I-BIX-DAT

Data Integration and Interaction Networks

Assignment

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Aim

You will implement a REST API service for storing and sharing variant data for eukaryotic genomes.

Objectives

You will develop:

1. A relational database (SQLite) capable of storing variant data.

2. A tool for parsing annotated VCF files to populate the database.

Objectives

You will develop:

3. A REST API server deployable on Node.js and capable of serving the following requests:

- Listing all VCF samples (genomes) loaded into the database.
- Listing the number of variants (SNPs, InDels, or both) contained in each sample, grouped by chromosome.
- Listing genes impacted by moderate / high impact variants in a specified chromosomal region of a specific sample.
- Listing samples which contain variants that impact a specified gene.
- Visualizing chromosomes with high impact variants marked & labelled with the names of the genes they impact.

Input data

You will be using VCF data with variants contained in resequenced tomato genomes.

Three files (subsets of variants from three different cultivars) which you will need to process are on Canvas. They come from the following publication:

Aflitos et al., Exploring genetic variation in the tomato (*Solanum* section *Lycopersicon*) clade by whole-genome sequencing. Plant J. 2014 Oct;80(1):136-48. doi: 10.1111/tpj.12616.

```
##fileformat=VCFv4.1
##samtoolsVersion=0.1.14 (r933:170)
##INFO=<ID=DP,Number=1,Type=Integer,Description="Raw read depth">
##INFO=<ID=DP4,Number=4,Type=Integer,Description="# high-quality ref-forward bases, ref-reverse, alt-forward and alt-reverse bases">
##INFO=<ID=MQ,Number=1,Type=Integer,Description="Root-mean-square mapping quality of covering reads">
##INFO=<ID=FQ,Number=1,Type=Float,Description="Phred probability of all samples being the same">
##INFO=<ID=AF1,Number=1,Type=Float,Description="Max-likelihood estimate of the site allele frequency of the first ALT allele">
##INFO=<ID=CI95,Number=2,Type=Float,Description="Equal-tail Bayesian credible interval of the site allele frequency at the 95% level">
##INFO=<ID=PV4,Number=4,Type=Float,Description="P-values for strand bias, baseQ bias, mapQ bias and tail distance bias">
##INFO=<ID=INDEL,Number=0,Type=Flag,Description="Indicates that the variant is an INDEL.">
##INFO=<ID=PC2,Number=2,Type=Integer,Description="Phred probability of the nonRef allele frequency in group1 samples being larger (,smaller) than in group2.">
##INFO=<ID=PCHI2,Number=1,Type=Float,Description="Posterior weighted chi^2 P-value for testing the association between group1 and group2 samples.">
##INFO=<ID=QCHI2,Number=1,Type=Integer,Description="Phred scaled PCHI2.">
##INFO=<ID=RP,Number=1,Type=Integer,Description="# permutations yielding a smaller PCHI2.">
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
##FORMAT=<ID=GQ,Number=1,Type=Integer,Description="Genotype Quality">
##FORMAT=<ID=GL,Number=3,Type=Float,Description="Likelihoods for RR,RA,AA genotypes (R=ref,A=alt)">
##FORMAT=<ID=DP,Number=1,Type=Integer,Description="# high-quality bases">
##FORMAT=<ID=SP,Number=1,Type=Integer,Description="Phred-scaled strand bias P-value">
##FORMAT=<ID=PL,Number=-1,Type=Integer,Description="List of Phred-scaled genotype likelihoods, number of values is (#ALT+1)*(#ALT+2)/2">
##SnpEffVersion="3.2 (build 2013-05-23), by Pablo Cingolani"
##SnpEffCmd="SnpEff  -no-upstream -no-downstream -ud 0 -csvStats Slyc2.40 /home/assembly/tomato150/reseq/mapped/Heinz/RF_001_SZAXPI008746-45.vcf.gz "
##INFO=<ID=EFF,Number=.,Type=String,Description="Predicted effects for this variant.Format: 'Effect ( Effect_Impact | Functional_Class | Codon_Change | Amino_Acid_change| Amino_A
##reference=S_lycopersicum_chromosomes.2.50.fa
#CHROM  POS     ID      REF     ALT     QUAL    FILTER  INFO    FORMAT  RF_001
SL2.50ch01      20288   .       C       T       222.0   .       DP=25;AF1=1;CI95=1,1;DP4=0,0,15,8;MQ=60;FQ=-96;EFF=INTERGENIC(MODIFIER|||||||||1)      GT:PL:DP:GQ     1/1:255,69
SL2.50ch01      57154   .       ATTTTTTTTT      ATTTTTTTTTT     40.5    .       INDEL;DP=17;AF1=1;CI95=1,1;DP4=0,0,5,9;MQ=58;FQ=-76.5;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      79378   .       ATTTTTTTTTT     ATTTTTTTTTTT    117.0   .       INDEL;DP=23;AF1=1;CI95=1,1;DP4=0,0,11,8;MQ=60;FQ=-91.5;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      107776  .       GAAAAAAAAA      GAAAAAAAAAA     55.5    .       INDEL;DP=21;AF1=1;CI95=1,1;DP4=0,0,7,10;MQ=59;FQ=-85.5;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      118005  .       CAAAAAAAAA      CAAAAAAAAAA     46.5    .       INDEL;DP=31;AF1=1;CI95=1,1;DP4=0,0,16,9;MQ=42;FQ=-110;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      146150  .       TAAAAAAAAAA     TAAAAAAAAAAA    55.5    .       INDEL;DP=41;AF1=1;CI95=1,1;DP4=0,0,15,19;MQ=59;FQ=-137;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      169786  .       GAAAAAAAAA      GAAAAAAAAAA     60.5    .       INDEL;DP=23;AF1=1;CI95=1,1;DP4=0,0,8,12;MQ=60;FQ=-94.5;EFF=INTERGENIC(MODIFIER|||||||||1)      GT
SL2.50ch01      226278  .       T       A       175.0   .       DP=18;AF1=1;CI95=1,1;DP4=0,0,17,0;MQ=60;FQ=-78;EFF=INTERGENIC(MODIFIER|||||||||1)      GT:PL:DP:GQ     1/1:208,51
SL2.50ch01      265708  .       A       AAAAC   183.0   .       INDEL;DP=32;AF1=0.5;CI95=0.5,0.5;DP4=5,2,6,5;MQ=57;FQ=63.5;PV4=0.64,1,1,1;EFF=INTERGENIC(MODIFIER|||||||||1)   GT
SL2.50ch01      276241  .       ATTTTTTT        ATTTTTTTT       46.5    .       INDEL;DP=14;AF1=1;CI95=1,1;DP4=0,0,5,4;MQ=52;FQ=-61.5;EFF=INTRON(MODIFIER|||||Solyc01g005390.2|||r
SL2.50ch01      294797  .       G       T       222.0   .       DP=31;AF1=1;CI95=1,1;DP4=0,0,26,4;MQ=60;FQ=-117;EFF=INTERGENIC(MODIFIER|||||||||1)      GT:PL:DP:GQ     1/1:255,90
SL2.50ch01      295720  .       T       G       222.0   .       DP=32;AF1=1;CI95=1,1;DP4=0,0,13,18;MQ=58;FQ=-120;EFF=INTERGENIC(MODIFIER|||||||||1)    GT:PL:DP:GQ     1/1:255,93
SL2.50ch01      296620  .       A       G       222.0   .       DP=28;AF1=1;CI95=1,1;DP4=0,0,14,11;MQ=51;FQ=-102;EFF=INTERGENIC(MODIFIER|||||||||1)    GT:PL:DP:GQ     1/1:255,75
SL2.50ch01      297210  .       CATATATATATATATATAT     CATATATAT       32.4    .       INDEL;DP=6;AF1=1;CI95=0.5,1;DP4=0,0,0,3;MQ=29;FQ=-43.5;EFF=INTERGENIC(MODIFIER|||||||||1)
```

Format specification: https://samtools.github.io/hts-specs/VCFv4.1.pdf

Annotation

The variants have been annotated using SnpEff. Note that these are the older “classic” SnpEff annotations, which use an “EFF” field instead of an “ANN” field. See the documentation: https://pcingola.github.io/SnpEff/snpsift/filter/

Example:

```
SL2.50ch09      71507830        .       ATTTTTTTTT      ATTTTTTTTTT     62.5    .       INDEL;DP=30;AF1=1;CI95=1,1;DP4=0,0,14,15;MQ=60;FQ=
:Solyc09g092400.1.1|4|1),SPLICE_SITE_ACCEPTOR(HIGH|||||Solyc09g092400.1|||mRNA:Solyc09g092400.1.1|5|1)  GT:PL:DP:GQ    1/1:103,87,0:29:99
```

Homozygous (1/1) **HIGH** impact InDel variant affecting the Solyc09g092400.1 gene

Database structure

You will need to design and implement a schema (i.e., write an SQL script which will create your tables) capable of storing all the data that you need in an appropriate form. An "appropriate" schema should make it easy to execute the queries you need – don't make it too complicated!

The SQL database schema creation script is part of the deliverables.

An ER diagram for the schema would be useful for visualising it in your technical document.

Parsing inputs and populating the database

You will need to implement a data import tool (using the programming language of your choice) which will populate the database with the data from the VCF files.

The data import tool must be included among the deliverables.

The database file must also be included, and it must contain the full data from all three datasets. If you decide to leave any data out, justify it in the documentation.

REST API server

You will implement a REST API server which can be deployed on localhost and accessed via HTTP (use curl for testing!).

The NPM package with your code must be included in the deliverables.

Do not include the `node_modules` directory in your submission – any dependencies should listed be in `package.json`.

REST API endpoints

You are responsible for designing reasonable API endpoints for each of the possible requests, as well as for the formatting of the output.

The outputs shown in the following slides are examples. If you decide a different format is more appropriate, use it. Make sure you justify your design choices in the documentation.

Each of the API endpoints should be documented.

Listing all the VCF datasets (genomes) loaded into the database

Example output:

```
[
    "RF_001",
    "RF_041",
    "RF_090"
]
```

Listing the number of variants (SNPs, InDels, or both) contained in each genome, grouped by chromosome

Example output: number of InDels for RF_001:


```
{
        "SL2.50ch01": 1152,
        "SL2.50ch02": 483,
        "SL2.50ch03": 729,
        "SL2.50ch04": 734,
        "SL2.50ch05": 508,
        "SL2.50ch06": 666,
        "SL2.50ch07": 557,
        "SL2.50ch08": 427,
        "SL2.50ch09": 602,
        "SL2.50ch10": 479,
        "SL2.50ch11": 645,
        "SL2.50ch12": 799
}
```

Listing genes impacted by moderate / high impact variants in a specified chromosomal region of a specific sample

Example output: genes affected by high impact variants within the first 20 megabases of chromosome 3 in RF_041:

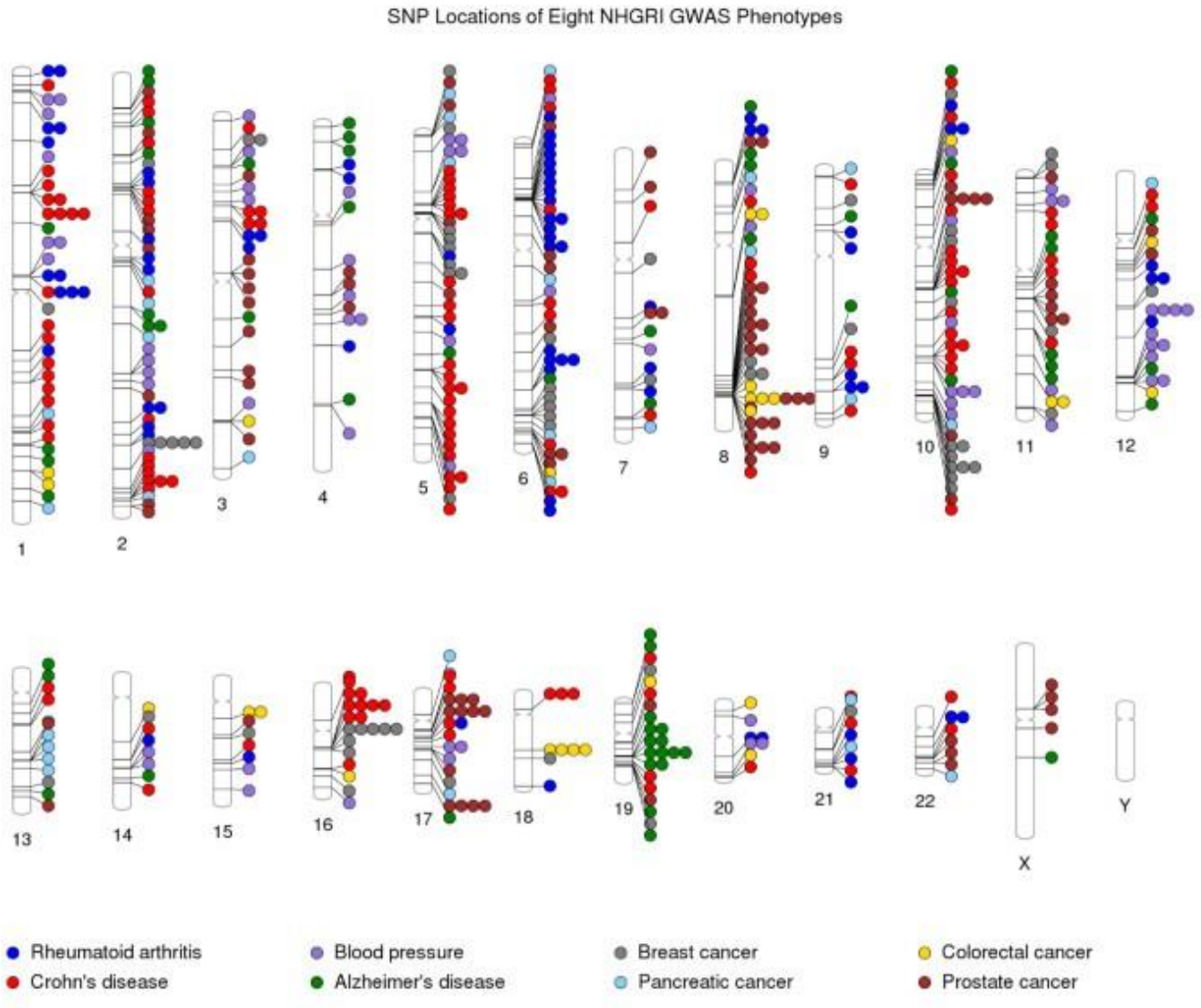

```
[
        {
                "position": 1068624,
                "gene": "Solyc03g006480.1"
        },
        {
                "position": 4910336,
                "gene": "Solyc03g033330.2"
        }
]
```

Listing samples which contain variants that impact a specified gene

Example output: samples which contain a variant in the Solyc01g056370.2 gene:

```
[
        "RF_041",
        "RF_090"
]
```

Visualizing chromosomes with high impact variants marked & labelled with the names of the genes they impact



Example of a (human!) chromosome visualisation.

Other files

You can download the full files, as well as others from the same dataset, at the Sol Genomics Network website:

- https://solgenomics.sgn.cornell.edu/organism/Solanum_lycopersicum/tomato_150
- https://solgenomics.net/ftp/genomes/tomato_150/150_VCFs_2.50/

They could prove useful for stress-testing your application and developing extra features.

Marking scheme

Specification	Marks
Software (70%)	
Functional SQLite database (database creation SQL script must be delivered).	**10**
Tool for processing VCF files exists and data from the three data sets from Canvas were placed in the database	**10**
REST API can list datasets	**5**
REST API can report the numbers of variants	**10**
REST API can list genes affected by moderate / high impact variants	**10**
REST API can list samples with variants in a specific gene	**5**
REST API can visualise chromosomes with high impact variants & impacted gene labels	**5**
Clean, well-structured and commented code	**5**
Extra functionalities	**5**
Stability	**5**
Documentation (30%)	
Technical documentation - relevance, conciseness, accuracy	**15**
User manual	**10**
Flowcharts, diagrams, ER diagram of database	**5**

Deliverables

Deadline: 22 February 2025 at 23:59 (Full-time)

8 March 2025 at 23:59 (Part-time)

Deliverables:

- Archive containing the REST API server project.
- Archive containing the parser tool (if separate from REST API).
- SQLite database file.
- SQL script for database creation.

- Documentation: Technical document and user manual.