Genome analysis

GTShark: Genotype compression in large project

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Associate Editor: XXXXXXX

Received on XXXXX; revised on XXXXX; accepted on XXXXX

Abstract

Summary: Nowadays large sequencing projects handle tens of thousands of individuals. The huge files summarizing the findings definitely require compression. We propose a tool able to compress large collections of genotypes as well as single samples in such projects to sizes not achievable to date.
Availability and Implementation: `https://github.com/refresh-bio/GTShark`
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Supplementary information: Supplementary data are available at publisher's Web site.

1 Introduction

Rapid decrease of genome sequencing costs allows many sequencing projects to grow to impressive sizes. The numbers of individuals covered by the Haplotype Resource Consortium (McCarthy *et al.*, 2016) or Exome Aggregate Consortium (Layer *et al.*, 2016) projects are counted in tens of thousands and even lager projects are on the go.

The aggregate results of such projects are usually stored in the Variant Call Format (VCF) files (Danecek *et al.*, 2011), in which the genome variations occupies successive rows. Each tab-separated row contains nine mandatory fields describing the variant and some (possibly large) number of optional values representing genotypes. The sizes of VCF files are huge, so gzip is a common solution partially resolving the storage and transfer problems. Nevertheless, a lot of effort was made to provide even better compression and sometimes speeding up the accession to the data. The most remarkable attempts were TGC (Deorowicz *et al.*, 2013), PBWT (Durbin, 2014), BGT (Li, 2015), GTC (Danek and Deorowicz, 2018). The first of them focused just on the compression ratio, while the remaining aimed at the rapid queries support with good compression ratios.

In this article, our goal is to provide the best compression ratio for a collection of genotypes. Moreover, the compressed database can serve as a knowledge base, which allows to astonishingly reduce sizes of files of newly sequenced individuals.

Our tool, GTShark, is based on the Positional Burrows–Wheeler Transform (PBWT) introduced in (Durbin, 2014). The key idea of PBWT is to permute a vector of genotypes for each single variant to order the samples according to the genotypes of previous variants. Due to the linkage disequilibrium property the neighbor genotypes (after the permutation) are likely to be the same. Thus, the permuted vector of genotypes is usually composed of a few runs of 1s (presence of alternate value) and 0s (presence of the referential value). PBWT and BGT (Li, 2015) store the run lengths using a simple run encoding scheme. BGT preserves also a permutation of samples each 8192nd variant to allow fast random access queries.

2 Methods

In GTShark, we essentially follow the same way. Nevertheless, there are several differences. First, we use a generalized PBWT (designed for non-binary alphabets in (Deorowicz *et al.*, 2018)) to directly support multi-alleles and unknown genotypes. Second, since we aim at the compression ratio, we do not store the intermediate permutations. Third, we employ an entropy coder (namely range coder) with special contextual modeling, which improves the compression ratio more than 2-fold. Fourth, we slightly modify the generalized PBWT, i.e., we resign from permuting vectors of samples for extremely rare (or frequent) variants. The experiments show that this improves the compression ratio by up to 10 percent.

A unique feature of GTShark is the ability to compress external, single-sample, VCF files with a use of the compressed collection as a reference. Such a scenario can appear, for example, in large sequencing projects, like the UK Biobank (Bycroft *et al.*, 2018), in which the genotypes are determined using microarrays, when a set of variants is fixed. To compress such sample we traverse the compressed collection and for each genotype we determine the position in the permuted vector in which this genotype would be placed if the sample were a part of the collection. We make use of the found neighborhood to predict and store the genotype compactly. More details of the algorithms can be found in the Supplementary Material.

The compressor was implemented in the C++14 language and is distributed under GNU GPL 3 licence. It is slightly parallelized: the PBWT making and the remaining parts are executed in separate threads. Thus, the maximal parallelization gain is 2-fold but in practice it is much smaller.

Table 1. Comparison of compressors of VCF files for HRC collection (40.40 M variants, 27,165 samples, 4310 GB of VCF, 69.7 GB of gzipped VCF).

	C-size [MB]	C-time [s]	C-RAM [GB]	D-time [s]
TGC	2,386	1,090,940	76.8	2,442
PBWT	3,693	134,065	0.8	33,499
BGT	6,717	146,178	**0.008**	25,610
GTC	3,731	142,474	5.0	**2,082**
GTShark	**1,678**	**97,716**	1.6	20,563

Hardware configuration: two AMD Opteron 6348 CPUs (2.8 GHz, 12 cores each), 128 GB of RAM. Column description: 'C-size' — compressed size, 'C-time' — compression time, 'D-time' — decompression time, 'C-RAM' — RAM usage in the compression stage. Bold font denotes the best results.

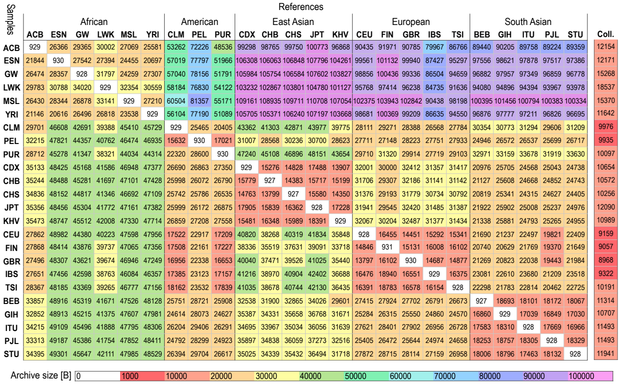
3 Results

For evaluation we used two *H.sapiens* datasets: the 1000 Genome Project Phase 3 (1000GP3: 2504 samples, 84.80 M variants) and the Haplotype Reference Consortium (HRC: 27,165 samples, 40.40 M variants).

The comparison of compression ratios and times of the state-of-the-art methods, i.e., TGC, PBWT, BGT, GTC, and the proposed GTShark is shown in Table 1 and Supplementary Material. GTShark is the clear winner in compression ratio. The running times of PBWT, BGT, GTC, GTShark algorithms are similar as they are dominated by processing of VCF files. GTShark is the fastest in compression due to slight parallelization of the code and some small technical improvements in parsing the VCF files. GTShark allows also to extract a single sample from a compressed collection in an average time about 11.5 minutes.

In the next experiment, we measured the compression of external samples. We used the HRC dataset here and processed as follows. We excluded 100 randomly chosen samples to obtain the collection of 27,065 samples, for which we built the compressed database of total size 1674 MB. Then we compressed the excluded samples one by one taking the compressed collection as a reference. On average GTShark processed a single sample in about 12 minutes and compacted it to 65.5 KB. To the best of our knowledge, the most recent experiment of this type was described in (Pavlichin *et al.*, 2013). The authors used a reference human genome and the dbSNP database as a knowledge base. They were able to compress single individual genotypes from the 1000GP Phase 1 (39.7 M variants) to about 2.5 MB. The results should not be, however, compared directly as in the Pavlichin *et al.* experiment the compressed samples contained variants absent from the reference database, and in our experiment we assumed that sets of variants in the sample and reference data are the same. Nevertheless, the comparison shows what is possible in such restricted scenario.

In the final experiment, we investigated the impact of the selected knowledge base. We used Chromosome 11 data from the 1000GP3 containing 2504 samples from 26 populations. Initially, we divided the VCF file into 26 files using the population criteria. The ASW and MXL populations were significantly smaller than the rest and we excluded them from further studies. The remaining populations have cardinalities at least 85 and we randomly subsampled the larger ones to obtain 24 VCF files each containing exactly 85 samples. Then we used GTShark to compress each VCF file obtaining 24 compressed collections serving as references in the rest of the experiment. We also constructed 24 larger referential collections. Each of them, composed of 23 population VCF files and containing $23 \times 85 = 1955$ samples, was also compressed using GTShark. Then we compressed each single-sample VCF file (i.e., $24 \times 85 = 2040$ samples in total) using each of the smaller (85-sample) collections as references. The results were averaged over all 85 samples from each population. For easier interpretability of Fig. 1 we grouped the populations in 5 superpopulations (African, American, East Asian, European, and South Asian). The columns are described by the referential population. As one could expect the compression is the best when a dataset from the same superpopulation is used as a reference. The last column (beyond the matrix) shows the results for larger collections (containing all populations except for the one that is compressed).



Samples	References																								Coll.
	African						American			East Asian					European					South Asian					
	ACB	ESN	GW	LWK	MSL	YRI	CLM	PEL	PUR	CDX	CHB	CHS	JPT	KHV	CEU	FIN	GBR	IBS	TSI	BEB	GIH	ITU	PJL	STU	
ACB	929	26366	29365	30002	27069	25581	53262	72226	48536	99298	98765	99750	100773	96868	90435	91971	90785	79967	86766	89440	90205	89758	89224	89359	12154
ESN	21844	930	27542	27394	24455	20697	57019	77797	51966	106308	106063	106848	107796	104261	99561	101132	99940	87427	95297	97556	98621	97878	97517	97386	12171
GW	26474	28357	928	31797	24259	27307	57040	78156	51791	105984	105754	106584	107602	103827	98856	100436	99336	86504	94659	96882	97957	97349	96859	96778	15268
LWK	29783	30788	34020	929	32354	30559	58184	76830	54122	103232	102867	103801	104780	101127	95768	97414	96238	84735	91636	94080	94896	94394	93967	93978	18537
MSL	26430	28344	26878	33141	929	27210	60504	81357	55171	109161	108935	109711	110708	107054	102375	103943	102842	90438	98198	100395	101456	100794	100383	100334	15370
YRI	21146	20616	26496	26818	23538	929	56104	77190	51089	105705	105371	106240	107197	103668	98681	100369	99209	86635	94550	96876	97777	97211	96826	96695	11642
CLM	29701	46608	42691	39388	45410	45729	929	25465	20405	43362	41303	42871	43977	39775	28111	29271	28388	26568	27784	30354	30773	31294	29606	31209	9976
PEL	32215	47821	44357	40762	46474	46935	15632	930	17021	31007	28568	30236	30700	28623	27711	27148	28223	27751	27933	24946	26572	26537	25699	26717	9935
PUR	28712	45278	41347	38321	44034	44314	22320	28600	930	47240	45108	46896	48151	43654	29710	31320	29914	27719	29103	32971	33159	33678	31919	33630	10097
CDX	35133	48425	45168	41586	46948	47377	26690	26863	27350	929	15276	14828	17488	13907	32001	30000	32412	31357	31417	20976	25705	24568	25043	24738	10654
CHB	35244	48488	45281	41697	47101	47428	25998	26072	26790	15779	927	14383	15717	15199	31706	29307	32186	31141	31142	21127	25608	24668	24852	24743	10572
CHS	34836	48152	44817	41346	46692	47109	25742	25786	26535	14763	13799	927	15580	14350	31376	29193	31779	30734	30792	20819	25341	24315	24627	24405	10256
JPT	35356	48456	45304	41772	47161	47382	25999	26172	26875	17905	15839	16362	928	17228	31941	29545	32420	31485	31387	21922	25902	25008	25237	24976	12090
KHV	35473	48747	45512	42008	47330	47714	26859	27208	27558	15481	16348	15989	18391	929	32067	30204	32487	31377	31434	21338	25881	24793	25265	24955	10989
CEU	27862	48982	44380	40223	47598	47956	17522	22917	17209	40820	38268	40319	41834	35848	928	16455	14451	15292	15341	21690	21237	22497	19821	22409	9159
FIN	27868	48414	43876	39737	47065	47356	17508	22161	17227	38336	35519	37631	39091	33718	14846	931	15131	16008	16102	20740	20629	21769	19370	21649	9057
GBR	27496	48307	43621	39674	46946	47249	16956	22338	16653	40040	37471	39526	41025	35440	13797	16102	930	14687	14877	21269	20823	22038	19443	21984	8968
IBS	27651	47456	42598	38763	46084	46357	17385	23123	17157	41216	38970	40904	42402	36688	16476	18940	16551	929	16375	23081	22610	23680	21209	23518	9322
TSI	28367	48185	43369	39265	46777	47156	18162	23532	17839	41035	38678	40744	42130	36435	16391	18783	16578	16154	928	22298	21783	22814	20462	22725	10191
BEB	33857	48916	45319	41671	47526	48128	25751	28721	25908	32538	31900	32865	34026	29601	27415	27924	27702	26791	26673	927	18693	18101	18172	18067	11314
GIH	32852	48913	45215	41375	47607	47981	24614	28073	24627	35387	34331	35658	36768	31671	25284	26315	25550	24860	24570	16860	929	17039	16849	17030	10707
ITU	34215	49109	45496	41888	47795	48306	26204	29406	26291	34695	33967	35034	36056	31639	27621	28401	27902	26956	26728	17583	18310	928	17669	16966	11493
PJL	33313	49187	45386	41754	47852	48411	24792	28299	24923	35897	34838	36059	37273	32516	25405	26472	25644	24974	24658	18253	18757	18305	928	18329	11493
STU	34395	49301	45647	42111	47985	48529	26394	29704	26617	35025	34339	35432	36494	31718	27872	28715	28114	27159	26958	18006	18796	17463	18132	928	11941

Fig. 1. Comparison of single-sample GTShark compression for 24 populations (data: 1000GP3, Chromosome 11), sizes of sample archives. The references with population codes are made up of 85 samples from the population. The "Coll." reference is a collection of 1955 samples from 23 population (without population matching compressed sample).

4 Conclusions

The proposed algorithm compressed large collections of genotype data significantly better than the existing methods and was the fastest. Its unique feature is a mode in which the compressed collection of genotypes serves as a reference for external single-sample data. In this scenario we were able to shrink down the human genome to about 65 KB.

Funding

The work was supported by National Science Centre, Poland, project DEC-2017/25/B/ST6/01525 and by POIG.02.03.01-24-099/13 grant: "GeCONiI—Upper Silesian Center for Computational Science and Engineering" (the infrastructure).

Conflict of Interest: none declared.

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