

SOFTWARE DOCUMENTATION

BIO727P Software Group Project – SNP data portal

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Project Philosophy

This web application was designed to allow bio scientists to retrieve information on SNPs and calculate simple genetic population genomic statistics of their choice within a downloadable text file and visualise the distribution. SNP, gene names, gene alias, and chromosomal region of interest can be entered in the search bar and these search terms will be checked off in the form below. The server will retrieve either single or multiple SNPs depending on the requested input, which could be associated with many SNPs. Furthermore, chromosomal coordinates, derived allele frequency, allele and genotype frequencies for each population corresponding to each SNP would be retrieved. The user can select one or more summary statistics of interest and a number of populations. For storage reasons and due to the short amount of time of this software project, the available summary statistics are Shannon Diversity index, Expected Heterozygosity, and Tajima's D, while the five populations that can be chosen from are British, Dai Chinese, Gujarati, Luhya, and Mexican. When there is more than one population requested by a user, a FST analysis can additionally be done with the option to download the selected statistics in a text file.

The web application is structured as shown in Figure 1: Collecting the SNP, annotation, population (meta) data, and gene aliases, all data sets were processed using different tools and packages, such as The data base was built based on the pre-processed and joined data

Software Architecture

The database was built using SQLite3 (Hipp, 2020) and integrated into the Website using the Python Standard (Van Rossum and Drake Jr, 1995) and Flask framework (Grinberg, 2018). Figure 2 shows how the main components were integrated into the web application. Red boxes show implementation and coding languages used, while the blue box shows the data that will be eventually seen on the user interface once a query has been made.

The web application design is implemented using HTML templates and CSS/JavaScript stylesheets, which create the theme of the website. Information is posted on HTML templates in either the results or visualisation app route. Summary statistics and visualisation were implemented in Python, with “calculate” and “download” buttons provided in HTML. CSS stylesheets are connected to HTML template by href

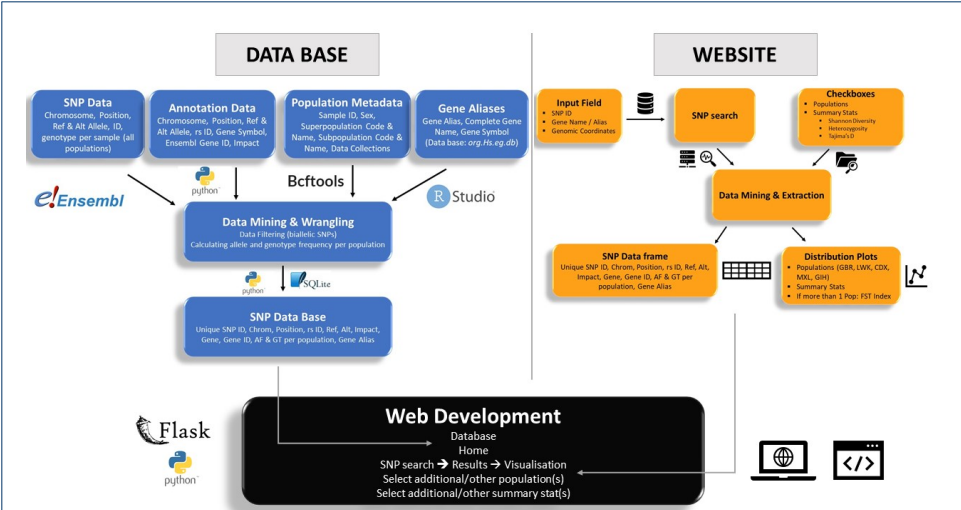


Figure 1: **Sample figure title.** A short description of the figure content should go here.

links. Navigation bar, search bar, population and gene/ SNP ID/position forms were created in HTML template and CSS.

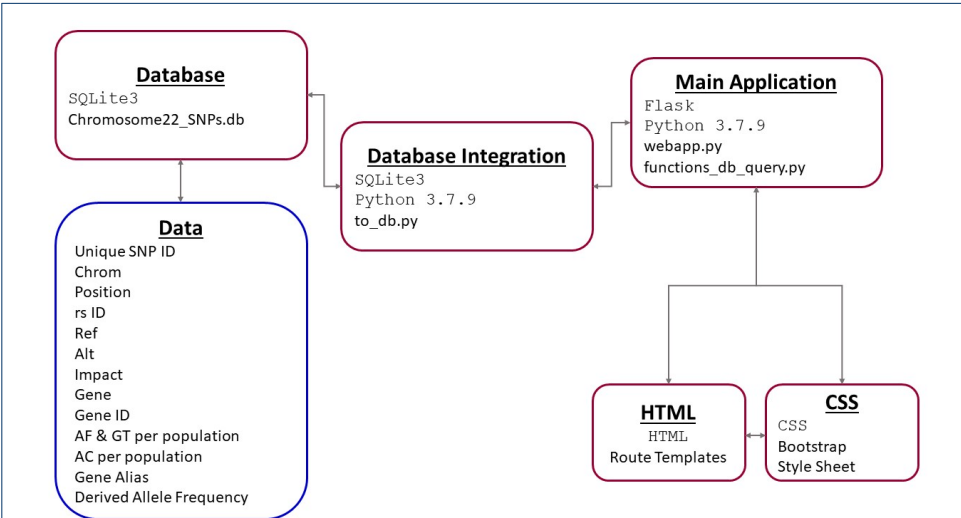


Figure 2: **Sample figure title.** A short description of the figure content should go here.

Running the software

In order to deploy the website locally, download the *team_celine_webapp* directory from the GitHub page (see https://github.com/graciaandr/bioinf_group_project) and the database file in .db format from Google Drive using the following link: [Drivelink](#)

The user needs to ensure to download the database file into the webapp folder.

Install the required packages to the local machine by running:

```
$python -m pip install -upgrade pip
$pip install -r requirements.txt
```

Run the software on <http://localhost:5000/> using:

```
$git clone
https://github.com/graciaandr/bioinf_group_project.git
$cd webapp
$FLASK_APP=webapp.py
$flask run
```

Required packages:

Flask

Flask-Bootstrap

SQLite3

Scikit-allel

Pandas

Numpy

Matplotlib.pyplot

Seaborn

Pybase64 (base64)

Markupsafe

Flask and SQLite3

The software was built using **Flask** ([Grinberg, 2018](#)) because the tools it provides as a lightweight web framework allow beginners to learn setting up and running a web application. It is a microframework with little dependencies to external libraries, making it simple to use with clean and concise code. Furthermore, connecting **Flask** with the **SQL** database which was generated using **SQLite3** ([Hipp, 2020](#)) is straightforward using **SQL** query commands written in **Python**. User inputs from **HTML** forms can be easily processed and passed as parameters in data querying. **Flask** uses **jinja2** as its template engine resulting in simplicity and efficiency in creating layout for the web pages. In addition, the feature of downloading data from the website as a text file was easily performed using a **Flask** route.

HTML/CSS

HTML coupled with CSS were used to deliver a presentable and professional website. HTML was used to format and display the web pages' contents including displaying data in a table format and plot distribution images, while CSS allowed the addition of stylistic elements to the webpage. Bootstrap was also utilised to provide the page design template and navigation bar. HTML forms which consisted of text input, radio buttons, and checkboxes were generated to take user's input.

Data Collection

SNP Data

The SNPs used for creating the database were extracted from Phase 3 Chromosome 22 VCF file from the Ensembl FTP Server at http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000G_2504_high_coverage/working/20201028_3202_phased/CCDG_14151_B01_GRM_WGS_2020-08-05_chr22.filtered.shapeit2-duohmm-phased.vcf.gz.

Annotation Data

In order to link the gene regions the SNPs in the database lie in, annotated data from the Ensembl FTP server was used. The data can be found under the following link:

http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000G_2504_high_coverage/working/20201028_3202_raw_GT_with_annot/20201028_CCDG_14151_B01_GRM_WGS_2020-08-05_chr22.recalibrated_variants.annotated.txt

Population Metadata

Mapping the sample names to the super- and subpopulations was done by extracting the population samples from downloading the 3202 samples from the 100 genomes data portal (see <https://www.internationalgenome.org/data-portal/data-collection/30x-grch38>).

Gene Aliases

As users are also permitted to look for SNPs by entering a gene alias into the search field, the annotated genes need to be linked to their correlating gene aliases. The R Bioconductor `org.Hs.eg.db` library contains these pieces of information and was used therefore. The data frame for connecting gene and gene aliases was stored as a CSV file for further data processing.

Derived Allele Frequency

To calculate derived and ancestral allele frequency using VCFTools, data was sourced from an annotated VCF file with ancestral allele (AA) in the info field. The file was collected from 1000 Genome FTP site which underwent downstream data processing (see http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/ALL.chr22.phase3_shapeit2_mvncall_integrated_v5b.20130502.genotypes.vcf.gz) .

Data Mining & Wrangling

Population Selection

The Phase 3 Chromosome 22 VCF file was filtered using `bcftools` ([Danecek et al., 2021](#)) to obtain 5 sub-population specific VCF files. The chosen populations are:

- GBR - British (European)
- GIH - Gujarati (South Asian)
- LWK - Luhya (Africa)
- CDX - Dai Chinese (East Asian)
- MXL - Mexican (America)

Populations were selected due to the ability to cover wider genetic variation between populations and between SNPs also each population lives in different environments. We selected one representative sub-population per super-population, and those with a similar number of samples as GBR, which was the first population we chose. The VCF files were converted to CSVs and filtered by population using the following commands:

```
# filter VCF for samples of a selected population
# (saved in pop_samples.txt)
bcftools view -S pop_samples.txt
chr22.vcf
> filtered_for_pop.vcf

# remove "##" lines in vcf file and store it in CSV file
egrep -v "^##" filtered_for_pop.vcf > filtered_for_pop.csv
```

After conversion to CSVs, only biallelic SNPs were retained using the Python data management library `pandas` ([The pandas Development Team, 2020](#); [Wes McKinney, 2010](#)). The data sets were filtered for biallelic alleles for more manageable data processing when calculating reference, alternative allele counts and frequencies, as well as, genotype frequencies. The genotype was converted from numeric format to alpha-bet format in `to_db.py` in order to apply `genotype()` and `summary()` functions from the `genetics` ([Warnes et al., 2021](#)) R package in the `calculate_frequencies.R` script ([R Core Team, 2020](#)), as these functions required the genotypes to be in letter format. The `genetics` package was more feasible than other packages which required a specific file format, e.g. `genepop`. The `summary()` function calculated allele counts and frequencies at SNP level and accepted only genotype data as the genotype object, which was generated by the `genotype()` function at SNP level.

Derived Allele Frequency Extraction

The ancestral annotated VCF file was required to calculate the derived and ancestral allele frequencies using `VCFtools` ([Danecek et al., 2011](#)). The derived and ancestral frequencies considered all populations in the 1000 genomes project to measure occurrence of non-ancestral/derived allele in the human population. Ancestral allele and chromosomes were extracted from the SNP VCF using `bcftools` and saved in a text file. Next, the text file was read as data frame in R followed by extracting data with missing ancestral allele and insertion of chromosome number column as

VCftools required a text file in chromosome and number format. VCF filtered by positions using **VCftools** and text file which contained the positions that should be excluded from the VCF file. These positions were removed from the VCF, as the `-derived` parameter in **VCftools** command could not read VCF data which have missing ancestral alleles. Previous studies found derived/mutated alleles that arose after the divergence from the outgroup (e.g chimpanzee) by identifying ancestral alleles which are non-mutated alleles that arose after the divergence from the outgroup (e.g chimpanzee). This could imply allele frequencies for the alternative are the same for derived allele frequencies as derived allele frequencies could be inferred when ancestral alleles are present (Koenig *et al.*, 2019; Naji *et al.*, 2021). Additionally, derived allele frequencies are usually much smaller than the ancestral allele frequencies (Gorlova *et al.*, 2012). Derived parameter outputs the ancestral and derived allele frequencies using the following command:

```
vcftools -vcffile test.vcf -freq -derived
--out derivedallele2
```

Database Generation from CSV File

After data mining and wrangling, the data was put together into a table and saved as a CSV file. The SQL database `chromosome22.snps.db` was generated using **SQLite3** extension in Python. By executing the following commands, the `.db` file was automatically generated and a connection to the database was established.

```
connection = sqlite3.connect("chromosome22_snps.db")
cursor = connection.cursor()
```

A table was created in the database using **SQL CREATE TABLE** statement which required the column names, and the `unique.SNP.ID` column was assigned as the **PRIMARY KEY**. `insert_table()` function in `to_db.py` script was then used to populate the database table with the data in the CSV data file. Even though there was only one table containing our data, SQL database was still used because SQL database connection and query functions had already been written as multiple tables were generated originally in our database.

Database Connection and Query

HTML forms were utilised to capture user's input using radio buttons and input text box, which were then passed on to **Flask** using `request.form.get()` function. Query functions in `functions_db_query.py` were called using `search.db()` function to request and retrieve data from the database based on the search type (SNP ID, gene name/alias, genomic coordinates) the user chose and the search value the user typed in. The query functions established a connection to the SQL database using `sqlite3.connect` and `connection.cursor()` which then retrieved requested data from the database using **SQL SELECT** statement and `fetchall()`.

Data Visualisation

The summary statistics sliding window plot distributions were generated using `matplotlib.pyplot` (alias `plt`) (Hunter, 2007), while the FST heatmap was generated using `seaborn` (Waskom, 2021). However, these plots could not be assigned into a variable to be passed on to the HTML to be displayed on the web page. Instead, `base64` – an encoding algorithm – was used to convert the image plots into a readable string that would be saved as a variable without any data loss (?) [find citation for base64](#).

```
img=io.BytesIO()
plt.savefig(img, format='png')
img.seek(0)
plot_url=base64.b64encode(img.getvalue()).decode()
image=Markup(''.format(plot_url))
```

command over line urgh

`Plot_url`, which contained the image data in strings, was then decoded using `Markup` to a HTML image tag `image` that could be returned to Flask and passed to HTML for the plot to be displayed on the web page.

Features of the Software

SNP Search

The search engine allows the user to search for SNPs based on three main features: gene name, gene alias, and genomic coordinates - so start and end positions in the chromosome. One singular position can also be entered instead of a range. The gene name looks for matches in the gene or gene alias attributes of the database.

Population Selection

From the provided populations, a user can select one or more, including all five of them, to calculate one or more of the given summary statistics.

Summary Statistics Selection

Shannon's Diversity

Shannon's diversity was calculated manually using Python by normalising the alternative allele frequency and calculating the natural logarithm of the normalised frequencies (see Equation . Although Shannon diversity is affected by small sample, this would not impact the results as it is being applied to large data sets. The population data set is largely homozygous, therefore it would be less influenced by error rate, which is prevalent in heterozygous datasets. Also, it is commonly used for population genetics (Konopiński, 2020).

$$H_{Shannon} = - \sum_{i=1}^N p_i \cdot \ln(p_i) ; p_i \hat{=} \text{normalised alternative allele frequencies}$$

Expected Heterozygosity

A python function was built to calculate the expected heterozygosity per SNP using alternative and reference allele frequencies to estimate genetic diversity at locus level (Bepari et al., 2015; Harris and DeGiorgio, 2017). The following formula is applied per SNP:

$$H_{het} = 1 - \sum_{i=1}^I p_i^2$$

As I describes the number of alleles per SNP. Since only biallelic SNPs are in the database, I will always be 2 for each SNP, while p_i refers to the alternative and reference allele frequency per SNP.

Expected heterozygosity was chosen as a metric to compare the effect of urbanisation/agricultural society on genetic variation between populations and investigate physiological responses Rudan et al. (2008).

Tajima's D

Tajima's D was calculated for each SNP with the `tajima_d()` function from `scikit-allel` package (Miles et al., 2021) which used allele counts to work out dissimilarity between observed allele frequency in the VCF and expected frequency under neutrality (Ferretti et al., 2012). Chromosomal loci which underwent natural selection can be inferred by Tajima statistics when testing Wright Fisher model (Cadzow et al., 2014).

Hudson's FST

Hudson's FST method (extended by Bhatia et al.) was recommended when using multiple SNPs data based on 'Ratio of averages' as it does not affect FST estimates because they combine FST estimate (variances) by calculating the average of FST estimates (defined by Weir and Hill) to provide a single FST value for the complete genome. Hudson is a suitable method for pairwise population analysis. Alternative methods such as Weir & Cockerham are influenced by differences in sample size which leads to false positive signals as their estimates may be magnified (Bhatia et al., 2013).

Visualisation of Statistics

Sliding window created using python function which takes a pandas data frame and uses a fixed window size of rounded-up 10% of total queried SNPs. It is common for researchers to choose a random window size (Beissinger et al., 2015), however due to the limited time frame of the project in an extended project it would be possible to let the user decide what window size they want and make it robust against potential mistakes or misconceptions by the user (e.g. too large window sizes for a small query). Additionally a line graph was chosen as it is a suitable technique to show variation throughout the chromosome or within a region to possibly allow researcher to identify selection in a region. In comparison to overlapping windows, a distinct window size promotes statistical power as there is a reduction in sampling error and statistical test (Beissinger et al., 2014).

The y-axis shows statistical measurements for each window and the x-axis provides the median position value which corresponds to the SNP in the middle of the window as each window represents the average statistic value. To avoid gaps in the sliding window visualisation statistics were imputed with zeros. The FST heatmap requires a data frame which contains the FST for any combination of populations for the `heatmap()` function from the `seaborn` package ([Waskom, 2021](#)). A heatmap was selected to visualise FST to highlight the genetic difference between populations ([Fehren-Schmitz and Georges, 2016](#)).

Download data

After the user selects their population and summary statistics of interest, the software will calculate the statistics and it will put the statistics data frame into a text file. The user has the option to download the sliding window summary statistics data as a text file using the download button. If the user chooses more than one population, FST values for each population pair can also be downloaded as a text file.

Limitations

The database only stores biallelic human data from a single chromosome, and a limited number of sub-populations are included in the database due to data storage issues. Results produced from the website can't be applied to studies with x-linked chromosome diseases, as databases contain autosomal chromosomes. Also, unable to study genetic variation within and between other sub-populations which belong to either the same/different super populations.

When uniform window sizes are defined it could lead to regions where genetic events occur, such as recombination and linkage disequilibrium, being split when uniform window boundaries are defined.

Opportunities for future development

Using a non-uniform approach, could resolve the problem of breaking genetically significant regions. This approach is referred to as smoothing spline. The smoothing spline method fits cubic spline at SNP level statistical estimates (e.g FST) followed by identifying inflection points along the model which defines window boundaries by ensuring peaks in the model are allocated to a window. Therefore, SNPs in a window can be inferred as having a relationship associated with genomic events. Cross validation determines smoothness of the spline before it's fitted and enables suitable window sizes (Beissinger *et al.*, 2015). This technique is implemented in the R package GenWin (Beissinger, 2014).

The database should store more chromosomes to increase accuracy of the genetic analysis, which would consider SNP data which arises within the human genome to obtain a complete picture of genetic variation within and between subpopulations. Include more genetic statistics such as linkage disequilibrium (LD) which is the relationship between genes mapped at multiple chromosomal positions which is event by genetic events e.g. mutation and genetic drift (Slatkin, 2008). By finding LD value, researchers could use this to identify SNP associated with inherited diseases and measure the time an allele arises within the population.

Author's contributions

Implementation:

- Data Pre-processing for derived allele frequency (Vcftools) – Amanah
- Data Pre-processing (Bcftools) & Data Wrangling – Gracia
- Data Collection – everyone
- Web Deployment (Flask, HTML, CSS)
- Python to SQL data base (SQLite3) – Celine
- Genotype & Allele Frequency Calculation – Amanah, Gracia
- FST statistic – Amanah
- Tajima's D and Shannon diversity – Celine
- Sliding Window – Gracia

Documentation:

- Description of each contributed coding / implementation – everyone
- Justification of summary stats – Amanah
- Running of software – Celine
- Structure / Outline – Gracia
- Literature research / References – Amanah
- Transfer documentation into L^AT_EX – Gracia

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