

Hierarchical Alignment (HAL) Format API (v1.2)

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HAL is a structure to efficiently store and index multiple genome alignments and ancestral reconstructions. HAL is a graph-based representation which provides several advantages over matrix/block-based formats such as MAF, such as improved scalability and the ability to perform queries with respect to an arbitrary reference or subtree.

This package includes the [HAL API](#) and several analysis and conversion tools which are described below. HAL files are presently stored in [HDF5](#) format, but we note that the tools and most of the API are format-independent, so other databases could be implemented in the future.

Citing

Glenn Hickey, Benedict Paten, Dent Earl, Daniel Zerbino, and David Haussler. *HAL: A Hierarchical Format for Storing and Analyzing Multiple Genome Alignments*. (submitted).

Installation

Requirements

- gcc 4.2 or newer
- git

Downloading HAL

From the parent directory of where you want HAL installed:

```
git clone git://github.com/glennhickey/hal.git
```

Installing Dependencies

HDF5 1.8 with C++ API enabled

- Using [MacPorts](#):

```
sudo port install hdf5-18 +cxx
```

- From [Source](#):

```
wget http://www.hdfgroup.org/ftp/HDF5/current/src/hdf5-1.8.9.tar.gz
tar xzf hdf5-1.8.9.tar.gz
```

```
cd hdf5-1.8.9
./configure --enable-cxx
make && make install
```

- Local install from source into DIR (do not need root)

```
mkdir DIR/hdf5
wget http://www.hdfgroup.org/ftp/HDF5/current/src/hdf5-1.8.9.tar.gz
tar xzf hdf5-1.8.9.tar.gz
cd hdf5-1.8.9
./configure --enable-cxx --prefix DIR/hdf5
make && make install
```

Before building HAL, update the following environment variables:

```
export PATH=DIR/hdf5/bin:${PATH}
export h5prefix=-prefix=DIR/hdf5
```

sonLib

From the same parent directory where you downloaded HAL:

```
git clone git://github.com/benedictpaten/sonLib.git
pushd sonLib && make && popd
```

If sonLib and HAL are not sister directories, update hal/include and change

```
sonLibRootPath=${rootPath}/../sonLib
```

to reflect the directory where you installed sonLib

Building HAL

From the hal/ directory:

```
`make`
```

Before using HAL, add it to your path:

```
`export PATH=<path to hal>/bin:${PATH}`
```

HAL Tools

General Options

Detailed command line options can be obtained by running each tool with the `--help` option.

All HAL tools compiled with HDF5 support expose some caching parameters. Tools that create HAL files also include a chunking and compression parameters. In most cases, the default values of these options will suffice.

`--cacheBytes <value>`: The maximum size of each array cache. 3 such caches can be allocated per

genome in the alignment.

`--cacheRDC <value>`: The number of slots in each cache. This number should be set to a prime number that is roughly $50 \times [\text{cacheBytes} / \text{chunk}]$.

`--cacheMDC <value>`: Size of the metadata cache. There is presently no reason to touch this.

`--chunk <value>`: The chunk size for the hdf5 arrays. Unreasonable chunk sizes can adversely affect cache performance. Larger chunks can lead to better compression. [default = 1000]

`--deflate <value>`: Compression level. Higher levels tend to not significantly decrease file sizes but do increase run time. [0:none - 9:max] [default = 2]

Importing from other formats

MAF Import

The (MAF)[<http://genome.ucsc.edu/FAQ/FAQformat.html#format5>] is a text format used at UCSC to store genome alignments. MAF's are typically stored with respect to a reference genome. MAFs can be imported into HAL as subtrees using the `maf2hal` command.

To import `primates.maf` as a star tree where the first alignment row specifies the root, and all others the leaves:

```
maf2hal primates.maf primates.hal
```

To import `primates.maf` using "chimp" as the root

```
maf2hal primates.maf primates.hal --refGenome chimp
```

The more the underlying tree looks like a star tree, the less efficient HAL is as all genomes will be fragmented with respect to each other. If ancestral (or multiple reference) sequences are available, or if it is acceptable to use a non-reference species as a reference proxy, then trees of arbitrary typologies can be constructed using the `--append` option.

```
maf2hal mammals.maf mammals.hal --refGenome mouse --targetGenomes human,rat,chimp,dog
maf2hal mammals.maf mammals.hal --append --refGenome human --targetGenomes chimp,gorilla
maf2hal mammals.maf mammals.hal --append --refGenome dog --targetGenomes cow,horse
```

This will create a tree that looks like

```
((chimp, gorilla,orang)human, rat,(cow,horse)dog)mouse;
```

Progressive Cactus Import

HAL is most beneficial when consensus reference or ancestral sequences are available at the internal nodes of the tree. This is the type of information generated by progressive alignment pipelines.

Progressive Cactus (manuscript in preparation) is our implementation of such a pipeline. A beta version is presently available on [GitHub](#). A tool to convert from Cactus graphs to HAL graphs, `cactus2hal`, can be [downloaded](#) as well.

```
cactus2hal.py mammals_cactusProject.xml mammals.hal
```

Exporting to other formats

MAF Export

MAF files can be generated from HAL alignments or sub-alignments. The reference genome and alignment scope (subsequence of the reference and/or phylogenetic distance) are chosen through command-line options.

Export the HAL alignment as a MAF referenced at the root

```
hal2maf mammals.hal mammals.maf
```

Export a MAF with referenced at sequence *chr6* in the human genome

```
hal2maf mammals.hal mammals.maf --refGenome human --refSequence chr6
```

Export a MAF consisting of the alignment of human with respect to *chr2* in chimp

```
hal2maf mammals.hal mammals.maf --refGenome chimp --refSequence chr2 --targetGenome
```

Export a MAF consisting of the alignment of all apes referenced on gorilla

```
hal2maf mammals.hal mammals.maf --rootGenome ape_ancestor --refGenome gorilla
```

By default, no gaps are written to the reference sequence. The `--maxRefGap` can be specified to allow gaps up to a certain size in the reference. This is achieved by recursively following indels in the graph that could correspond to reference gaps.

Summary Information

halValidate

It is a good idea to check if a hal file is valid after creating it.

```
halValidate mammals.hal
```

halStats

Some global information from a HAL file can be quickly obtained using `halStats`. It will return the number of genomes, their phylogenetic tree, and the size of each array in each genome.

```
halStats mammals.hal
```

The `--tree`, `--sequences`, and `--genomes` options can be used to print out only specific information to simply iterating over the alignment in shell or Python scripts.

halSummarizeMtutions

A count of each type of mutation (Insertions, Deletions, Inversions, Duplications, Transpositions, Gap Insertions, Gap Deletions) in each branch of the alignment can be printed out in a table.

```
halSummarizeMutations mammals.hal
```

Subtrees can be specified using the `--targetGenomes` or `--rootGenome` option. The `--maxGap` option is used to distinguish from small, 'gap' indels and larger indels. This distinction is somewhat arbitrary (but conventional). HAL allows gap indels to be nested within larger rearrangements: ex. an inversion with a gap deletion inside would be counted as a single inversion, but an inversion containing a non-gap event would be identified as multiple independent inversions.

```
halSummarizeMutations mammals.maf --maxNFraction 0
```

Will prevent rearrangements with missing data as being identified as such. More generally, if an insertion of length 50 contains c N-characters, it will be labeled as missing data (rather than an insertion) if $c/N > \text{maxNFraction}$.

Analysis

Liftover

Annotations in [BED](#), ie tab-delimited files whose first three columns are

```
SequenceName      StartPosition      LastPosition+1
```

can be lifted over between genomes using `halLiftover`. `halLiftover` does a base-by-base mapping between any two sequences in the alignment (following paralogy relations as well).

```
halLiftover mammals.hal human human_annotation.bed dog dog_annotation.bed
```

will map all annotations in `human_annotation.bed`, which must refer to sequences in the human genome, to their corresponding locations in dog (if they exist), outputting the resulting annotations in `dog_annotation.bed`

Mutation Annotation

Annotation files, as described above, can be generated from the alignment to provide the locations of substitutions and rearrangements. Annotations are done on a branch-by-branch basis, but can be mapped back to arbitrary references using `halLiftover` if so desired. The produced annotation files have the format

```
SequenceName      StartPosition      LastPosition+1  MutationID  ParentGenome  ChildGenome
```

The ID's refer to the types of mutations described above, and are explained in the header of each generated file. To generate tables of rearrangement mutations between human and its most recent ancestor in the alignment, run

```
halBranchMutations mammals.hal human --refFile ins.bed --parFile del.bed
```

Two bed files must be specified because the coordinates of inserted (and by convention inverted and

transposed) segments are with respect to bases in the human genome (reference), where as deleted bases are in ancestral coordinates (parent).

Point mutations can optionally be written using the `--snpFile <file>` option. The '`--maxGap`' and '`--maxNFraction`' options can specify the gap indel threshold and missing data threshold, respectively, as described above in the *halSummarizeMtutions* section.

Example of HAL Genome Representation

The following is obtained by running `h5ls -v -r` (included with `hdf5`) on an ancestral genome, in this case a small simulated human-chimp ancestor named `sHuman-sChimp`. The genome itself is stored as a group. It contains four important 1-dimensional arrays:

- **BOTTOM_ARRAY**: The bottom segments of the genome (containing alignment mapping to the descendants). The size of each entry is dependent on the number of descendants.
- **DNA_ARRAY**: The DNA bases, stored as two bases / byte
- **SEQUENCE_ARRAY**: The names and lengths of subsequences (ie chromosomes or scaffolds in the genome)
- **TOP_ARRAY**: The top segments in the genome (containing alignment mapping to the parent). Paralogous top segments are presently stored in a circular linked list.

More information can be found in the manuscript:

Glenn Hickey, Benedict Paten, Dent Earl, Daniel Zerbino, and David Haussler. *HAL: A Hierarchical Format for Storing and Analyzing Multiple Genome Alignments*. (submitted)

and [API manual](#).

```
/sHuman-sChimp          Group
  Location:  1:204059420
  Links:     1
/sHuman-sChimp/BOTTOM_ARRAY Dataset {1595768/1595768}
  Location:  1:365340961
  Links:     1
  Chunks:    {1000} 42000 bytes
  Storage:   67022256 logical bytes, 12879397 allocated bytes, 520.38% utilization
  Filter-0:  deflate-1 OPT {2}
  Filter-1:  deflate-1 OPT {2}
  Type:      struct {
    "genomeIdx"      +0    native long
    "length"         +8    native unsigned long
    "topIdx"         +16   native long
    "childIdx0"      +24   native long
    "reverseFlag0"   +32   native signed char
    "childIdx1"      +33   native long
    "reverseFlag1"   +41   native signed char
  } 42 bytes
/sHuman-sChimp/DNA_ARRAY Dataset {92368315/92368315}
  Location:  1:253117606
  Links:     1
  Chunks:    {1000} 1000 bytes
  Storage:   92368315 logical bytes, 55478173 allocated bytes, 166.49% utilization
  Filter-0:  deflate-1 OPT {2}
```

```

    Filter-1: deflate-1 OPT {2}
    Type:      native 8-bit field
/sHuman-sChimp/Meta      Group
    Location:  1:204060452
    Links:     1
/sHuman-sChimp/Rup      Group
    Attribute: Rup scalar
               Type:      variable-length null-terminated ASCII string
               Data:      "0"
    Location:  1:204061484
    Links:     1
/sHuman-sChimp/SEQUENCE_ARRAY Dataset {1/1}
    Location:  1:253117878
    Links:     1
    Storage:   96 logical bytes, 96 allocated bytes, 100.00% utilization
    Type:      struct {
        "start"          +0      native unsigned long
        "length"         +8      native unsigned long
        "numSequences"    +16     native unsigned long
        "numBottomSegments" +24   native unsigned long
        "topSegmentArrayIndexOffset" +32   native unsigned long
        "bottomSegmentArrayIndexOffset" +40   native unsigned long
        "name"            +48     384-bit little-endian integer
        (8 bits of precision beginning at bit 0)
        (376 zero bits at bit 8)
    } 96 bytes
/sHuman-sChimp/TOP_ARRAY Dataset {2273166/2273166}
    Location:  1:253118446
    Links:     1
    Chunks:    {1000} 33000 bytes
    Storage:   75014478 logical bytes, 13067609 allocated bytes, 574.05% utilization
    Filter-0:  deflate-1 OPT {2}
    Filter-1:  deflate-1 OPT {2}
    Type:      struct {
        "genomeIdx"      +0      native long
        "bottomIdx"      +8      native long
        "paralogyIdx"    +16     native long
        "parentIdx"      +24     native long
        "reverseFlag"    +32     native signed char
    } 33 bytes

```