Correspondence

GW: ultra-fast chromosome-scale visualisation of genomics data

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Abstract

Genome-Wide (GW) is an interactive genome browser that expedites analysis of aligned sequencing reads and data tracks, and introduces novel interfaces for exploring, annotating and quantifying data. GW's high-performance design enables rapid rendering of data at speeds approaching the file reading rate, in addition to removing the memory constraints of visualizing large regions. We report substantial gains in performance and demonstrate GW's utility in exploring massive genomic regions or chromosomes without requiring additional processing.

Genome browsers such as the Integrative Genomics Viewer (IGV) and JBrowse2 (1, 2) are invaluable for exploring aligned sequencing reads and verifying variant calls, but lack the speed offered by high-performance libraries and frameworks. In particular, current tools struggle to visualise large genomic regions which is a common need when investigating complex chromosomal rearrangements that can encompass megabases (3, 4). Exploring collections of variants and manually annotating data remains cumbersome due to slow loading times or requiring static image generation.

Here we describe GW, an interactive browser for rapidly visualising aligned sequencing reads, data tracks and genome-variation datasets, featuring a multithreaded architecture for desktop or command-line use on multiple platforms, including cloud environments (e.g. AWS servers or the Genomics England Research Environment) (Fig. 1a-c, Supplementary Movie1.mp4, Supplementary Table1).

GW supports extensive data interactions using 35 built-in commands, enabling users to load, save, navigate and search files, filter and count reads, change appearances and organise data (Fig. 1e-g). Data is displayed using either the 'alignment-view' or 'image-view'. With the alignment-view (Fig. 1b), sequencing reads are arranged as stacks with colours representing information such as mismatches or discordant reads. Coverage profiles appear above and users can arrange multiple files and regions in rows and columns. Data tracks are placed below, and can be expanded, collapsed, and dynamically resized. Interactive elements display information to the terminal (Fig. 1c). GW supports themes including ‘slate’ (shown) and ‘dark’ to reduce eye strain, and ‘igv’ (Supplementary Fig. 1) (1).

The ‘image-view’ (Fig. 1d) organises images into a grid, simplifying exploration and curation of large datasets. Images can be loaded from disk or generated in real-time from files, while

52 right-clicking an image will switch between alignment and image-views, permitting static-
53 image exploration and dynamic data interactions. Multiple input files are supported for
54 comparing variant sets and manual curation is facilitated by customizable labels or information
55 parsed from input VCF's. Labels are displayed over thumbnail images, and can be cycled,
56 tagged with comments, loaded from disk, or encoded within files (Fig. 1d).

57 GW can create static images from variant files, reference genome indexes, or genome
58 coordinates, and can save images of every chromosome in <1min30s (Supplementary Fig. 2).
59 Images can later be explored as filenames encode genome locations. Loading of chromosome-
60 images alongside bam files (Supplementary Fig. 3), permits right-clicking on a chromosome-
61 image which switches the user to the alignment-view, zooming into a 500kb genome region
62 for rapid data exploration.

63 GW also introduces new tools for data analysis not available in other browsers, including
64 composable filtering and counting commands, allowing for tasks such as counting the number
65 of reads that support a structural variant (SV), eliminating the need for manual counting or
66 extra tools (Fig. 1e, f). Eight additional analysis tasks are provided as examples (Supplementary
67 Fig. 4), including filtering/counting reads containing kmers (e.g. 'count seq contains TTAGGG'
68 or 'filter seq omit AAAAAA'), regional-overlaps ('filter pos >= 10000 and ref-end < 20000'), or
69 sam-tag properties ('count AS > 100', 'filter NM = 0'), which would be difficult or impossible
70 using other browsers. Additional display modalities in GW include drawing modified bases,
71 representing SV patterns using coloured arcs (Fig. 1g, h), and scaling read-position by template-
72 length and (Supplementary Fig. 5).

73 GW links to online databases using the 'online' command, providing web-links to UCSC,
74 Gnomad, Ensemble, NCBI and DECIPHER browsers with the matching genome location as seen

in GW, making it straightforward to compare samples against data tracks and population or disease databases.

We compared GW's speed to other browsers like IGV and JBrowse2 (jb2export plugin), along with static image tools like samplot (1, 2, 5–7). GW generated images close to the file reading speed (Supplementary Fig. 6), significantly outpacing other tools on all datasets (Supplementary Fig. 7-12, Supplementary_Data.xlsx). For example, compared to IGV using a 2 Mb region size, GW showed >146-fold improvement in rendering speed (median 185-fold), while also using up to 109-fold less memory (Illumina data). Using a smartphone, GW was >30× quicker than IGV on a desktop. For large-scale analysis, GW visualized chr8 (146Mb, 26× coverage) from a sample with a complex rearrangement pattern (4) in 7.2 seconds using 736Mb of memory, showcasing its efficiency in processing entire chromosomes without additional steps (Fig. 1h).

Future work will focus on adapting GW for rendering alignments against pangenome graphs. In summary, GW permits rapid exploring, analysing and annotating genomic data on a much larger scale.

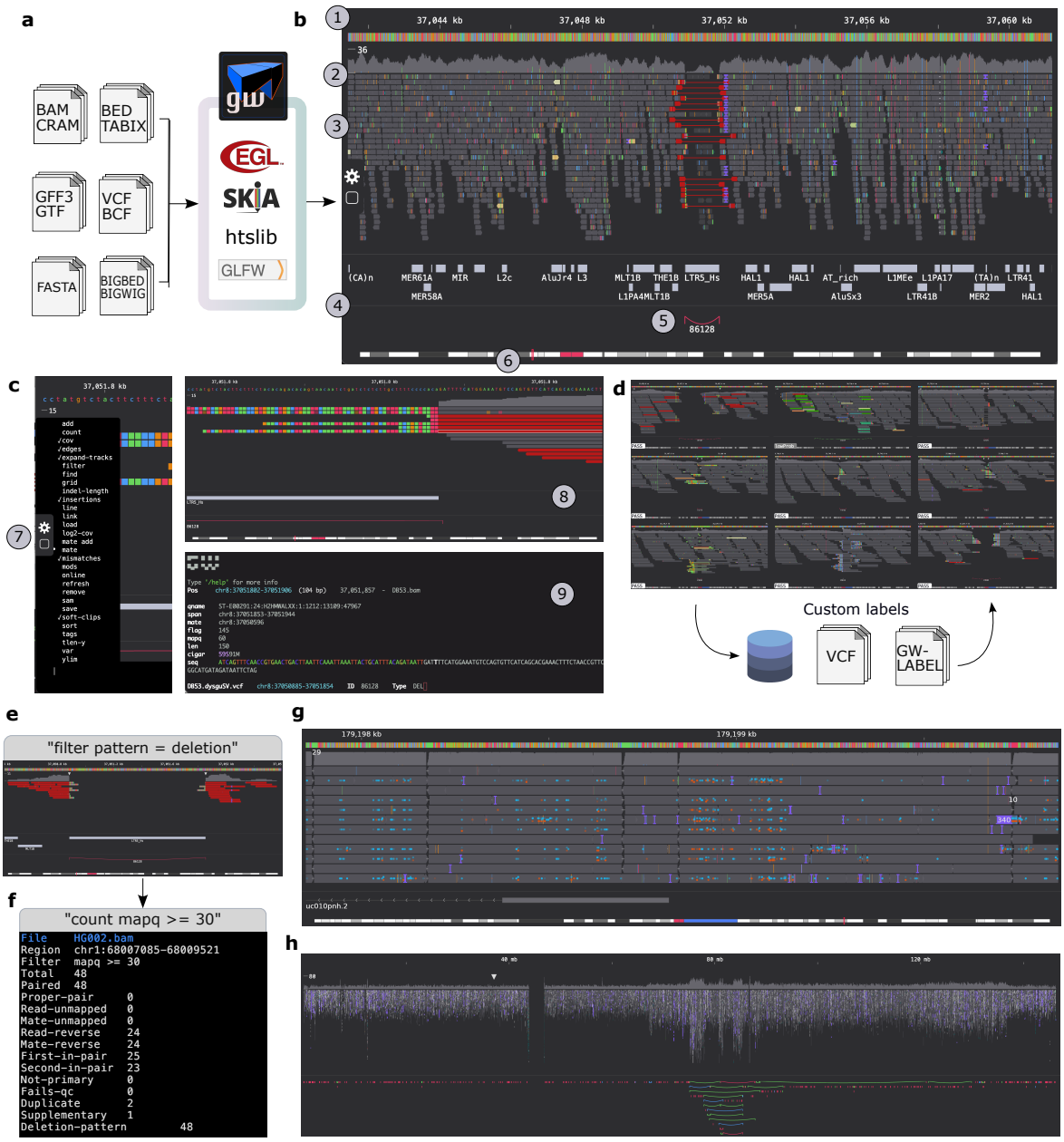

Fig. 1. Genome browsing and variant annotation using GW. (**a**) GW accepts common data formats and uses libraries such as Skia and htslib for faster visualization. (**b**) The alignment-view displays a reference genome with scale bar (1), coverage and SNP profiles (2), stacked reads (3), and data tracks below (4). An SV is indicated with a colored arc (5). An ideogram is overlayed with a box to indicate chromosome location that can be used as a slider to change position (6). (**c**) Access commands and functions via the bubble (6) or the command box (7). Data interactions (8) display information to the terminal (9). (**d**) The image-view displays a grid of images, enabling manual annotation. GW supports versatile filtering (**e**) and counting (**f**) commands and supports display of multiple base modifications simultaneously (**g**). (**h**) Dynamic visualization of chr8 (146Mb), showing a complex rearrangement pattern and copy-number profile, where the white arrow shows the location of (**a**).

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Online Methods

Fast data rendering

GW relies on several high-performance libraries to achieve fast data rendering, including htslib (8) for alignment file reading, Skia for fast 2D vector graphics rendering (9), and GLFW for window management (10). GW is written in C++ and has an efficient design, where for smaller regions minimal data is buffered in memory, while for larger regions, alignment data can be streamed without buffering.

GW employs various Level Of Detail (LOD) thresholds according to the region size being displayed, above which certain image details are not drawn, or elided. These user-customisable threshold are designed to both increase the clarity of images and speed up rendering. For example, above a region size of 20 kb, the reference track is not drawn, whilst above 500 kb, mismatches are not drawn. Another method to speed up drawing is using gap elision, where deletion-gaps in alignments are not drawn if they are too small to be visualised on-screen, occurring when their size falls below a threshold (1 + region-size / image-width), where width is measured in pixels and region-size is in base-pairs.

Window management and graphics

GW utilizes the GLFW library for managing user inputs via the keyboard, mouse or other devices like a touchpad, and managing the interface between the operating system window and a graphics surface which can reside in GPU memory or main memory. For drawing, GW uses the Skia graphics library from Google, which translates drawing calls to a target graphics API, and manages drawing batches. For systems other than MacOS, Skia is built with the EGL

backend allowing the use of the OpenGL ES API, whilst for MacOS the native OpenGL API is utilised.

When rendering a static image, GW creates a graphics context in main memory rather than on the GPU which allows for efficient parallel drawing between multiple threads and multiple contexts. When rendering to screen, surfaces are created on both the GPU and CPU side. Most rendering is carried out on the CPU side using a raster surface. As most draw operations consist of simple rectangles, these are efficiently handled by the CPU, and we found transporting these commands to the GPU incurred a non-trivial time penalty which was large enough to warrant performing rendering using a raster surface. Once the frame has been rendered to the raster surface, the image is transferred to the GPU surface for display using the GLFW interface.

Each frame rendered by GW is cached, allowing GW to redraw only sections of the screen that have experienced on update since the last frame. For example, for multi-sample or multi-region views, updates to one screen panel do not invoke re-processing or redrawing of other panels which speeds up the frame rate.

Finding Y-position of reads

The on-screen y position, or row, of reads is determined before drawing and can take an integer value in the range [-1, ylim], where ylim defaults to 60 but can also be set by the user. Reads that are out-of-view will have ylim = -1. To determine the on-screen position of reads, an end-array is used with length equal to ylim, with each value representing the reference end position of each row. For each incoming read, the y-position is set as the index in the end-array whose value is less than the alignment position. The value in the end-array is then updated to reflect the reference-end position of the new read. This operation is used to

199 append reads to the right-hand-side of the read queue. To append reads to the left-hand-side
200 of the read queue a separate start-array is used (length = ylim) that performs the opposite
201 function, keeping track of the start position of each row of reads. Left-appending reads would
202 ideally require input reads to be sorted by reference-end position, although reading the
203 alignment file returns reads sorted by reference start. To avoid having to sort input reads,
204 reads are appended to the left-hand side in reverse order. Using these arrays allows for
205 appending new reads to either side of the read queue in linear time without needing to re-
206 analyse buffered data.
207
208 Fast scrolling
209 To speed up drawing GW buffers in-view data only, up until a threshold region size is
210 reached which is 1.5Mb by default. Above this threshold then the entire frame is rendered by
211 streaming data from disk which removes the memory constraints of visualising large regions.
212 However, below this threshold, to speed up scrolling, GW reuses buffered reads from the
213 previous frame and only loads reads from newly requested regions, whilst avoiding fetching
214 reads from out-of-view loci, which reduces file loading pressure. Newly fetched data is added
215 to the left or right-hand-side of the read queue, maintaining position sorted-order and any out-
216 of-view data is dropped. Zooming-out involves appending reads to both sides of the queue,
217 whilst zooming-in involves culling reads from both sides of the queue. To ensure stacks of
218 alignments remain in the same position on-screen during scrolling and zooming, the y-positions
219 of new read alignments are determined using the end-array and start-array.
220

221 Grid layout and image generation

222 GW can display images in a grid layout by loading files from the filesystem (png format), or
223 generating images on the fly from a VCF/BCF or BED files. Files loaded from disk are processed
224 in parallel. Images are stored in memory making scrolling to previously-seen images much
225 faster. If the window size changes or there is a change to image settings, or the refresh
226 command is used, buffered images are discarded.

227 Filtering and counting reads

228 GW supports 'filter' and 'count' commands that can accept a simple expression for filtering
229 and quantifying aligned sequencing reads. Reads can be filtered or counted using an expression
230 of the form '{property} {operation} {value}', where a 'property' relates to the alignment,
231 'operation' is a standard operator, and 'value' is the desired filtering value. Currently, over 40
232 different properties can be used, derived from attributes of the alignment (mapq, pos, tlen
233 etc), flag values ('paired', 'proper-pair' etc or numeric values, 1, 2, respectively), or standard
234 SAM-tag values (Alignment score AS, Edit distance NM etc). These properties can be combined
235 with up to 10 operators which include common comparison operators (greater than '>', equal
236 to '==' etc) as well as bitwise '&' operator, and sequence specific operators ('contains' and its
237 opposite 'omit'). The value side of the expression is chosen by the user and is typically a
238 numeric value, but can also be a string value. Expressions can also be chained to create more
239 complex subsets of the data and may be useful for many analytical tasks that would normally
240 require additional bioinformatics tools. To illustrate some brief examples, sub setting the data
241 by mapping quality, insert size or location-of-mate is possible, and more complex analysis such
242 as counting the intersection of reads with a genome feature, or filtering/selecting reads by the
243 occurrence of a kmer is also possible.

244

245 Benchmarking

246 We benchmarked visualisation tools using paired-end Illumina data from the HG002 human
247 sample sequenced to 40X coverage (148bp reads), and PacBio HiFi data at around 8X. Reads
248 were aligned to the ucsc.hg19 reference using bwa mem (v0.7.17, paired-end reads), or
249 minimap2 (v2.21 long-reads) (11). The benchmark scripts (benchmark.py and plot.py) and
250 results are available online in the GW repository at
251 https://github.com/kcleal/gw/tree/master/test. GW (v1.0.3), IGV (v2.16.0), JBrowse2 (v2.4.0,
252 jb2export "img" plugin), samplot (v1.3.0), and genomeview (v1.1.4) were invoked from the
253 command line to generate a single image of a target region. Regions that overlapped gaps in
254 the reference genome were ignored, as were regions with zero coverage. Sampled regions
255 (n=20) were the same for each application. All tools were run in single-thread mode, while GW
256 and IGV were also tested using 4 threads. IGV was configured using the desktop interface to
257 display large regions by setting the "Visibility range threshold to 250Mb". Other parameters
258 were configured to try and make a fair comparison with GW, turning off "Quick consensus
259 mode", "Compute insert size thresholds", "Show insertion markers", "Downsample reads",
260 whilst it was ensured the following options were turned on "Show mismatched bases", "Show
261 soft-clipped bases". Mean elapsed wall time was measured using hyperfine (12), and memory
262 (resident set size) were measured using the GNU-time application. The time taken to visualize
263 a 2bp region was taken as the initialisation time of the application, which included task such as
264 file opening, saving of the image and application shutdown. For larger regions, the additional
265 time taken on top of this was taken as the render time of the application. The maximum speed
266 that the alignment file could be read was approximated as the average time to run "samtools
267 view -c -@{t}" to count the number of reads in the region, employing the same number of
268 threads as the comparison visualization tool, setting {t} to either 1 or 4. The benchmark was

run on an Intel i9-11900K (Iris graphics), NVMe WD 2TB, 64 GB memory. If a tool took more than 3 hours to complete the benchmark, it was not included in the results. For displaying modified bases, GW was compared to IGV as other tools either did not support modified bases, or we were unable to configure the tool to do so using their command-line interface.

Benchmarking of GW was also performed on a Google Pixel 6 smartphone, using HG002 40X Illumina sample. Here, the benchmark was limited to chromosome 1 due to space limitations and execution time was measured using hyperfine (12). Movie1.mp4 was generated on a MacBook Pro M2 16 Gb memory.

Data Availability

The HG002 human sample (13), sequenced using Illumina (40× coverage), was downloaded from GIAB ftp://ftp-trace.ncbi.nlm.nih.gov/giab/ftp/data/AshkenazimTrio/HG002_NA24385_son/NIST_HiSeq_HG002_Homogeneity-10953946/HG002Run01-11419412/HG002run1_S1.bam). PacBio HiFi data for HG002 (8× coverage) was downloaded from SRA (https://www.ncbi.nlm.nih.gov/sra) under accession SRR10188368. ONT data from HG002, sequenced using the R9.4.1 HAC protocol, was downloaded from SRA accession SRR11537600. Additionally, ONT data from HG002, sequenced using the “Kit14” workflow with methylation base calls, was downloaded from AWS s3://ont-open-data/giab_2023.05/analysis/hg002/sup/, sample PAO89685. A synthetic high-coverage sample was created by duplicating the PAO89685 sample. The benchmark script and results can be found online in the GW repository at https://github.com/kcleal/gw/tree/master/test. Sample DB53 has been reported previously in (4), and is available from NCBI BioProject PRJNA417592.

Availability of supporting source code and requirements

Project name: GW (Genome Wide)

Project homepage: https://github.com/kcleal/gw

Operating system(s): unix based, Windows.

Programming language: C++

Other requirements: glfw, htslib

License: MIT

Abbreviations

IGV Integrative Genome Viewer, GIAB Genome In A Bottle consortium, GPU graphics processing unit, NVMe non-volatile memory express, SV structural variant, ONT Oxford Nanopore Technologies, AWS Amazon Web Services.

Conflict of interest disclosure

The authors declare that they have no competing interests.

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Author contributions

KC designed and wrote the software, performed experiments, and wrote the manuscript. AK contributed code, help create distributions and design ideas, and tested the software. DMB provided feedback and performed manuscript editing. All authors read and approved the final manuscript.