
Morten Johansen
Vegard Nygaard
Merete M. Worren
Daniel Vodák
...

The Genomics Task Force

- 4 professors of Biology/Bioinformatics/Statistics (via Statistics for Innovation)
- 3 researchers of Statistics from Norwegian Computing Center
- 4 postdocs of Biology/Bioinformatics/Statistics
- 4 PhD students of Bioinformatics/Statistics
- 5 bioinformaticians connected to the core facility
- 5 master students of (Bio)informatics

The Norwegian Radium Hospital
& University of Oslo

The Genomic HyperBrowser

- Implemented on top of Galaxy
- Launched in Dec 2010:

  Sandve, G. K., Gundersen, S., Rydbeck, H., Glad, I. K., et al. The Genomic HyperBrowser: inferential genomics at the sequence level. Genome biology 11, R121 (2010).

- The Genomic HyperBrowser provides hypothesis testing and descriptive statistics on any:
  - *single genomic track*
  - *pair of genomic tracks*
  - *more than two genomic tracks*
- Available at http://hyperbrowser.uio.no

Genomic track:
Anything that can be positioned on a reference genome

Example analysis

- Track 1:
  - 57 genomic regions associated with multiple sclerosis (MS) from a recent GWAS study:
    - *Sawcer, S., Hellenthal, G., Pirinen, M., Spencer, C. C., et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476, 214-219 (2011)*
  - One BED-file with 57 regions:

```
chr1   2396586     2827369
chr1   92014277    93306499
chr1   100983315   101455310
chr1   116832232   116909542
chr1   190733439   190814781
chr1   199128354   199336605
...
```

Example analysis (cont.)

- Track 2:
  - Genome-wide chromatin profiling from another recent Nature paper:
    - *Ernst, J., Kheradpour, P., Mikkelsen, T. S., Shoresh, N., et al. Mapping and analysis of chromatin state dynamics in nine human cell types. Nature 473, 43-49 (2011).*
  - We want to compare active promoter regions in B-lymphoblastoid cells (GM12878) with those in normal epidermal keratinocytes (NHEK).
  - These are two separate datasets, already included in the track repository (> 200 000 tracks) in the HyperBrowser.
  - We want to combine them into one case/control track. The HyperBrowser has a webtool for this (around 90 custom Galaxy tools)

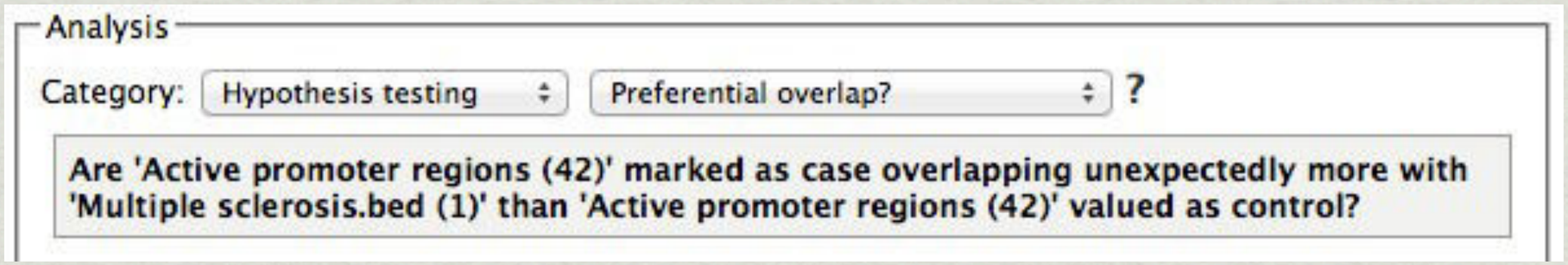
Example analysis (cont.)

- Track 2 (cont.):
  - We end up with a GTrack file (which contains headers specifying that this is a case/control track). Here 1 (case) is GM12878 and 0 (control) is NHEK:

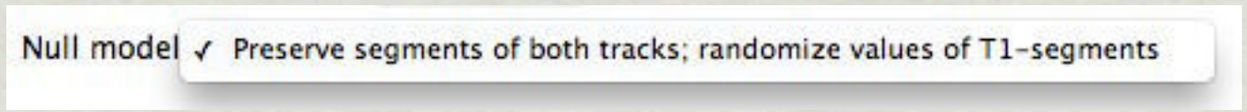
```
##gtrack version: 1.0
##track type: valued segments
##value type: binary
###seqid  start   end     value
chr1      29737   29937   0
chr1      715337  715537  0
chr1      715537  715737  1
chr1      752737  753137  0
chr1      761737  761937  0
chr1      894537  894737  1
...
```

Example analysis (cont.)

- We want to find whether MS-related regions overlap with active promoter regions more in B- lymphoblastoid cells (GM12878) than in normal epidermal keratinocytes (NHEK)
- In the Genomic HyperBrowser, we select tracks 1 and 2 as specified before, and the following analysis (out of around 100 different analyses):



Null model selection



- A null model is a model of the observed system where the effect under study has been "nullified" in some way
- Defined via:
  - Preservation rule
  - Stochastic process of non-preserved elements
- The null model should reflect biological realism, but also allow sufficient variation to permit the construction of tests.
- The results of a hypothesis test is highly dependent on the null model
- The most difficult choice when calculating p-values. Often overlooked
- In this example, only one null model has been implemented

Answer

You asked:

Are 'Active promoter regions' marked as case overlapping unexpectedly more with 'Multiple sclerosis.bed' than 'Active promoter regions' valued as control?

Simplistic answer:

Yes - the data suggests this (p-value: 0.004975)

Precise answer:

The p-value is 0.004975.

Low p-values are evidence against H0.

The test was also performed for each bin separately, resulting in 0 significant bins out of 26, at 10% FDR* (17 bins excluded from FDR-analysis due to lacking p-values).

Please note that both the effect size and the p-value should be considered in order to assess the practical significance of a result.

* False Discovery Rate: The expected proportion of false positive results among the significant bins is no more than 10%.

P-values were computed under the **null model** defined by the following preservation and randomization rules:

Preserve segments of both tracks; randomize values of T1-segments

---

The **test statistic** used is:

Main result of analysis

The value of the test statistic is 105 737.

The p-values may be subject to further parameter choices, which are listed in the run description. See note for a more complete description of the test.

See full details of the results in table form.

Answer (local results)

Region	P-value	FDR-adjusted p-values	Test statistic: Main result	Mean of null distribution	Median of null distribution	Standard deviation of null distribution	Difference from mean	Number of Monte Carlo samples
chr1:1-121535434 [chr1p]	0.09967	0.3396	5 200	1 549.	1600.0	2 782.	3 651.	300
chr1:142535435-249250621 [chr1q]	1.0	1.0	0	0.0	0.0	0.0	0.0	100
chr2:1-90545103 [chr2p]	0.3168	0.6865	1 000	380.0	600.0	923.3	620.0	100
chr2:95326172-243199373 [chr2q]	0.1045	0.3396	3 400	788.0	600.0	1 842.	2612.0	200
chr3:1-90504854 [chr3p]	1.0	1.0	0	0.0	0.0	0.0	0.0	100
chr3:93504855-198022430 [chr3q]	1.0	1.0	-4 600	680.0	1000.0	2 061.	-5280.0	100
chr4:1-49660117 [chr4p]	None	nan	0	0.0	0.0	0.0	0.0	100
chr4:52660118-191154276 [chr4q]	0.04790	0.3311	4 000	248.0	400.0	2 129.	3752.0	500
chr5:1-46405641 [chr5p]	0.9901	1.0	-4 000	920.0	3200.0	3 543.	-4920.0	100
chr5:49405642-180915260 [chr5q]	0.07481	0.3311	10 072	1 933.	3128.0	5 972.	8 139.	400
chr6:1-58830166 [chr6p]	None	nan	0	0.0	0.0	0.0	0.0	100
chr6:61830167-171115067 [chr6q]	0.2277	0.5383	7 800	1488.0	1000.0	6 248.	6312.0	100
chr7:1-58054331 [chr7p]	None	nan	0	0.0	0.0	0.0	0.0	100
chr7:61967158-159138663 [chr7q]	0.7030	1.0	600	1052.0	1000.0	1 481.	-452.0	100
chr8:1-43838887 [chr8p]	None	nan	0	0.0	0.0	0.0	0.0	100
chr8:46838888-146364022 [chr8q]	0.7624	1.0	200	728.0	1000.0	1 037.	-528.0	100

Publishable results

- *Disanto, G., Sandve, G. K., Berlanga-Taylor, A. J., Morahan, J. M., et al. Genomic regions associated with multiple sclerosis are active in B cells. PLoS One 7, e32281 (2012).*

- From the same authors (In total 3 publications using the HyperBrowser in half a year, 2 more coming):

It is possible to publish based on public datasets (all 3).

2 of these required some custom extensions that we helped with, the third used the HyperBrowser without modifications

Of course powerful to analyse own datasets

Disanto, G, G K Sandve, A J Berlanga-Taylor, G Ragnedda, J M Morahan, C T Watson, G Giovannoni, G C Ebers, and S V Ramagopalan. "Vitamin D Receptor Binding, Chromatin States and Association with Multiple Sclerosis." Human molecular genetics 21, no. 16 (2012): 3575-3586.

Watson, C. T., Disanto, G., Sandve, G. K., Breden, F., et al. Age-Associated Hyper-Methylated Regions in the Human Brain Overlap with Bivalent Chromatin Domains. PLOS ONE ***7,*** *e43840 (2012).*

The Genomics Task Force

- High competence in bioinformatics and statistics
- Can implement custom-tailored hypothesis tests, analyses, result plots and advanced Galaxy tools
- Everything will be available from a simple user interface in the Genomic HyperBrowser (http://hyperbrowser.uio.no)
- We are interested in collaborations (from simple extensions of existing functionality to new research collaborations).
- E-mail: hyperbrowser-requests@usit.uio.no

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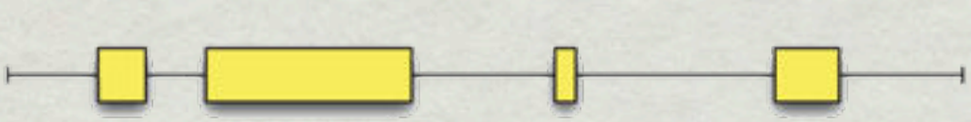
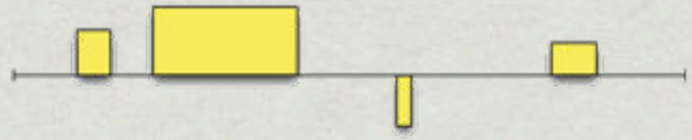
Track types

- Developed in:
  - *Gundersen, S., Kalas, M., Abul, O., Frigessi, A., et al. Identifying elemental genomic track types and representing them uniformly. BMC bioinformatics 12, 494 (2011).*



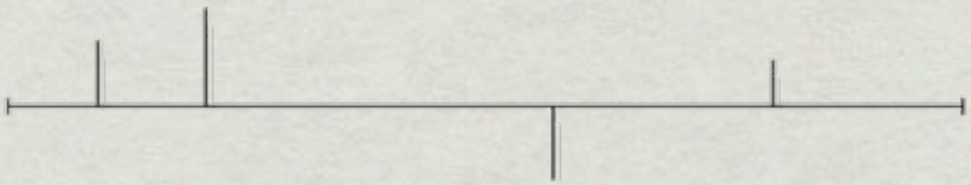
Segments (S)

BED



Valued Segments (VS)

BedGraph

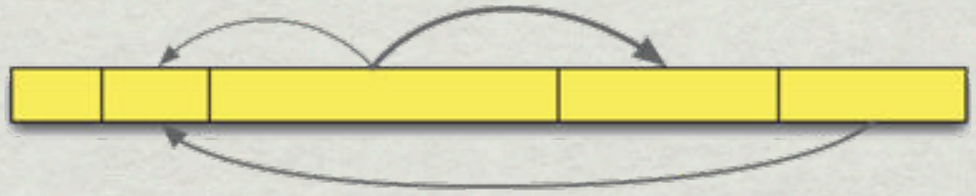


Valued Points (VP)

WIG

Function (F)

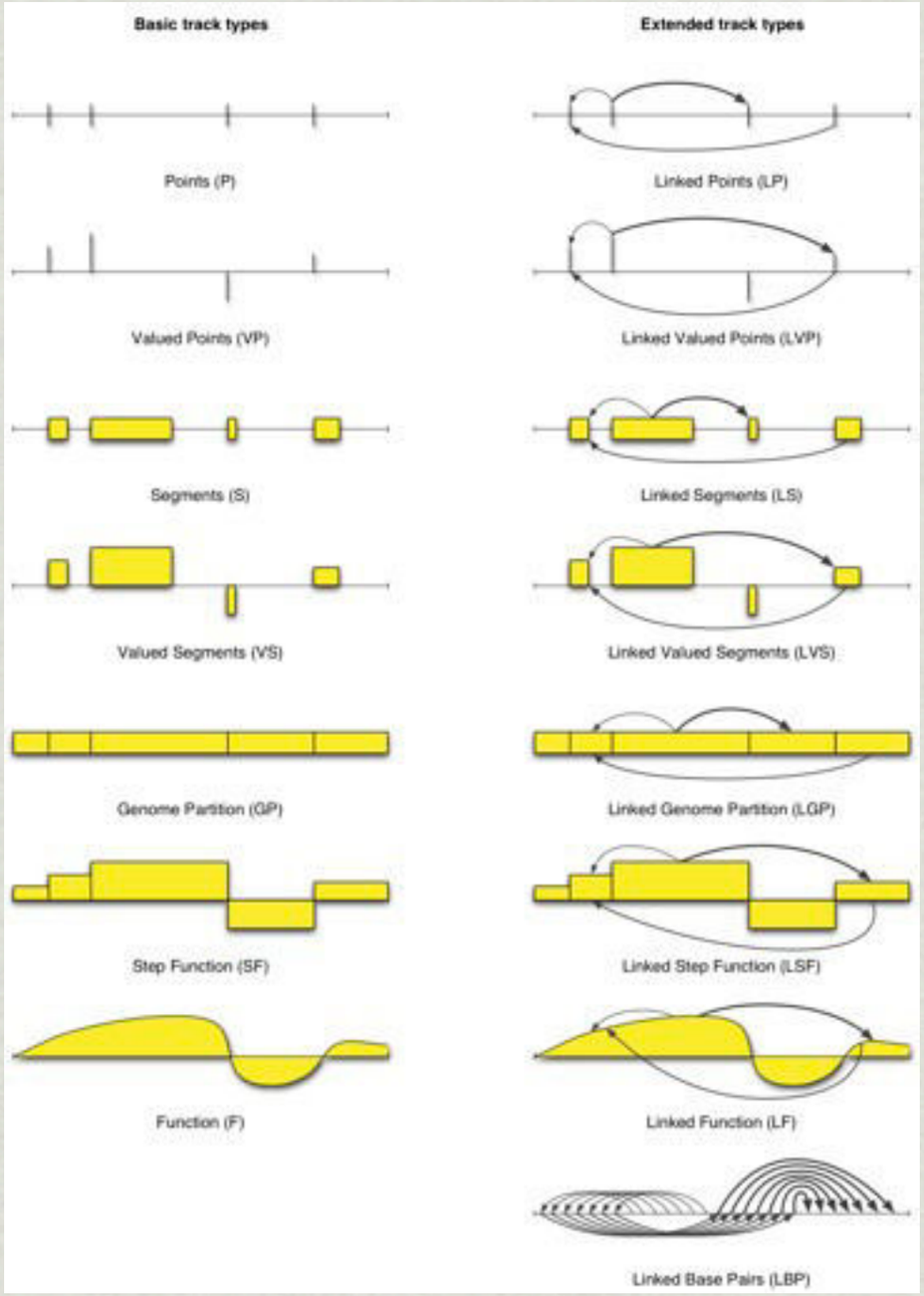
WIG



Linked Genome Partition (LGP)

Hi-C (no format yet)

15 track types



GTrack

- "Genomic Track" or "Generic Track"
- Supports all fifteen track types (using practical representations)
- Humanly readable
- Reasonably simple to parse
- Extensible for future extensions (can add custom columns)
- Research groups or tool developers can define their own specific GTrack subtypes
- GTrack fully supported by the HyperBrowser
- http://www.gtrack.no
- In the process of creating standalone Python library

GTrack example (simple)

```
chr1        2396586     2827369
chr1        92014277    93306499
chr1        100983315   101455310
chr1        116832232   116909542
chr1        190733439   190814781
chr1        199128354   199336605
...
```

Basic three-column BED file is directly compatible with a GTrack file

GTrack example (intermediate)

```
##gtrack version: 1.0
##track type: valued segments
##value type: binary
###seqid  start       end         value
chr1      2396586     2827369     1
chr1      92014277    93306499    1
chr1      100983315   101455310   0
chr1      116832232   116909542   0
chr1      190733439   190814781   1
chr1      199128354   199336605   0
...
```

More than standard 3-column BED, needs column specification line, and other basic headers lines

GTrack example (advanced)

```
##gtrack version: 1.0
##track type: linked genome partition
##edge weights: true
###end    id    edges

####seqid=chr1; start=1000; end=2000
1015        a       c=1.3,d=0.1
1060        b       a=1.0
1154        c       a=1.3
1267        d       .
...
```

3D data set

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Warping the Galaxy

- custom modifications of Galaxy

- Custom web tool definition framework:
  - Based on our own mako code (genericTool.mako)
  - New web tools are generated based on new python classes
  - We have defined an interface (GeneralGuiTool.py), which we subclass for each tool
  - We have defined a standard set of reusable GUI elements (textbox, selection box, genome and track lists, etc.)
  - The contents of the GUI can be dynamically changed according to the python code, (almost) anything is possible

Custom Galaxy webtools (example)

Create GTrack file

Select input source: Tabular file from history

Select tabular file: 14 – Active promoter regions

Character to use to split lines into columns: Tab

Number of lines to skip (from front): 6

Column selection method: Select individual columns

Select the name for column #1: seqid

Select the name for column #2: start

Select the name for column #3: end

Select the name for column #4: value

Select a specific genome? Yes

Genome build: Human Feb. 2009 (hg19/GRCh37)

Dependency between choices

Table created from dataset in history

seqid	start	end	value
chr1	28537	29337	1
chr1	28537	29737	0
chr1	540737	540937	1
chr1	713337	715337	0
chr1	713537	715137	1
chr1	715537	715737	0
chr1	761937	763537	0
chr1	761937	763537	1
chr1	893937	894737	0
chr1	893937	894737	1
chr1	895737	895937	1

Current track type (based on the selected column names):

Valued Segments (VS)

Warping the Galaxy

- custom modifications of Galaxy

- Advantages:
  - No need for knowledge on GUI coding or Galaxy to create a web tool
  - Quick prototyping => Simplifies sharing of new functionality with others
  - Independent of Galaxy, and could in principle be connected to another system
  - We have full control and can expand as needed
- Disadvantages:
  - Minimal workflow support

Warping the Galaxy

- custom modifications of Galaxy

- Other tweaks:
  - Separate, monolithic codebase (850 files, 72500 lines of code)
  - Separate data collection
  - Separate result files (linked to by HTML)
  - Batch run interface (of all analyses and tools)
  - And more...

Support

RIKSHOSPITALET

EMBIO Styringsgruppen for Molecular Life Sciences ved UiO

UNIVERSITY OF OSLO

NR Norsk Regnesentral NORWEGIAN COMPUTING CENTER

FUGE Functional genomics

(sfi)² Statistics for Innovation

sfi Centre for Research-based Innovation

Questions/comments?