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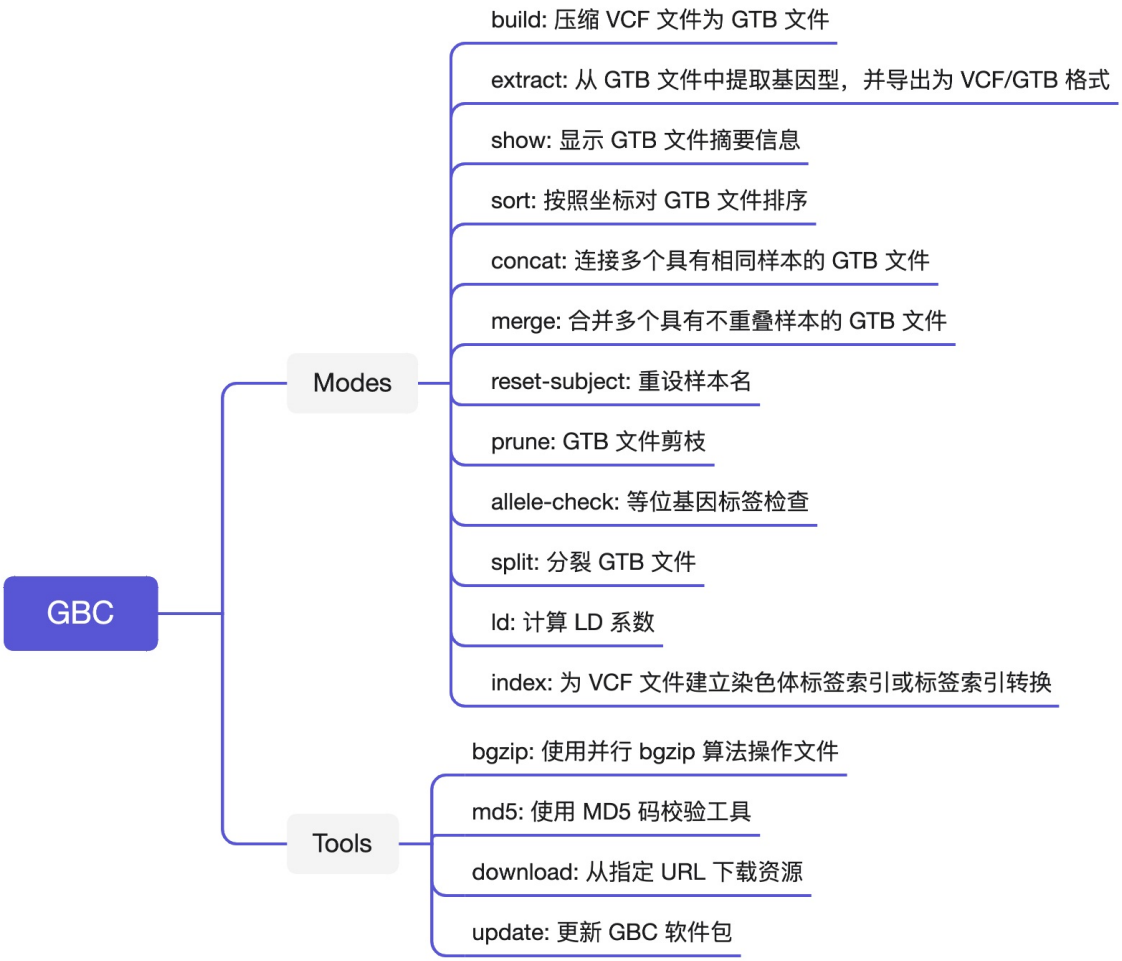
About GBC

GBC (short for GenoType Blocking Compressor) is a blocking compressor for genotype data, which aims at creating a unified and flexible structure-GenoType Block (GTB) for genotype data in the variant call format (VCF) files. There will be a less occupation of hard disk space, a faster data access and extraction function, a more convenient management of population files and a more efficient precess of data analysis with the GTB structure compared with the conventional gz format. GBC provides the following functions：

- **Efficient compression:** Linearly increasing time overhead with sample and variant size, stable memory utilization and competitive compression ratio.
    - Memory: Single-threaded compression with < 4 GB memory usage.
    - Speed: up to 78516269 genotypes/s.
- **Quality control:** Quality control at variant-level, genotype-level, population-allele frequency/count-level. The open API facilitates users to customize their own filtering methods.
- **Quick query:** query continuous/random variants, filter variants by allele frequency/count, extract subset of samples, etc;
- **File management:** merge, join, split, subset sample selection, sorting, allele label checking, etc;
- **Complex calculations:** LD calculations.
- **Genotype coding for a wide range of haploid/diploid species**.

GBC is a free standalone toolkit for improved the efficiency of storage and file management of large-scale genotypes. GBC is also a library of fundamental API development tools that can be easily integrated into existing tool flows to accelerate the analysis and computation process of genotype-based data.



> [!COMMENT|label:Contact Developer]
>
> Liubin Zhang, suranyi.sysu@gmail.com

Download

GBC is developed based on Oracle JDK 8. It is available on any computer device that supports or is compatible with Oracle JDK 8. Users are required to download and install the Oracle JDK or Open JDK firstly. Apple Silicon devices can use the zulu JDK as an alternative. In addition, we also provide Docker image for building the GBC runtime environment.

Type	URL
Software	http://pmglab.top/gbc/download/gbc.jar
Source Code	https://github.com/Zhangliubin/gbc
Online Manual	http://pmglab.top/gbc/
API docs	http://pmglab.top/gbc/api-docs/
Example Data	http://pmglab.top/gbc/download/example.zip http://pmglab.top/genotypes/#/

Download software package by wget

```
# Download GBC software
wget http://pmglab.top/gbc/download/gbc.jar -O gbc.jar

# setup GBC
java -jar gbc.jar
```

Use the GBC in Docker

```
# download dockerfile
wget http://pmglab.top/gbc/download/Dockerfile -O Dockerfile

# build image
docker build -t gbc .

# setup GBC
docker run -it --rm gbc
```

Download GBC from Github

```
# download source code from github
git clone https://github.com/Zhangliubin/gbc gbc-source

# go to the folder
cd gbc-source

# setup GBC
java -jar gbc.jar
```

Update GBC

GBC has now iterated to a stable release, and generally we only add new features to existing packages, or minor code architecture updates to enhance stability and improve performance. To check the availability of new releases, please use:

```
java -jar gbc.jar update
```

System requirements

GBC has a strict memory requirement control and can usually be run at the default memory allocation for small genomic data. For large scale genomic data, the memory usage of GBC is limited to a maximum of 4 GB for a single thread, therefore, we recommend running GBC programs in a heap memory of no less than 4 GB at all times. The user allocates the GBC runtime heap memory with the following command:

```
java -Xms4g -Xmx4g -jar gbc.jar
```

When running GBC with Docker, we recommend using the following template command:

```
# Macos or Linux
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc [options]

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -e -m 4g gbc [options]
```

In this command, `-v` means to map the specified host path to the container path (`host_path:container_path`), `-w` means to set the current working path (equivalent to running the `cd path` command), `-it` means to run in an interactive terminal, and `-m 4g` means to set the maximum heap size of the JVM to 4GB.

Updates

> [!UPDATE|label:2022/07/01]
>
> - Release the second version of GBC, version number 1.2,
>   - Github repository address: https://github.com/Zhangliubin/gbc
>   - Online Manual: http://pmglab.top/gbc/
> - Note that GBC-1.1 and GBC-1.2 are fully compatible versions, but GBC-1.2 and later versions will focus on the development of API tools and no longer maintain GUI programs.

> [!UPDATE|label:2022/04/02]
>
> - Release the first version of GBC, version number 1.1.
>   - Github repository address：https://github.com/Zhangliubin/Genotype-Blocking-Compressor
>   - Online Manual: http://pmglab.top/gbc/history/

Input and Output File Format

GBC supports the conversion between VCF format, compressed VCF format (by BGZIP), and GTB format. In general, we recommend user to use GTB as input and output format, which will get full multi-threaded support.

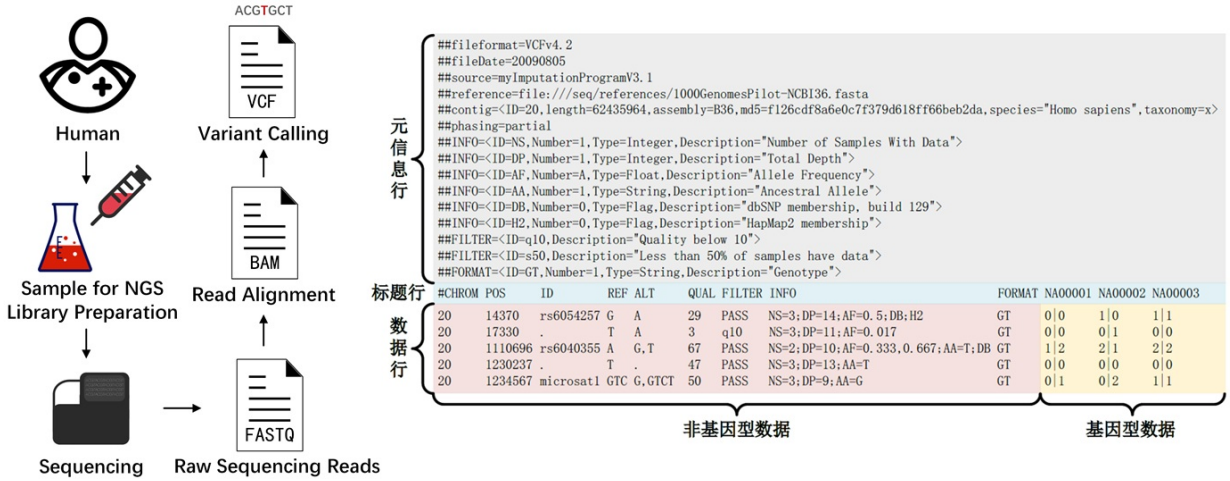
$$\text{Other Formats} \Longleftrightarrow \text{VCF / compressed VCF (by BGZIP)} \Longleftrightarrow \text{GTB}$$

Input Format	Output Format	Tool
Other Formats	VCF or VCF.GZ	Other tools
VCF	compressed VCF	GBC - bgzip - -c
compressed VCF (by BGZIP)	VCF	GBC - bgzip - -d
compressed VCF (by GZIP)	VCF / compressed VCF (by BGZIP)	GBC - bgzip - -d
VCF / compressed VCF (by BGZIP)	GTB	GBC - build
GTB	VCF / compressed VCF (by BGZIP)	GBC - extract

VCF Format

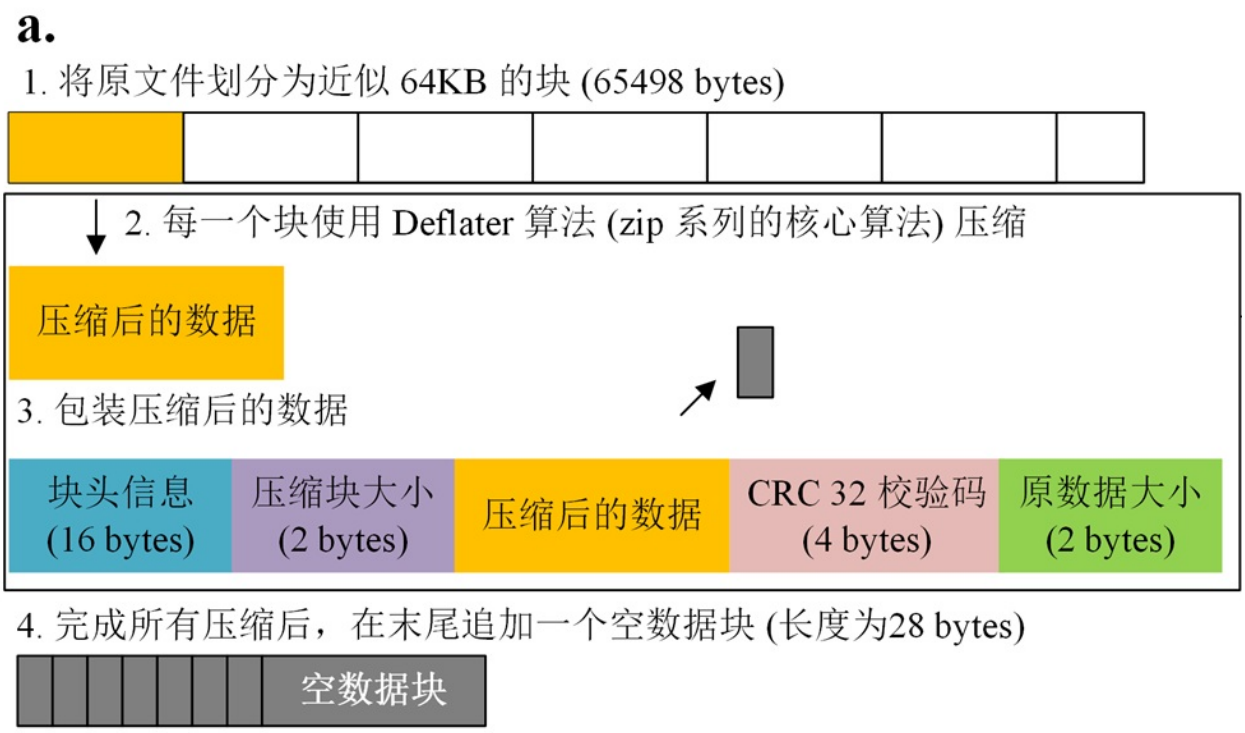
VCF (Variant Call Format) is a standard format for storing variant sites, which is a text format specifically designed for recording and describing variant information such as SNP, InDel, SV, and CNV.

> [!NOTE|label:For the details of the VCF file, we recommend reading: https://samtools.github.io/hts-specs/VCFv4.2.pdf and https://en.wikipedia.org/wiki/Variant_Call_Format]



Compressed VCF with BGZIP

VCF files usually take up a large amount of disk space, so it is common to compress VCFs using BGZIP (the files produced using BGZIP compression are also called BGZF). BGZIP is a block compression method implemented on the standard GZIP file format, which aims to provide a good compression ratio while allowing random access to the data.



Java Implementation of Parallel BGZIP Compression Algorithm：http://pmglab.top/commandParser/en/example/BGZToolkit.html

> [!NOTE|label:About BGZIP: http://www.htslib.org/doc/bgzip.html]

GTB Format

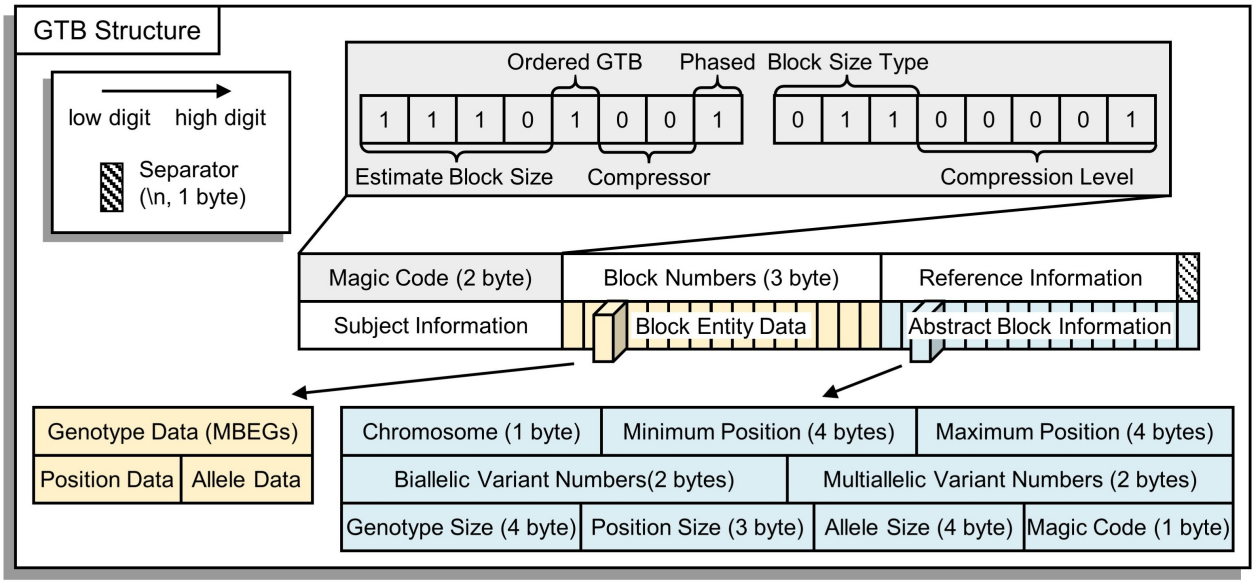
The GTB format is proposed for compressing and storing genotypes data of haploid and diploid species with various allele numbers, chromosome numbers, scales and phased or unphased statuses. It has the following excellent features:

- **Uniform:** In comparison to other file formats (e.g. GTShark, GTC, BGT, PBWT), GTB format has only separate files as output. In addition, it supports the organization of genotypes from multiple chromosomes within a single file (but not for PBWT). This facilitates file storage and transfer.
- **Decoupling:** GTB uses a decoupled design, allowing file modifications to involve as little data as possible. In addition, the independent structure feature makes parallelization computations very easy - parallelization by sites, block or chromosome can be easily implemented.
- **Extensible:** GTB is essentially a double-indexed key (chromosome, position) MDRT format, which is designed with a number of good easy-to-use API methods for fast random access to genotypes. MDRT allows variable multi-indexed keys with a similar structure to GTB, which is also used to store non-genotypic data in VCF files.

The file format of GTB is shown in the figure below. The meaning of each part is as follows:

- **Magic Code**: The first two bytes are used to store the compressed parameters;
- **Block Numbers**: The total number of blocks contained in the compressed file, which also indicates that the "Block Abstract Information" at the end of the file has (25*numbers) bytes of memory;
- **Reference Information**: The version of the reference genome and other reference data;
- **Subjects Information**: List of subjects;
- **Block Entity Data**: The compressed data is combined according to the order of the abstract block information;

- **Abstract Block Information**: Abstract information of the GTB nodes for building first-level fast index table.



Setup GBC

Launch the GBC in the command line program (terminal) with the following command:

```
# The program document is printed by default when no parameters are passed in.
java -Xms4g -Xmx4g -jar gbc.jar

# When passing -h, -help or --help, the program will also print the program document.
java -Xms4g -Xmx4g -jar gbc.jar -h
```

The results are as follows:

```
Usage: java -jar gbc.jar [mode/tool] [options]
Version: GBC-1.2 (last edited on 2022.06.20, http://pmglab.top/gbc)
Mode:
  build          Compress and build *.gtb for vcf/vcf.gz files.
                 format: build <input(s)> -o <output> [options]
  extract        Retrieve variants from *.gtb file, and export them to
                 (compressed) VCF format or GTB format.
                 format: extract <input> -o <output> [options]
  show           Display summary of the GTB File.
                 format: show <input> [options]
  sort           Sort variants in GTB by coordinates (chromosome and position).
                 format: sort <input> -o <output> [options]
  concat         Concatenate multiple VCF files. All source files must have the
                 same subjects columns appearing in the same order with
                 entirely different sites, and all files must have to be the
                 same in parameters of the status.
                 format: concat <input(s)> -o <output> [options]
  merge          Merge multiple GTB files (with non-overlapping subject sets)
                 into a single GTB file.
                 format: merge <input(s)> -o <output> [options]
  reset-subject  Reset subject names (request that same subject number and no
                 duplicated names) for gtb file directly. Subject names can be
                 stored in a file with ',' delimited form, and pass in via
                 '--reset-subject @file'.
                 format: reset-subject <input> -o <output> [options]
  prune          Prune GTB files by node-level or chromosome-level.
                 format: prune <input> -o <output> [options]
  allele-check   Correct for potential complementary strand errors based on
                 allele labels (A and C, T and G; only biallelic variants are
                 supported).
                 format: allele-check <template_input> <input> -o <output>
                 [options]
  split          Split a single GTB file into multiple subfiles (e.g. split by
                 chromosome).
                 format: split <input> -o <output> [options]
  ld             Calculate pairwise the linkage disequilibrium or genotypic
                 correlation.
                 format: ld <input> -o <output> [options]
  index          Index contig file for specified VCF file or reset contig file
                 for specified GTB file.
```

```
                format: index <input (VCF or GTB)> -o <output> [options]
Tool:
  bgzip     Use parallel bgzip to compress a single file.
            format: bgzip <string> <string> ...
  md5       Calculate a message-digest fingerprint (checksum) for file.
            format: md5 <string> <string> ...
  download  Download resources from an URL address.
            format: download <string> <string> ...
  update    Update GBC software packages.
            default: ./gbc.jar
            format: update <gbc.jar>
```

Use GBC in interactive mode

When running program commands multiple times with GBC, we recommend doing so in interactive mode (like ipython), which provides real-time feedback on program input and reduces the time required to start the JVM (especially when running in Docker, using interactive mode avoids frequent container creation and destruction). To start interactive mode, run:

```
java -Xmx4g -Xms4g -jar gbc.jar -i
```

Of course, the user can also choose to enter interactive mode after running the command once, with the following command:

```
java -Xmx4g -Xms4g -jar gbc.jar [mode/tool] [options] -i
```

When you type a command, you no longer need to specify `java -Xmx4g -Xms4g -jar gbc.jar`. The command line interaction mode has four additional parameters in addition to the parameters in command line mode:

Parameters	Description
exit, q, quit	Exit program, exit the command line interaction mode.
clear	Clearing the screen (actually printing out multiple blank lines).
reset	Clear the data buffer.
Lines begin with "#"	For annotation.

Compress Genotypes

Use the following command to compress the genomic VCF file(s):

```
build <input(s)> -o <output> [options]
```

- GBC help compress the file in compliance with VCF Specification, and all GBC operations are based on the assumption that the file format is compliant with this specification.
- The inputFileName can be a single .vcf file or .vcf.gz file, and it can also be the path of the folder containing all the files to be compressed. When a folder path is given, the GBC will help filter out all .vcf or .vcf.gz files in this folder (and its sub-folders) for compression.
- The GBC currently only supports compression of the human genome, for chromosome, GBC only supports 1-22, X, Y and 1-22, X, Y with the "chr" prefix (such as chr1, chrY); For other species, please use command `GBC index <input> -o <contigFile>` to build the contig file first, and users should add the command `--contig <contigFile>` when compressing.
- When using GBC to combine and compress multiple files, the files are required to have the same samples (can be disordered). If the sample of a file is a subset of other files, it can also be compressed correctly, and the missing genotypes will be replaced by `.|.` .
- When input files are unordered (in coordinates), GBC also compresses them correctly and produces GTB files marked as `unordered` . In general we recommend that users further sort this file using the `sort <input> -o <output> [options]` command, otherwise it will not work for some functions (e.g. calculating LD coefficients) or affect the performance of other operations (e.g. merging VCF files).

Program Options

```
Usage: build <input(s)> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --yes,-y      Overwrite output file without asking.
GTB Archive Options:
  --phased,-p          Set the status of genotype to phased.
  --biallelic          Split multiallelic variants into multiple biallelic
                       variants.
  --simply             Delete the alternative alleles (ALT) with allele counts
                       equal to 0.
  --blockSizeType,-bs  Set the maximum size=2^(7+x) of each block. (-1 means
                       auto-adjustment)
                       default: -1
                       format: --blockSizeType <int> (-1 ~ 7)
  --no-reordering,-nr  Disable the Approximate Minimum Discrepancy Ordering
                       (AMDO) algorithm.
```

```
  --windowSize,-ws     Set the window size of the AMDO algorithm.
                       default: 24
                       format: --windowSize <int> (1 ~ 131072)
  --compressor,-c      Set the basic compressor for compressing processed data.
                       default: ZSTD
                       format: --compressor <string> ([ZSTD/LZMA/GZIP] or
                       [0/1/2] (ignoreCase))
  --level,-l           Compression level to use when basic compressor works.
                       (ZSTD: 0~22, 3 as default; LZMA: 0~9, 3 as default;
                       GZIP: 0~9, 5 as default)
                       default: -1
                       format: --level <int> (-1 ~ 31)
  --readyParas,-rp     Import the template parameters (-p, -bs, -c, -l) from an
                       external GTB file.
                       format: --readyParas <file> (Exists,File)
  --seq-ac             Exclude variants with the alternate allele count (AC)
                       per variant out of the range [minAc, maxAc].
                       format: --seq-ac <int>-<int> (>= 0)
  --seq-af             Exclude variants with the alternate allele frequency
                       (AF) per variant out of the range [minAf, maxAf].
                       format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an             Exclude variants with the non-missing allele number (AN)
                       per variant out of the range [minAn, maxAn].
                       format: --seq-an <int>-<int> (>= 0)
  --max-allele         Exclude variants with alleles over --max-allele.
                       default: 15
                       format: --max-allele <int> (2 ~ 15)
Quality Control Options:
  --no-qc     Disable all quality control methods.
  --gty-gq    Exclude genotypes with the minimal genotyping quality (Phred
              Quality Score) per genotype < gq.
              default: 20
              format: --gty-gq <int> (>= 0)
  --gty-dp    Exclude genotypes with the minimal read depth per genotype < dp.
              default: 4
              format: --gty-dp <int> (>= 0)
  --seq-qual  Exclude variants with the minimal overall sequencing quality
              score (Phred Quality Score) per variant < qual.
              default: 30
              format: --seq-qual <int> (>= 0)
  --seq-dp    Exclude variants with the minimal overall sequencing read depth
              per variant < dp.
              default: 0
              format: --seq-dp <int> (>= 0)
  --seq-mq    Exclude variants with the minimal overall mapping quality score
              (Mapping Quality Score) per variant < mq.
              default: 20
              format: --seq-mq <int> (>= 0)
```

Example

Use the GBC to compress the example file `. /example/assoc.hg19.vcf.gz`, and set the following properties:

- Store the genotype as phased.

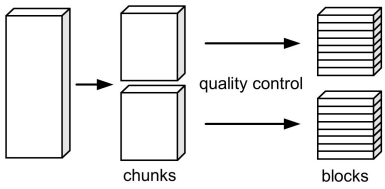
- Set compressor compression level to 16 (ZSTD).
- Split multiallelic variants into multiple biallelic variants.
- Exclude variants with the MAF (minor allele frequency) < 0.01.
- Overwrite the output file if it already exists.

The commands to complete the task are as follows:

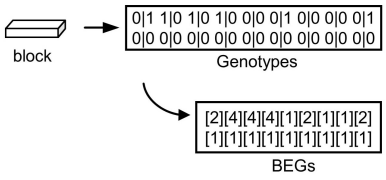
```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/assoc.hg19.vcf.gz -o ./example/assoc.hg19.gtb -p -l 16 --biallelic --se
q-af 0.01-0.99 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/assoc.hg19.vcf.gz -o
 ./example/assoc.hg19.gtb -p -l 16 --biallelic --seq-af 0.01-0.99 -y
```

Algorithm Details

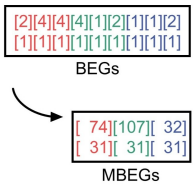
At the beginning of compression, the input genotype file (in VCF format) is divided into several chunks and subsequently processed with multiple threads. In each thread, every chunk is further divided into many smaller blocks. Here, a block is the smallest unit of compression, in which the number of variants is balanced with the sample size given the maximal array length $2^{31} - 1 (\approx 2\text{GB})$(Fig.a). Then, the genotypes of the variants are encoded into byte codes (Fig.b). For biallelic variants, their byte codes are further combined into one-byte codes by combining three phased or four unphased consecutive genotypes (Fig.c). Next, the approximate minimum discrepancy ordering (AMDO) algorithm is applied on the variant level (Fig.d) to sort the variants with similar genotype distributions for improving the compression ratio. The ZSTD algorithm is then adopted to compress the sorted data in each block (Fig.e). Finally, all the compressed blocks and metadata are written into a single GTB file (Fig.f). The procedure has a linear time complexity regarding the number of subjects and variants with small memory usage (less than 4GB), and it provides almost the fastest compression speed and the most competitive compression ratio to date.



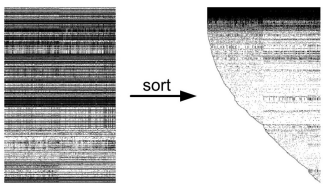
a. Chunking inputs and blocking each chunk by variants



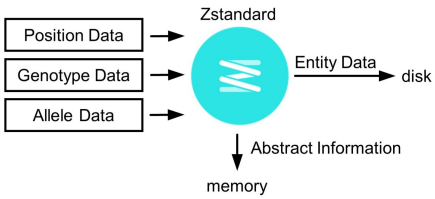
b. Coding genotypes with byte-encoded genotype (BEG)



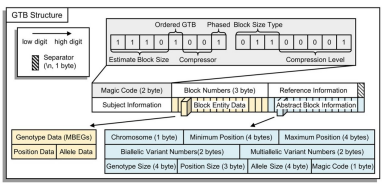
c. Combining multiple biallelic BEG into maximized byte-encoded genotype (MBEG)



d. Sorting variants by approximate minimum discrepancy ordering (AMDO)



e. Compressing the processed data with advanced compressor



f. Storing in the Genotype Block (GTB) format

Input VCF File(s) for compression

One or multiple VCF files can be merged into a single GTB file. For a single input file, GBC reads the file directly. For an input of multiple files, GBC first treats the file with the largest sample size as the major file and uses it to build the sample primary indexes. Other input files will be handled in turns after matching the sample indexes of the major file. In the matching process, the genotypes of missing subjects will be set as '.|.' subsequently to ensure that all the input files can be compressed together consistently in subsequent steps.

> [!NOTE|label:Motivation]
>
> Various human genome projects (e.g. 1000GP3, SG10K) store genotypes according to different chromosome tags (i.e. chr1.gz, chr2.gz, ...). In addition, female individuals are usually not included in the Y chromosome files, resulting in Y chromosome files that usually have smaller sample sizes than autosomes or X chromosome files.
>
> This strategy allows for combining and compressing multiple scattered files of the genome, as well as combining and compressing sex chromosome files with autosomal files in the human genome.

Initialization

To control the maximum memory usage per thread, when the total sample size M is determined, the maximum number of variants per GTB block N is also determined. Typically, the block size parameter (or number of variants in a block) corresponding to the sample size range is related as follows:

Parameters	N	M	**Parameters**	N	M
-bs 7	16384	≤ 65536	-bs 3	1024	≤ 1048576
-bs 6	8192	≤ 131072	-bs 2	512	≤ 2097152
-bs 5	4096	≤ 262144	-bs 1	256	≤ 4194303
-bs 4	2048	≤ 524288	-bs 0	64	≤ 16777215

Chunking Inputs

The input files are compressed sequentially. During compressing each file, it is approximately equally divided into k blocks according to the number of parallel threads k, with each thread processing 1 block. When the input file is in BGZIP-compressed VCF format, the GBC checks the byte-data at the block boundaries and adjusts the pointers to ensure that all variants in the block are intact.

Quality Control by Variant's Non-Genotypic Fields and Genotypic Fields

When processing a single block, the thread reads variant by row and parses the non-genotypic fields. Initial variant-level quality control (e.g., QC based on Phred Quality Score or Mapping Quality Score) is preformed by the non-genotypic fields, and when variant do not meet QC requirements, the thread continues to read the next variant (skipping the current variant).

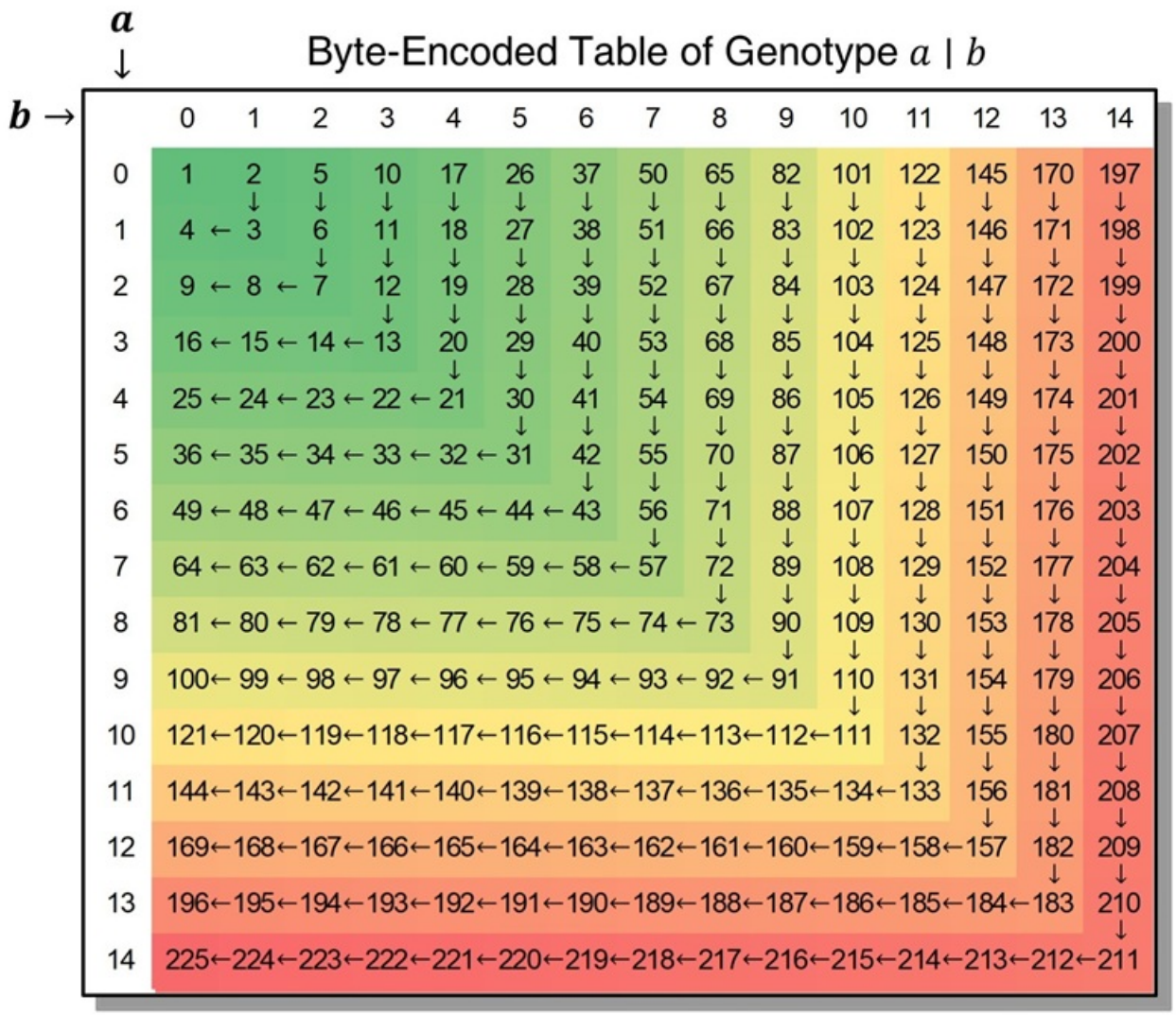
Variant that satisfy variant-level QC are parsed for their genotypes. When the value of the locus `FORMAT` is `GT`, no genotype-level QC is performed; if the value also contains other key fields, the genotype is quality-controlled for each read (e.g., QC based on DP, GQ). When a genotype does not meet the QC requirements, the genotype is `.` `|.` .

Byte-Encoded of Genotype (BEG)

For a given variant v, the non-missing phased genotype $a \mid b$ will be encoded as:

$$a \mid b \rightarrow \begin{cases} (a+1)^2 - b & , a \geq b \\ b^2 + a + 1 & , a < b \end{cases}$$

(1) For a missing genotype `.|.` , it is encoded to 0; (2) For an unphased genotype `a/b` , it is encoded as above after being transformed to $\min\{a, b\} \mid \max\{a, b\}$; (3) For a genotype `a` (in a male's chromosome X and Y), it is encoded as above after being converted into `a|a` .



Write Variant to the Buffer of GTBWriter

When the genotypes of the variant are all encoded, the variant is transferred to the GTBWriter buffer to proceed to the subsequent compression step. In this step, the variant are subjected to additional filtering or conversion operations.

- If the parameter "--simply" is passed in: the ALT tag with an allele count of 0 will be removed.
- If the parameter "--biallelic" is passed in: the multiallelic variant will be split into multiple biallelic variants.
- If the variant-level QC is activated: the variant will be subjected to variant-level quality control and the variant be skipped when it does not meet QC requirements.

Once the GTBWriter buffer size does not reach the maximum number of variants in the GTB block N or the chunk file is not finished reading, repeat the above variant read, quality control, encoding, and write buffer operations. Otherwise, perform the following compression session.

Approximate minimum discrepancy ordering of variants (AMDO)

AMDO starts with extracting the genotype accumulated down-sampling features. Supposing that each block contains M variants and N subjects, a zero-count matrix is denoted as $C = [c_{mn}]_{M\times N}$, where c_{mn} is the count of reference alleles (namely 0 alleles) of the m^{th} variant for the n^{th} subject. Then, the genotype vector of a variant m $C_m = [c_{m0}, c_{m1}, \cdots, c_{m(N-1)}]$ is merged into a shorter s-element vector,

$$C_m^{(l)} = \left[C_{m,0}^{(l)}, C_{m,1}^{(l)}, \cdots, C_{m,s-1}^{(l)}\right]$$

where $C_{m,i}^{(l)}$ covers a maximum of $l = \lceil N/s \rceil$ consecutive genotypes and s is 24 by default. Each element $C_{m,i}^{(l)}$ in the vector is defined as an accumulated count, i.e. :

$$C_{m,i}^{(l)} = \sum_{j=i\cdot l}^{\min\{N-1,(i+1)l-1\}} \sum_{k=i\cdot l}^{j} c_{mk} = \begin{cases} \sum_{j=i\cdot l}^{(i+1)l-1} ((i+1)l - j)c_{mj} & , i < s-1 \\ \sum_{j=i\cdot l}^{N-1} (N-j)c_{mj} & , i = s-1 \end{cases}$$

The accumulation helps discriminate genotype distribution effectively. All the variants in a block are divided into two groups, i.e., the biallelic and the multiallelic groups. In the biallelic variants group, the order of the variant v_i and the biallelic variant v_j is defined as the dictionary order of $C_i^{(l)}$ and $C_j^{(l)}$, which are described as below:

- If $\exists k_0 \in \left[0, \lceil \frac{N}{s} \rceil - 1\right], \forall k \in [0, k_0 - 1]$, such that $C_{i,k_0}^{(s)} < C_{j,k_0}^{(s)}, C_{i,k}^{(s)} = C_{j,k}^{(s)}$, then $v_i > v_j$;
- If $\exists k_0 \in \left[0, \lceil \frac{N}{s} \rceil - 1\right], \forall k \in [0, k_0 - 1]$, such that $C_{i,k_0}^{(s)} > C_{j,k_0}^{(s)}, C_{i,k}^{(s)} = C_{j,k}^{(s)}$, then $v_i < v_j$;
- If $\forall k \in \left[0, \lceil \frac{N}{s} \rceil - 1\right]$, such that $C_{i,k}^{(s)} = C_{j,k}^{(s)}$, then $v_i = v_j$。

On the contrary, the order will be inverted for multiallelic variants, which helps maximize the length of similar genotype vectors. Finally, the corresponding information of positions, alleles and MBEGs for variants are sorted according to the ordered variants ($I = [m_0, m_1, \cdots, m_{M-1}]$).

Maximized Byte-Encoded of Genotype (MBEG)

For biallelic variants, we further combine 3(phased)~4(unphased) multiple consecutive BEG codes into a single byte as follow:

$$\begin{aligned} &\text{phased} : [\text{BEG}_0, \text{BEG}_1, \text{BEG}_2] \to 5^2 \cdot \text{BEG}_0 + 5 \cdot \text{BEG}_1 + \text{BEG}_2 \\ &\text{unphased} : [\text{BEG}_0, \text{BEG}_1, \text{BEG}_2, \text{BEG}_3] \to 4^3 \cdot \text{BEG}_0 + 4^2 \cdot \text{BEG}_1 + 4 \cdot \text{BEG}_2 + \text{BEG}_3 \end{aligned}$$

When the number of genotypes at a variant does not constitute a multiple of 3 or 4, the "null genotype" at the end will be set to the same as the previous one, i.e., $\text{BEG}_i = \text{BEG}_{i-1} (\text{if } i \geq 1)$.

Merge data stream after compressing with advanced compressors

All the sorted MBEG and BEG codes in each block are further compressed by advanced compressors. Popular compression algorithms (e.g., Gzip, LZMA and zlib) can achieve a compression ratio of 100x or more on genotypes. We chose the ZSTD (short for Zstandard[19]) by default because it provides the fastest speed with a similar compression ratio among the widely used compression algorithms. In detail, the byte codes of each variant are concatenated into a byte array B_1 directly. Next, the position of each variant is converted into 4 bytes, and then all variants' positions are concatenated into a byte array B_2. Finally, the alleles of all variants are concatenated into another byte array B_3 with a '/' delimiter. Then, these concatenated data B_1,B_2 and B_3 are compressed by the latest ZSTD to produce $\hat{B}_1$,$\hat{B}_2$ and $\hat{B}_3$ respectively. The data entity is a long vector composed of three sections of compressed data, including encoded genotypes, positions, alleles. Two types of information of each packed block, including abstract information and data entity, are subsequently written to the GTB file. The abstract information include the chromosome number (1 byte), minimum and maximum positions (4 bytes respectively), number of biallelic variants (2 bytes), number of multiallelic variants (2 bytes), length of $\hat{B}_1$ (4 bytes), length of $\hat{B}_2$ (3 bytes), length of $\hat{B}_3$ (4 bytes) and magic code (1 byte) in a block.

GBC can be integrated with different compression algorithms. ZSTD and LZMA algorithms have been embedded to compress each uncoupled genotype block. We also reserve two types of compressors for developers to extend in the future.

Finish Compression

When a thread completes compression, the block summary information is stitched into the thread's corresponding output file. Then, the file pointer is moved to the file header and the block header information is modified.

When all threads have completed compression, the GBC main program calls the `Concat` method to stitch the GTB files produced by each thread into a single GTB file.

Extract Genotypes

Use the following command to extract genotypes from the GTB:

```
extract <input> -o <output> [options]
```

- If the `[options]` contains `--o-gtb` or the output file specified by `-o` is end with `.gtb`, the program will output genotypes in GTB format.
- If the `[options]` contains `--o-bgz` or the output file specified by `-o` is end with `.gz`, the program will output genotypes in BGZIP-compressed VCF format.
- If the `[options]` contains `--o-vcf` or the output file specified by `-o` is not end with `.gz` or `.gtb`, the program will output genotypes in VCF format.

In general, bioinformatics tools (such as PLINK) are compatible with the BGZIP-compressed VCF file format, and we recommend that users use the `--o-bgz` or `--o-gtb` format as output to enhance the parallel output performance of the program.

Program Options

```
Usage: extract <input> -o <output> [options]
Output Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --o-text      Output VCF file in text format. (this command will be executed automati
cally if
                '--o-bgz' or '--o-gtb' is not passed in and the output file specified b
y '-o' is
                not end with '.gz' or '.gtb')
  --o-bgz       Output VCF file in bgz format. (this command will be executed automatic
ally if
                '--o-text' or '--o-gtb' is not passed in and the output file specified
by '-o' is
                end with '.gz')
  --o-gtb       Output VCF file in gtb format. (this command will be executed automatic
ally if
                '--o-text' or '--o-bgz' is not passed in and the output file specified
by '-o' is
                end with '.gtb')
  --level,-l    Compression level to use when basic compressor works. (ZSTD: 0~22, 3 as
 default;
                LZMA: 0~9, 3 as default; BGZIP: 0~9, 5 as default)
                default: -1
                format: --level <int> (-1 ~ 31)
  --no-clm      Parallel output is not controlled using the cyclic locking mechanism (C
LM). With
                this parameter, parallel output means output to multiple temporary file
s and
```

```
                finally concatenating them together.
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --phased,-p   Force-set the status of the genotype. (same as the GTB basic informatio
n by
                default)
                format: --phased [true/false]
  --hideGT,-hg  Do not output the sample genotypes (only CHROM, POS, REF, ALT, AC, AN,
AF).
  --yes,-y      Overwrite output file without asking.
GTB Archive Options:
  --biallelic          Split multiallelic variants into multiple biallelic variants.
  --simply             Delete the alternative alleles (ALT) with allele counts equal to
0.
  --blockSizeType,-bs  Set the maximum size=2^(7+x) of each block. (-1 means auto-adjus
tment)
                       default: -1
                       format: --blockSizeType <int> (-1 ~ 7)
  --no-reordering,-nr  Disable the Approximate Minimum Discrepancy Ordering (AMDO) algo
rithm.
  --windowSize,-ws     Set the window size of the AMDO algorithm.
                       default: 24
                       format: --windowSize <int> (1 ~ 131072)
  --compressor,-c      Set the basic compressor for compressing processed data.
                       default: ZSTD
                       format: --compressor <string> ([ZSTD/LZMA/GZIP] or [0/1/2] (igno
reCase))
  --readyParas,-rp     Import the template parameters (-p, -bs, -c, -l) from an externa
l GTB file.
                       format: --readyParas <file> (Exists,File)
Subset Selection Options:
  --subject,-s   Extract the information of the specified subjects. Subject name can be
 stored in a
                 file with ',' delimited form, and pass in via '-s @file'.
                 format: --subject <string>,<string>,...
  --range,-r     Extract the information by position range.
                 format: --range <chrom>:<minPos>-<maxPos> <chrom>:<minPos>-<maxPos> ..
.
  --random       Extract the information by position. (An inputFile is needed here, wit
h each line
                 contains 'chrom,position' or 'chrom position'.
                 format: --random <file>
  --retain-node  Extract variants in the specified coordinate range of the specified ch
romosome.
                 format: --retain-node <string>:<int>-<int> <string>:<int>-<int> ...
  --seq-ac       Exclude variants with the alternate allele count (AC) per variant out
of the range
                 [minAc, maxAc].
                 format: --seq-ac <int>-<int> (>= 0)
  --seq-af       Exclude variants with the alternate allele frequency (AF) per variant
out of the
                 range [minAf, maxAf].
                 format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an       Exclude variants with the non-missing allele number (AN) per variant o
ut of the
```

```
                  range [minAn, maxAn].
                  format: --seq-an <int>-<int> (>= 0)
  --max-allele    Exclude variants with alleles over --max-allele.
                  default: 15
                  format: --max-allele <int> (2 ~ 15)
```

Example

Use the GBC to decompress the example file `. /example/assoc.hg19.gtb` and set the following properties.

- Store the genotype as unphased.
- Extract the variants with $\mathrm{POS} \geq 1000000$.
- Extract the variants with $\mathrm{AF} \in [0.4, 0.6]$.
- Extract the genotypes with sample names NA18963,NA18977,HG02401,HG02353,HG02064.

The commands to complete the task are as follows:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
extract ./example/assoc.hg19.gtb -o ./example/assoc.hg19.extract.vcf \
-p true -r 1:1000000- --seq-af 0.4-0.6 -s NA18963,NA18977,HG02401,HG02353,HG02064 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc extract ./example/assoc.hg19.gtb -o
./example/assoc.hg19.extract.vcf -p true -r 1:1000000- --seq-af 0.4-0.6 -s NA18963,NA18
977,HG02401,HG02353,HG02064 -y
```

Display Summary Information

Use the following command to display summary information from the GTB:

```
show <input> [options]
```

This command is used to quickly access the information of a GTB file and output it to the terminal. `show` mode contains three output functions:

- Output the summary information about the GTB file (such as shape of genotypes, GTBNodes, etc.).
- Output the sample names of the GTB file.
- Output the summary information (e.g., coordinates, allele labels, allele frequency, etc.) for the variants that satisfy the filtering criteria (if specified).

For detailed genotypes and diverse output formats, please use the `extract` mode.

Program Options

```
Usage: show <input> [options]
Options:
  --contig  Specify the corresponding contig file.
            default: /contig/human/hg38.p13
            format: --contig <file> (Exists,File,Inner)
Summary View Options:
  --add-md5      Print the message-digest fingerprint (checksum) for file
                 (which may take a long time to calculating for huge files).
  --add-subject  Print subjects names of the GTB file.
  --add-tree     Print information of the GTBTrees (chromosome only by
                 default).
  --add-node     Print information of the GTBNodes.
  --full,-f      Print all abstract information of the GTB file (i.e.,
                 --list-baseInfo, --list-subject, --list-node).
GTB View Options:
  --list-subject-only   Print subjects names of the GTB file only.
  --list-position-only  Print coordinates (i.e., CHROM,POSITION) of the GTB
                        file only.
  --list-site-only      Print coordinates, alleles and INFOs (i.e.,
                        CHROM,POSITION,REF,ALT,INFO) of the GTB file.
Subset Selection Options:
  --subject,-s   Print the information of the specified subjects. Subject name
                 can be stored in a file with ',' delimited form, and pass in
                 via '-s @file'.
                 format: --subject <string>,<string>,...
  --range,-r     Print the information by position range.
                 format: --range <chrom>:<minPos>-<maxPos>
                 <chrom>:<minPos>-<maxPos> ...
  --random       Print the information by position. (An inputFile is needed
                 here, with each line contains 'chrom,position' or 'chrom
                 position'.
                 format: --random <file>
```

```
  --retain-node  Print variants in the specified coordinate range of the
                 specified chromosome.
                 format: --retain-node <string>:<int>-<int>
                 <string>:<int>-<int> ...
  --seq-ac       Exclude variants with the alternate allele count (AC) per
                 variant out of the range [minAc, maxAc].
                 format: --seq-ac <int>-<int> (>= 0)
  --seq-af       Exclude variants with the alternate allele frequency (AF) per
                 variant out of the range [minAf, maxAf].
                 format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an       Exclude variants with the non-missing allele number (AN) per
                 variant out of the range [minAn, maxAn].
                 format: --seq-an <int>-<int> (>= 0)
  --max-allele   Exclude variants with alleles over --max-allele.
                 default: 15
                 format: --max-allele <int> (2 ~ 15)
```

Example

Use the GBC to list the summary information for the GTB file `./example/assoc.hg19.gtb` and set the following properties.

- Print all GTB nodes' abstract information.
- Print the MD5 checksum of the GTB.

The commands to complete the task are as follows:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
show ./example/assoc.hg19.gtb \
--full --add-md5

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc extract ./example/assoc.hg19.gtb s
how ./example/assoc.hg19.gtb --full --add-md5
```

Here, the terminal prints the following message:

```
Summary of GTB File:
  GTB File Name: /Users/suranyi/Documents/project/GBC/GBC-1.1/example/assoc.hg19.gtb
  GTB File Size: 938.092 KB
  Genome Reference: ftp://ftp.1000genomes.ebi.ac.uk//vol1/ftp/technical/reference/phase
2_reference_assembly_sequence/hs37d5.fa.gz
  MD5 Code: dcb53e6a9844d413e05ea2a95cae7289
  Suggest To BGZF: false
  Phased: true
  Ordered GTB: true
  BlockSize: 16384 (-bs 7)
  Compression Level: 16 (ZSTD)
  Dimension of Genotypes: 1 chromosome, 18339 variants and 983 subjects
  Subject Sequence: HG01583 HG01586 HG01589 HG01593 HG02490 HG02491 HG02493 HG02494 HG0
2597 HG02600
                    HG02601 HG02603 HG02604 HG02648 HG02649 HG02651 HG02652 HG02654 HG02
```

```
655 HG02657
                HG02658 HG02660 HG02661 HG02681 HG02682 HG02684 HG02685 HG02687 HG02
688 HG02690
                HG02691 HG02694 HG02696 HG02697 HG02699 HG02700 HG02724 HG02725 HG02
727 HG02728
                HG02731 HG02733 HG02734 HG02736 HG02737 HG02774 HG02775 HG02778 HG02
780 HG02783
                HG02784 HG02786 HG02787 HG02789 HG02790 HG02792 HG02793 HG03006 HG03
007 HG03009
                HG03012 HG03015 HG03016 HG03018 HG03019 HG03021 HG03022 HG03228 HG03
229 HG03234
                HG03235 HG03237 HG03238 HG03488 HG03490 HG03491 HG03585 HG03589 HG03
593 HG03594
                HG03595 HG03598 HG03600 HG03603 HG03604 HG03607 HG03611 HG03615 HG03
616 HG03619
                HG03624 HG03625 HG03629 HG03631 HG03634 HG03636 HG03640 HG03642 HG03
643 HG03644
                HG03645 HG03646 HG03649 HG03652 HG03653 HG03660 HG03663 HG03667 HG03
668 HG03672
                HG03673 HG03679 HG03680 HG03681 HG03684 HG03685 HG03686 HG03687 HG03
689 HG03690
                HG03691 HG03692 HG03693 HG03694 HG03695 HG03696 HG03697 HG03698 HG03
702 HG03703
                HG03705 HG03706 HG03708 HG03709 HG03711 HG03713 HG03714 HG03716 HG03
717 HG03718
                HG03720 HG03722 HG03727 HG03729 HG03730 HG03731 HG03733 HG03736 HG03
738 HG03740
                HG03741 HG03742 HG03743 HG03744 HG03745 HG03746 HG03750 HG03752 HG03
753 HG03754
                HG03755 HG03756 HG03757 HG03760 HG03762 HG03765 HG03767 HG03770 HG03
771 HG03772
                HG03773 HG03774 HG03775 HG03777 HG03778 HG03779 HG03780 HG03781 HG03
782 HG03784
                HG03785 HG03786 HG03787 HG03788 HG03789 HG03790 HG03792 HG03793 HG03
796 HG03800
                HG03802 HG03803 HG03805 HG03808 HG03809 HG03812 HG03814 HG03815 HG03
817 HG03821
                HG03823 HG03824 HG03826 HG03829 HG03830 HG03832 HG03833 HG03836 HG03
837 HG03838
                HG03844 HG03846 HG03848 HG03849 HG03850 HG03851 HG03854 HG03856 HG03
857 HG03858
                HG03861 HG03862 HG03863 HG03864 HG03866 HG03867 HG03868 HG03869 HG03
870 HG03871
                HG03872 HG03873 HG03874 HG03875 HG03882 HG03884 HG03885 HG03886 HG03
887 HG03888
                HG03890 HG03894 HG03895 HG03896 HG03897 HG03898 HG03899 HG03900 HG03
902 HG03905
                HG03907 HG03908 HG03910 HG03911 HG03913 HG03914 HG03916 HG03917 HG03
919 HG03920
                HG03922 HG03925 HG03926 HG03928 HG03931 HG03934 HG03937 HG03940 HG03
941 HG03943
                HG03945 HG03947 HG03949 HG03950 HG03951 HG03953 HG03955 HG03960 HG03
963 HG03965
                HG03967 HG03968 HG03969 HG03971 HG03973 HG03974 HG03976 HG03977 HG03
978 HG03985
                HG03986 HG03989 HG03990 HG03991 HG03995 HG03998 HG03999 HG04001 HG04
```

```
002 HG04003
                HG04006 HG04014 HG04015 HG04017 HG04018 HG04019 HG04020 HG04022 HG04
023 HG04025
                HG04026 HG04029 HG04033 HG04035 HG04038 HG04039 HG04042 HG04047 HG04
054 HG04056
                HG04059 HG04060 HG04061 HG04062 HG04063 HG04070 HG04075 HG04076 HG04
080 HG04090
                HG04093 HG04094 HG04096 HG04098 HG04099 HG04100 HG04106 HG04107 HG04
118 HG04131
                HG04134 HG04140 HG04141 HG04144 HG04146 HG04152 HG04153 HG04155 HG04
156 HG04158
                HG04159 HG04161 HG04162 HG04164 HG04171 HG04173 HG04176 HG04177 HG04
180 HG04182
                HG04183 HG04185 HG04186 HG04188 HG04189 HG04194 HG04195 HG04198 HG04
200 HG04202
                HG04206 HG04209 HG04210 HG04211 HG04212 HG04214 HG04216 HG04219 HG04
222 HG04225
                HG04227 HG04229 HG04235 HG04238 HG04239 NA20845 NA20846 NA20847 NA20
849 NA20850
                NA20851 NA20852 NA20853 NA20854 NA20856 NA20858 NA20859 NA20861 NA20
862 NA20863
                NA20864 NA20866 NA20867 NA20868 NA20869 NA20870 NA20872 NA20875 NA20
876 NA20877
                NA20878 NA20881 NA20882 NA20884 NA20885 NA20886 NA20887 NA20888 NA20
889 NA20890
                NA20891 NA20892 NA20894 NA20895 NA20896 NA20897 NA20899 NA20900 NA20
901 NA20902
                NA20903 NA20904 NA20905 NA20906 NA20908 NA20911 NA21086 NA21087 NA21
088 NA21089
                NA21090 NA21091 NA21092 NA21093 NA21094 NA21095 NA21097 NA21098 NA21
099 NA21100
                NA21101 NA21102 NA21103 NA21104 NA21105 NA21106 NA21107 NA21108 NA21
109 NA21110
                NA21111 NA21112 NA21113 NA21114 NA21115 NA21116 NA21117 NA21118 NA21
119 NA21120
                NA21122 NA21123 NA21124 NA21125 NA21126 NA21127 NA21128 NA21129 NA21
130 NA21133
                NA21135 NA21137 NA21141 NA21142 NA21143 NA21144 HG00403 HG00404 HG00
406 HG00407
                HG00409 HG00410 HG00419 HG00421 HG00422 HG00428 HG00436 HG00437 HG00
442 HG00443
                HG00445 HG00446 HG00448 HG00449 HG00451 HG00452 HG00457 HG00458 HG00
463 HG00464
                HG00472 HG00473 HG00475 HG00476 HG00478 HG00479 HG00500 HG00513 HG00
525 HG00530
                HG00531 HG00533 HG00534 HG00536 HG00537 HG00542 HG00543 HG00556 HG00
557 HG00559
                HG00560 HG00565 HG00566 HG00580 HG00583 HG00589 HG00590 HG00592 HG00
593 HG00595
                HG00596 HG00598 HG00599 HG00607 HG00608 HG00610 HG00611 HG00613 HG00
614 HG00619
                HG00620 HG00622 HG00623 HG00625 HG00626 HG00628 HG00629 HG00631 HG00
632 HG00634
                HG00650 HG00651 HG00653 HG00654 HG00656 HG00657 HG00662 HG00663 HG00
671 HG00672
                HG00674 HG00675 HG00683 HG00684 HG00689 HG00690 HG00692 HG00693 HG00
```

```
698 HG00699
                    HG00701 HG00704 HG00705 HG00707 HG00708 HG00717 HG00728 HG00729 HG00
759 HG00766
                    HG00844 HG00851 HG00864 HG00879 HG00881 HG00956 HG00982 HG01028 HG01
029 HG01031
                    HG01046 HG01595 HG01596 HG01597 HG01598 HG01599 HG01600 HG01794 HG01
795 HG01796
                    HG01797 HG01798 HG01799 HG01800 HG01801 HG01802 HG01804 HG01805 HG01
806 HG01807
                    HG01808 HG01809 HG01810 HG01811 HG01812 HG01813 HG01815 HG01816 HG01
817 HG01840
                    HG01841 HG01842 HG01843 HG01844 HG01845 HG01846 HG01847 HG01848 HG01
849 HG01850
                    HG01851 HG01852 HG01853 HG01855 HG01857 HG01858 HG01859 HG01860 HG01
861 HG01862
                    HG01863 HG01864 HG01865 HG01866 HG01867 HG01868 HG01869 HG01870 HG01
871 HG01872
                    HG01873 HG01874 HG01878 HG02016 HG02017 HG02019 HG02020 HG02023 HG02
025 HG02026
                    HG02028 HG02029 HG02031 HG02032 HG02035 HG02040 HG02047 HG02048 HG02
049 HG02050
                    HG02057 HG02058 HG02060 HG02061 HG02064 HG02069 HG02070 HG02072 HG02
073 HG02075
                    HG02076 HG02078 HG02079 HG02081 HG02082 HG02084 HG02085 HG02086 HG02
087 HG02088
                    HG02113 HG02116 HG02121 HG02122 HG02127 HG02128 HG02130 HG02131 HG02
133 HG02134
                    HG02136 HG02137 HG02138 HG02139 HG02140 HG02141 HG02142 HG02151 HG02
152 HG02153
                    HG02154 HG02155 HG02156 HG02164 HG02165 HG02166 HG02178 HG02179 HG02
180 HG02181
                    HG02182 HG02184 HG02185 HG02186 HG02187 HG02188 HG02190 HG02250 HG02
351 HG02353
                    HG02355 HG02356 HG02360 HG02364 HG02367 HG02371 HG02374 HG02375 HG02
379 HG02380
                    HG02382 HG02383 HG02384 HG02385 HG02386 HG02389 HG02390 HG02391 HG02
392 HG02394
                    HG02395 HG02396 HG02397 HG02398 HG02399 HG02401 HG02402 HG02406 HG02
407 HG02408
                    HG02409 HG02410 HG02512 HG02513 HG02521 HG02522 NA18525 NA18526 NA18
528 NA18530
                    NA18531 NA18532 NA18533 NA18534 NA18535 NA18536 NA18537 NA18538 NA18
539 NA18541
                    NA18542 NA18543 NA18544 NA18545 NA18546 NA18547 NA18548 NA18549 NA18
550 NA18552
                    NA18553 NA18555 NA18557 NA18558 NA18559 NA18560 NA18561 NA18562 NA18
563 NA18564
                    NA18565 NA18566 NA18567 NA18570 NA18571 NA18572 NA18573 NA18574 NA18
577 NA18579
                    NA18582 NA18591 NA18592 NA18593 NA18595 NA18596 NA18597 NA18599 NA18
602 NA18603
                    NA18605 NA18606 NA18608 NA18609 NA18610 NA18611 NA18612 NA18613 NA18
614 NA18615
                    NA18616 NA18617 NA18618 NA18619 NA18620 NA18621 NA18622 NA18623 NA18
624 NA18625
                    NA18626 NA18627 NA18628 NA18629 NA18630 NA18631 NA18632 NA18633 NA18
```

```
634 NA18635
                    NA18636 NA18637 NA18638 NA18639 NA18640 NA18641 NA18642 NA18643 NA18
644 NA18645
                    NA18646 NA18647 NA18648 NA18740 NA18745 NA18747 NA18748 NA18749 NA18
757 NA18939
                    NA18940 NA18941 NA18942 NA18943 NA18944 NA18945 NA18946 NA18947 NA18
948 NA18949
                    NA18950 NA18951 NA18952 NA18953 NA18954 NA18956 NA18957 NA18959 NA18
960 NA18961
                    NA18962 NA18963 NA18964 NA18965 NA18966 NA18967 NA18968 NA18969 NA18
970 NA18971
                    NA18972 NA18973 NA18974 NA18975 NA18976 NA18977 NA18978 NA18979 NA18
980 NA18981
                    NA18982 NA18983 NA18984 NA18985 NA18986 NA18987 NA18988 NA18989 NA18
990 NA18991
                    NA18992 NA18993 NA18994 NA18995 NA18997 NA18998 NA18999 NA19000 NA19
001 NA19002
                    NA19003 NA19004 NA19005 NA19006 NA19007 NA19009 NA19010 NA19011 NA19
012 NA19054
                    NA19055 NA19056 NA19057 NA19058 NA19059 NA19060 NA19062 NA19063 NA19
064 NA19065
                    NA19066 NA19067 NA19068 NA19070 NA19072 NA19074 NA19075 NA19076 NA19
077 NA19078
                    NA19079 NA19080 NA19081 NA19082 NA19083 NA19084 NA19085 NA19086 NA19
087 NA19088
                    NA19089 NA19090 NA19091

Summary of GTB Nodes:
└─ Chromosome 1: posRange=[10177, 4999852], numOfNodes=4, numOfVariants=18339
    ├─ Node 1: posRange=[10177, 1787378], seek=1157, blockSize=241089, variantNum=4430 (
4430 + 0)
    ├─ Node 2: posRange=[1788685, 2914618], seek=242246, blockSize=228815, variantNum=3
998 (3998 + 0)
    ├─ Node 3: posRange=[2915041, 4063039], seek=471061, blockSize=249262, variantNum=4
818 (4818 + 0)
    └─ Node 4: posRange=[4063447, 4999852], seek=720323, blockSize=240183, variantNum=5
093 (5093 + 0)
```

Use the GBC to list the variants in the GTB file `. /example/assoc.hg19.gtb` that meet the following conditions:

- Print the variants with $\mathrm{POS} \in [0, 100000]$.
- Print the variants with $\mathrm{AF} \in [0.45, 0.55]$.
- Limit the samples to NA18963,NA18977,HG02401,HG02353,HG02064.

The commands to complete the task are as follows:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
show ./example/assoc.hg19.gtb \
-r 1:0-100000 --seq-af 0.45-0.55 -s NA18963,NA18977,HG02401,HG02353,HG02064 --list-site
-only

# Windows
```

```
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc show ./example/assoc.hg19.gtb -r 1
:0-100000 --seq-af 0.45-0.55 -s NA18963,NA18977,HG02401,HG02353,HG02064 --list-site-onl
y
```

Here, the terminal prints the following message:

```
1    15211    T    G        AC=5;AF=0.50000000;AN=10
1    54712    T    TTTTC    AC=5;AF=0.50000000;AN=10
```

Sort Variants by Coordinates

Use the following command to sort variants by coordinate from the GTB:

```
sort <input> -o <output> [options]
```

Generally, VCF files are ordered and this feature can be ignored. When you convert the reference version (e.g., from hg19 to hg38), the coordinates of the variants may change, causing the file to become unordered.

Program Options

```
Usage: sort <input> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --subject,-s  Extract the information of the specified subjects. Subject name
                can be stored in a file with ',' delimited form, and pass in
                via '-s @file'.
                format: --subject <string>,<string>,...
  --yes,-y      Overwrite output file without asking.
GTB Archive Options:
  --phased,-p          Force-set the status of the genotype. (same as the GTB
                       basic information by default)
                       format: --phased [true/false]
  --biallelic          Split multiallelic variants into multiple biallelic
                       variants.
  --simply             Delete the alternative alleles (ALT) with allele counts
                       equal to 0.
  --blockSizeType,-bs  Set the maximum size=2^(7+x) of each block. (-1 means
                       auto-adjustment)
                       default: -1
                       format: --blockSizeType <int> (-1 ~ 7)
  --no-reordering,-nr  Disable the Approximate Minimum Discrepancy Ordering
                       (AMDO) algorithm.
  --windowSize,-ws     Set the window size of the AMDO algorithm.
                       default: 24
                       format: --windowSize <int> (1 ~ 131072)
  --compressor,-c      Set the basic compressor for compressing processed data.
                       default: ZSTD
                       format: --compressor <string> ([ZSTD/LZMA/GZIP] or
                       [0/1/2] (ignoreCase))
  --level,-l           Compression level to use when basic compressor works.
                       (ZSTD: 0~22, 3 as default; LZMA: 0~9, 3 as default;
                       GZIP: 0~9, 5 as default)
                       default: -1
```

```
                      format: --level <int> (-1 ~ 31)
  --readyParas,-rp    Import the template parameters (-p, -bs, -c, -l) from an
                      external GTB file.
                      format: --readyParas <file> (Exists,File)
  --seq-ac            Exclude variants with the alternate allele count (AC)
                      per variant out of the range [minAc, maxAc].
                      format: --seq-ac <int>-<int> (>= 0)
  --seq-af            Exclude variants with the alternate allele frequency
                      (AF) per variant out of the range [minAf, maxAf].
                      format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an            Exclude variants with the non-missing allele number (AN)
                      per variant out of the range [minAn, maxAn].
                      format: --seq-an <int>-<int> (>= 0)
  --max-allele        Exclude variants with alleles over --max-allele.
                      default: 15
                      format: --max-allele <int> (2 ~ 15)
```

Example

Use the GBC to compress the unordered VCF file `./example/randomsimu100000V_100S.chr1.vcf.gz` :

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
build ./example/randomsimu100000V_100S.chr1.vcf.gz -o ./example/randomsimu100000V_100S.
chr1.gtb -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc build ./example/randomsimu100000V_
100S.chr1.vcf.gz -o ./example/randomsimu100000V_100S.chr1.gtb -y
```

Then, use `show` to print the summary information of `./example/randomsimu100000V_100S.chr1.gtb` :

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
show ./example/randomsimu100000V_100S.chr1.gtb

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc show ./example/randomsimu100000V_1
00S.chr1.gtb
```

Here, the terminal prints the following message, note that this file is an `unordered` file:

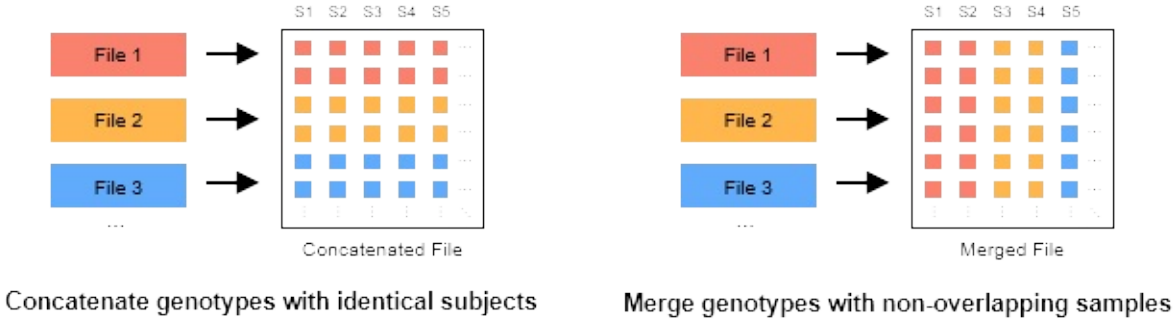
```
Summary of GTB File:
  GTB File Name: /Users/suranyi/Documents/project/GBC/GBC-1.1/example/randomsimu100000V
_100S.chr1.gtb
  GTB File Size: 2.764 MB
  Suggest To BGZF: false
  Phased: false
  Ordered GTB: false
  BlockSize: 16384 (-bs 7)
  Compression Level: 3 (ZSTD)
  Dimension of Genotypes: 1 chromosome, 100000 variants and 100 subjects
```

Sort the current GTB file using the `sort` mode:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
sort ./example/randomsimu100000V_100S.chr1.gtb -o ./example/randomsimu100000V_100S.chr1
.order.gtb

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc sort ./example/randomsimu100000V_1
00S.chr1.gtb -o ./example/randomsimu100000V_100S.chr1.order.gtb
```

Combine Multiple GTBs

There are two main types of combining multiple GTB files: concatenation (concat, left panel) and merge (merge, right panel). The former is usually used to concatenate multiple single chromosome GTB files (e.g. chr1.gtb, chr2.gtb, ...), and the coordinates of these GTB files do not overlap with each other. The latter is usually used to combine genotypes from several different sequencing projects to increase the sample size of the study, and the samples of these GTB files do not overlap with each other.



Concatenate multiple GTBs

Use the following command to concatenate multiple GTBs (left panel):

```
concat <input(s)> -o <output> [options]
```

- When the input multiple files with the same status of genotype, compressor, and the samples, the operation of concatenation will be completed in seconds. Otherwise, GBC needs more time for file pre-conversion.
- The input files can be single or multiple .gtb files, or they can be the path to the folder containing them. When the path is a folder path, GBC will filter all .gtb files in that folder (and its subfolders) for concatenation. Note that GBC only determines the file type based on the file extension, so the correct file extension is the only one that can be concatenated.

Program Options

```
Usage: concat <input(s)> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --yes,-y      Overwrite output file without asking.
```

Example

Use the GBC to compress an example file that containing multiple chromosome `./example/simu100.coding.vcf.gz` :

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
build ./example/simu100.coding.vcf.gz -o ./example/simu100.coding.gtb -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc build ./example/simu100.coding.vcf
.gz -o ./example/simu100.coding.gtb -y
```

Then, we split the GTB file into multiple single chromosome subfiles according to chromosome tags:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
split ./example/simu100.coding.gtb -o ./example/simu100.coding --by chromosome

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc split ./example/simu100.coding.gtb
 -o ./example/simu100.coding --by chromosome
```

Finally, we use `concat` to concatenate all the GTB files in the `./example/simu100.coding` folder.

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
concat ./example/simu100.coding -o ./example/simu100.coding.concat.gtb

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc concat ./example/simu100.coding -o
 ./example/simu100.coding.concat.gtb
```

Merge Multiple GTBs

Use the following command to merge multiple GTBs (right panel) from non-overlapping sample sets:

```
merge <input(s)> -o <output> [options]
```

- If the sample names of the files overlap, the sample names need to be reset using the `reset-subject` mode (see: Reset the Subject Names).
- When no GTB archive format is set, the output GTB archive format defaults to same as the first incoming file.
- The input files can be single or multiple .gtb files, or they can be the path to the folder containing them. When the path is a folder path, GBC will filter all .gtb files in that folder (and its subfolders) for concatenation. Note that GBC only determines the file type based on the file extension, so the correct file extension is the only one that can be concatenated.

Program Options

```
Usage: merge <input(s)> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
```

```
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --union       Method for handing coordinates in different files (union or
                intersection, and intersection is the default), the missing
                genotype is replaced by '.'.
  --yes,-y      Overwrite output file without asking.
GTB Archive Options:
  --phased,-p          Force-set the status of the genotype. (same as the GTB
                       basic information by default)
                       format: --phased [true/false]
  --biallelic          Split multiallelic variants into multiple biallelic
                       variants.
  --simply             Delete the alternative alleles (ALT) with allele counts
                       equal to 0.
  --blockSizeType,-bs  Set the maximum size=2^(7+x) of each block. (-1 means
                       auto-adjustment)
                       default: -1
                       format: --blockSizeType <int> (-1 ~ 7)
  --no-reordering,-nr  Disable the Approximate Minimum Discrepancy Ordering
                       (AMDO) algorithm.
  --windowSize,-ws     Set the window size of the AMDO algorithm.
                       default: 24
                       format: --windowSize <int> (1 ~ 131072)
  --compressor,-c      Set the basic compressor for compressing processed data.
                       default: ZSTD
                       format: --compressor <string> ([ZSTD/LZMA/GZIP] or
                       [0/1/2] (ignoreCase))
  --level,-l           Compression level to use when basic compressor works.
                       (ZSTD: 0~22, 3 as default; LZMA: 0~9, 3 as default;
                       GZIP: 0~9, 5 as default)
                       default: -1
                       format: --level <int> (-1 ~ 31)
  --readyParas,-rp     Import the template parameters (-p, -bs, -c, -l) from an
                       external GTB file.
                       format: --readyParas <file> (Exists,File)
  --seq-ac             Exclude variants with the alternate allele count (AC)
                       per variant out of the range [minAc, maxAc].
                       format: --seq-ac <int>-<int> (>= 0)
  --seq-af             Exclude variants with the alternate allele frequency
                       (AF) per variant out of the range [minAf, maxAf].
                       format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an             Exclude variants with the non-missing allele number (AN)
                       per variant out of the range [minAn, maxAn].
                       format: --seq-an <int>-<int> (>= 0)
  --max-allele         Exclude variants with alleles over --max-allele.
                       default: 15
                       format: --max-allele <int> (2 ~ 15)
```

Example

Download the 1000GP3 dataset from `http://pmglab.top/genotypes` and store it in `./example/1000GP3` folder with the following path structure:

```
- 1000GP3
  - AFR
  - AMR
  - EAS
  - EUR
  - SAS
- randomsimu100000V_100S.chr1.vcf.gz
- rare.disease.hg19.vcf.gz
- query.txt
- query_1000GP3.txt
- simu100.coding.vcf.gz
- assoc.hg19.vcf.gz
```

Use the GBC to compress genotype data for each population.

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/1000GP3/AFR -o ./example/1000GP3/AFR.gtb -l 16 -p -y
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/1000GP3/AMR -o ./example/1000GP3/AMR.gtb -l 16 -p -y
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/1000GP3/EAS -o ./example/1000GP3/EAS.gtb -l 16 -p -y
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/1000GP3/EUR -o ./example/1000GP3/EUR.gtb -l 16 -p -y
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/1000GP3/SAS -o ./example/1000GP3/SAS.gtb -l 16 -p -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/1000GP3/AFR -o ./exa
mple/1000GP3/AFR.gtb  -l 16 -p -y
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/1000GP3/AMR -o ./exa
mple/1000GP3/AMR.gtb  -l 16 -p -y
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/1000GP3/EAS -o ./exa
mple/1000GP3/EAS.gtb  -l 16 -p -y
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/1000GP3/EUR -o ./exa
mple/1000GP3/EUR.gtb  -l 16 -p -y
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/1000GP3/SAS -o ./exa
mple/1000GP3/SAS.gtb  -l 16 -p -y
```

Merge the GTB files of the 5 populations in the `1000GP3` folder:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
merge ./example/1000GP3/AFR.gtb ./example/1000GP3/AMR.gtb ./example/1000GP3/EAS.gtb ./e
xample/1000GP3/EUR.gtb ./example/1000GP3/SAS.gtb -o ./example/1000GP3.gtb -l 16 -p true
 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc merge ./example/1000GP3/AFR.gtb ./ex
ample/1000GP3/AMR.gtb ./example/1000GP3/EAS.gtb ./example/1000GP3/EUR.gtb ./example/100
```

```
0GP3/SAS.gtb -o ./example/1000GP3.gtb -l 16 -p true -y
```

Reset the Subject Names

Use the following command to reset subject (or sample) names of GTB:

```
reset-subject <input> -o <output> [options]
```

Program Options

```
Usage: reset-subject <input> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --yes,-y      Overwrite output file without asking.
  --subject     Reset subject names (request that same subject number and no
                duplicated names) for gtb file directly. Subject names can be
                stored in a file with ',' delimited form, and pass in via
                '--subject @file'.
                format: --subject <string>,<string>,...
  --prefix      Use the format `[prefix][number][suffix]` to reset the subject
                names.
                default: S_
                format: --prefix <string>
  --suffix      Use the format `[prefix][number][suffix]` to reset the subject
                names.
                format: --suffix <string>
  --begin       Use the format `[prefix][number][suffix]` to reset the subject
                names.
                default: 1
                format: --begin <int>
```

Example

Use the GBC to compress an example file `./example/rare.disease.hg19.vcf.gz`:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
build ./example/rare.disease.hg19.vcf.gz -o ./example/rare.disease.hg19.gtb -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc build ./example/rare.disease.hg19.vc
f.gz -o ./example/rare.disease.hg19.gtb -y
```

Reset the subject names to `CASE_6_1`, `CASE_7_1` and `CASE_8_1`:

```
# Linux or MacOS
```

```
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
reset-subject ./example/rare.disease.hg19.gtb -o ./example/out.gtb --prefix CASE_ --beg
in 6 --suffix _1 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc reset-subject ./example/rare.disease
.hg19.gtb -o ./example/out.gtb --prefix CASE_ --begin 6 --suffix _1 -y
```

or:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
reset-subject ./example/rare.disease.hg19.gtb -o ./example/out.gtb --subject CASE_6_1,C
ASE_7_1,CASE_8_1 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc reset-subject ./example/rare.disease
.hg19.gtb -o ./example/out.gtb --subject CASE_6_1,CASE_7_1,CASE_8_1 -y
```

Prune GTB Tree

Use the following command to prune the GTB Tree:

```
prune <input> -o <output> [options]
```

Compared with `extract`, `prune` does not need to decompress any data for node extraction or deletion, which is faster and less memory-intensive, and all operations can be completed in seconds.

Program Options

```
Usage: prune <input> -o <output> [options]
Options:
  --contig        Specify the corresponding contig file.
                  default: /contig/human/hg38.p13
                  format: --contig <file> (Exists,File,Inner)
  *--output,-o    Set the output file.
                  format: --output <file>
  --yes,-y        Overwrite output file without asking.
  --delete-node   Delete the specified GTBNodes.
                  format: --delete-node <string>:<int>,<int>,... <string>:<int>,<int>,..
. ...
  --retain-node   Retain the specified GTBNodes.
                  format: --retain-node <string>:<int>,<int>,... <string>:<int>,<int>,..
. ...
  --delete-chrom  Delete the specified Chromosomes.
                  format: --delete-chrom <string>,<string>,...
  --retain-chrom  Retain the specified Chromosomes.
                  format: --retain-chrom <string>,<string>,...
```

Example

Use the GBC to extract the sex chromosomes (chrX and chrY) of `1000GP3.gtb`.

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
prune ./example/1000GP3.gtb -o ./example/1000GP3.chrXY.gtb \
--retain-chrom X,Y \
-y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc prune ./example/1000GP3.gtb -o ./exa
mple/1000GP3.chrXY.gtb --retain-chrom X,Y -y
```

View the summary information of extracted GTB file:

```
# Linux or MacOS
```

```
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
show ./example/1000GP3.chrXY.gtb --add-tree

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc show ./example/1000GP3.chrXY.gtb --a
dd-tree
```

Here, the terminal prints the following message:

```
Summary of GTB File:
  GTB File Name: /Users/suranyi/Documents/project/GBC/GBC-1.1/example/1000GP3.chrXY.gtb
  GTB File Size: 66.759 MB
  Genome Reference: ftp://ftp.1000genomes.ebi.ac.uk//vol1/ftp/technical/reference/phase
2_reference_assembly_sequence/hs37d5.fa.gz
  Suggest To BGZF: false
  Phased: true
  Ordered GTB: true
  BlockSize: 16384 (-bs 7)
  Compression Level: 16 (ZSTD)
  Dimension of Genotypes: 2 chromosomes, 3530137 variants and 2504 subjects

Summary of GTB Nodes:
├─ Chromosome X: posRange=[60020, 155260478], numOfNodes=212, numOfVariants=3468095
└─ Chromosome Y: posRange=[2655180, 28770931], numOfNodes=4, numOfVariants=62042
```

Align Coordinates and Base Labels

When merging genotypes from different batches, the variants that with the same coordinate may introduce confusion (e.g., batch 1 uses forward-stranded DNA and batch 2 uses reverse-stranded DNA). With the same coordinates and base complementarity (e.g., [A, T] and [C, G]), GBC designs three functions to identify inconsistent allele labels:

- Check for allele frequency: the difference between the allele frequency of variant 1 and the allele frequency of variant 2 is less than the threshold (i.e., $\mid \mathrm{AF}_1 - \mathrm{AF}_2 \mid < \mathrm{gap}$). This will work for variants with minor allele frequencies much less than 0.5 (say 0.3).
- Check for allele count: 2×2 column tables were constructed using the number of reference alleles at a variant of two batches to be merged. The chi-square tests were performed. If the hypothesis test rejects the H_0 hypothesis (i.e., the allele frequencies of the two variants are identical), then the variants in different batches cannot be considered potentially identical. Note that this will not be suitable for the scenario that the two batches are used for cases and controls, respectively.
- Check for LD pattern: identifies other variants in which the absolute value of the genotypic correlation is over a threshold (say, 0.8) in two batches separately. We then count the positive signs of the correlation coefficients in the two batches. If the numbers of signs are very different between the two batches, the allele labels should be flipped; otherwise, the allele labels are not flipped. This function can be used for variants with minor allele frequencies close to 0.5.

Use the following command to correct for potential complementary strand errors:

```
allele-check <template_input> <input> -o <output> [options]
```

Program Options

```
Usage: allele-check <template_input> <input> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --union       Method for handing coordinates in different files (union or
                intersection, and intersection is the default), the missing
                genotype is replaced by '.'.
  --yes,-y      Overwrite output file without asking.
Alignment Coordinate Options:
  --p-value              Correct allele labels of rare variants (minor allele
                         frequency < --maf) with the p-value of chi^2 test >=
                         --p-value.
                         default: 0.05
                         format: --p-value <double> (1.0E-6 ~ 0.5)
  --freq-gap             Correct allele labels of rare variants (minor allele
                         frequency < --maf) with the allele frequency gap <=
```

```
                          --freq-gap.
                          format: --freq-gap <double> (1.0E-6 ~ 0.5)
  --no-ld                 By default, correct allele labels of common variants
                          (minor allele frequency >= --maf) using the ld pattern
                          in different files. Disable this function with option
                          '--no-ld'.
  --min-r                 Exclude pairs with genotypic LD correlation |R| values
                          less than --min-r.
                          default: 0.8
                          format: --min-r <double> (0.5 ~ 1.0)
  --flip-scan-threshold   Variants with flipped ld patterns (strong correlation
                          coefficients of opposite signs) that >= threshold
                          ratio will be corrected.
                          default: 0.8
                          format: --flip-scan-threshold <double> (0.5 ~ 1.0)
  --maf                   For common variants (minor allele frequency >= --maf)
                          use LD to identify inconsistent allele labels.
                          default: 0.05
                          format: --maf <double> (0.0 ~ 0.5)
  --window-bp,-bp         The maximum number of physical bases between the
                          variants being calculated for LD.
                          default: 10000
                          format: --window-bp <int> (>= 1)
GTB Archive Options:
  --phased,-p             Force-set the status of the genotype. (same as the GTB
                          basic information by default)
                          format: --phased [true/false]
  --biallelic             Split multiallelic variants into multiple biallelic
                          variants.
  --simply                Delete the alternative alleles (ALT) with allele counts
                          equal to 0.
  --blockSizeType,-bs     Set the maximum size=2^(7+x) of each block. (-1 means
                          auto-adjustment)
                          default: -1
                          format: --blockSizeType <int> (-1 ~ 7)
  --no-reordering,-nr     Disable the Approximate Minimum Discrepancy Ordering
                          (AMDO) algorithm.
  --windowSize,-ws        Set the window size of the AMDO algorithm.
                          default: 24
                          format: --windowSize <int> (1 ~ 131072)
  --compressor,-c         Set the basic compressor for compressing processed data.
                          default: ZSTD
                          format: --compressor <string> ([ZSTD/LZMA/GZIP] or
                          [0/1/2] (ignoreCase))
  --level,-l              Compression level to use when basic compressor works.
                          (ZSTD: 0~22, 3 as default; LZMA: 0~9, 3 as default;
                          GZIP: 0~9, 5 as default)
                          default: -1
                          format: --level <int> (-1 ~ 31)
  --readyParas,-rp        Import the template parameters (-p, -bs, -c, -l) from an
                          external GTB file.
                          format: --readyParas <file> (Exists,File)
  --seq-ac                Exclude variants with the alternate allele count (AC)
                          per variant out of the range [minAc, maxAc].
                          format: --seq-ac <int>-<int> (>= 0)
  --seq-af                Exclude variants with the alternate allele frequency
```

```
                      (AF) per variant out of the range [minAf, maxAf].
                      format: --seq-af <double>-<double> (0.0 ~ 1.0)
  --seq-an            Exclude variants with the non-missing allele number (AN)
                      per variant out of the range [minAn, maxAn].
                      format: --seq-an <int>-<int> (>= 0)
  --max-allele        Exclude variants with alleles over --max-allele.
                      default: 15
                      format: --max-allele <int> (2 ~ 15)
```

Example

Download the `EAS hg38` dataset from `http://pmglab.top/genotypes` and use the dataset as a template file to examine the allele tags of the local exome sequencing variants `SNP.gtb` :

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
allele-check ./example/EAS.gtb ./example/SNP.gtb -o ./example/SNP.checked.gtb --seq-af
0.000001-0.999999 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc allele-check ./example/EAS.gtb ./exa
mple/SNP.gtb -o ./example/SNP.checked.gtb --seq-af 0.000001-0.999999 -y
```

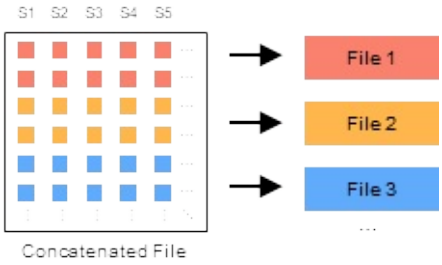
Here, the terminal prints the following message:

```
2022-06-27 01:16:02 INFO  [ThreadPool-thread-1] AlleleCheck chr11:244961 TempREF=G Temp
ALT=C TempAF=0.8035714285714286 REF=G ALT=C AF=0.6944444444444444 -> REF=C ALT=G
2022-06-27 01:16:02 INFO  [ThreadPool-thread-1] AlleleCheck chr11:251057 TempREF=C Temp
ALT=G TempAF=0.08630952380952381 REF=C ALT=G AF=0.22093023255813954 -> REF=G ALT=C
2022-06-27 01:16:04 INFO  [ThreadPool-thread-1] AlleleCheck chr17:42969194 TempREF=C Te
mpALT=G TempAF=0.9742063492063492 REF=C ALT=G AF=0.02608695652173913 -> REF=G ALT=C
2022-06-27 01:16:06 INFO  [ThreadPool-thread-2] AlleleCheck chr1:1041823 TempREF=G Temp
ALT=C TempAF=0.9990079365079365 REF=G ALT=C AF=0.0045045045045045045 -> REF=C ALT=G
```

Split GTB

Use the following command to split the GTB file into multiple independent subfiles:

```
split <input> -o <output> [options]
```



Program Options

```
Usage: split <input> -o <output> [options]
Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output folder.
                format: --output <file>
  --by          Split input files by node-level/chromosome-level into multiple
                subfiles, which can be rejoined by the concat mode.
                default: chromosome
                format: --by <string> ([chromosome/node] or [0/1])
  --yes,-y      Overwrite output file without asking.
```

Example

Split `./example/1000GP3.gtb` by chromosome tags:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 500m gbc \
split ./example/1000GP3.gtb -o ./example/1000GP3-chr -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 500m gbc split ./example/1000GP3.gtb -o ./e
xample/1000GP3-chr -y
```

After running this command, 24 GTB subfiles are generated in the folder `./example/1000GP30-chr` .

LD Calculation for GTB

GBC integrates the calculation of LD coefficients. Use the following command to calculate LD coefficients for GTB file:

```
ld <input> -o <output> [options]
```

Program Options

```
Usage: ld <input> -o <output> [options]
Output Options:
  --contig      Specify the corresponding contig file.
                default: /contig/human/hg38.p13
                format: --contig <file> (Exists,File,Inner)
  *--output,-o  Set the output file.
                format: --output <file>
  --o-text      Output LD file in text format. (this command will be executed
                automatically if '--o-bgz' is not passed in and the output file
                specified by '-o' is not end with '.gz')
  --o-bgz       Output LD file in bgz format. (this command will be executed
                automatically if '--o-text' is not passed in and the output
                file specified by '-o' is end with '.gz')
  --level,-l    Set the compression level. (Execute only if --o-bgz is passed
                in)
                default: 5
                format: --level <int> (0 ~ 9)
  --threads,-t  Set the number of threads.
                default: 4
                format: --threads <int> (>= 1)
  --yes,-y      Overwrite output file without asking.
LD Calculation Options:
  --hap-ld,--hap-r2    Calculate pairwise the linkage disequilibrium.
  --geno-ld,--gene-r2  Calculate pairwise the genotypic correlation.
  --window-bp,-bp      The maximum number of physical bases between the
                       variants being calculated for LD.
                       default: 10000
                       format: --window-bp <int> (>= 1)
  --min-r2             Exclude pairs with R2 values less than --min-r2.
                       default: 0.2
                       format: --min-r2 <double> (0.0 ~ 1.0)
  --maf                Exclude variants with the minor allele frequency (MAF)
                       per variant < maf.
                       default: 0.05
                       format: --maf <double> (0.0 ~ 0.5)
  --subject,-s         Calculate the LD for the specified subjects. Subject
                       name can be stored in a file with ',' delimited form,
                       and pass in via '-s @file'.
                       format: --subject <string>,<string>,...
  --range,-r           Calculate the LD by specified position range.
                       format: --range <chrom>:<minPos>-<maxPos>
                       <chrom>:<minPos>-<maxPos> ...
```

Example

Calculate the LD coefficients for the `EAS hg38` dataset.

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
ld ./example/EAS.gtb -o ./example/EAS.ld.gz -t 8 -y

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc ld ./example/EAS.gtb -o ./example/EA
S.ld.gz -t 8 -y
```

Contig File Format

The GBC application does not explicitly define the index of chromosome tags internally, but declares it through the contig file, where the index of the chromosome located in the first line of the contig file is 0, and the index of the chromosome in the second line is 1... Therefore, you can easily extend or modify the contig file for chromosome ploidy and chromosome tags modification.

By default, GBC supports genotype compression of human beings. It can also encode and compress genotypes of other haplotypic and diploid species. For non-human genomes, GBC only requires a different contig file to declare the label of the assigned chromosome (e.g., chrX, chrY, chrMT) and its ploidy. A contig file has "#chromosome,ploidy,length" as the header line, and then each line represents one chromosome. Since only 1 byte is reserved for storing chromosome numbers in GTB format, we require that the number of chromosomes in the input contig file does not exceed 256.

```
##reference=https://www.ncbi.nlm.nih.gov/grc/human/data?asm=GRCh38.p13
#chromosome,ploidy,length
1,2,248956422
2,2,242193529
3,2,198295559
4,2,190214555
5,2,181538259
6,2,170805979
7,2,159345973
8,2,145138636
9,2,138394717
10,2,133797422
11,2,135086622
12,2,133275309
13,2,114364328
14,2,107043718
15,2,101991189
16,2,90338345
17,2,83257441
18,2,80373285
19,2,58617616
20,2,64444167
21,2,46709983
22,2,50818468
X,2,156040895
Y,2,57227415
MT,2,4485509
```

Build Contig File For VCF

For non-human genotype files, use the following command to build a contig file for the original VCF file.

```
index <input> -o <output> [options]
```

This method will scan the comment information of VCF file and extract the `##contig=` field to build a contig file. If the VCF file is non-standard, the user can scan the entire VCF file by adding the parameter `--deep-scan`.

Reset Chromosome Tags With New Contig File

Use the following command to reset the chromosome tags of the GTB file (e.g. reset multiple chromosome tags to the same tag):

```
index <input> -o <output> --from-contig <from_contig> --to-contig <to_contig> [options]
```

For example, to set all the chromosome tags of 1000GP3 to `Unknown`, the following contig file needs to be created:

```
#chromosome,ploidy,length
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
Unknown,2,0
```

and then, run:

```
# Linux or MacOS
docker run -v `pwd`:`pwd` -w `pwd` --rm -it -m 4g gbc \
index ./example/1000GP3.gtb -o ./example/1000GP3.unknown.gtb --to-contig ./example/1000
GP3.contig

# Windows
docker run -v %cd%:%cd% -w %cd% --rm -it -m 4g gbc index ./example/1000GP3.gtb -o ./exa
mple/1000GP3.unknown.gtb --to-contig ./example/1000GP3.contig
```