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This is the online documentation for the COSGAP project, hosted at GitHub.com/CoMorMent/containers.
1.1 COSGAP: COnminated Statistical Genetics Analysis Pipelines

The goal of this github repository (https://github.com/comorment/containers) is to distribute software tools for statistical genetics analysis, alongside with their respective reference data and scripts (“analysis pipelines”) to facilitate application of these tools. The scope of this project is currently limited to genome-wide association studies (GWAS) and post-GWAS statistical-genetics analyses, including polygenic scoring (PGS). This project builds on earlier work by Tryggve consortium, with most recent major development done as part of the CoMorMent EU H2020 project (comorment.eu). For more information see our preprint manuscript, this presentation on PGC WWL meeting (Feb 9, 2024), or our online documentation here.

For an overview of available software, see here.

Most of these tools are packaged into singularity containers (https://sylabs.io/singularity/) and shared in the singularity folder of this repository. You can download individual containers using github’s Download button, or clone the entire repository from command line as described in the INSTALL.md file.

Many of the tools require additional reference data provided in the reference folder of this repository. Certain reference data can not be made publicly available, in which case we provide access instructions in a separate GitHub repository: https://github.com/comorment/reference. This repository is private - please approach your contact within CoMorMent project to enable your access.

Description of containers and usage instructions are provided in the docs folder.

More extensive use cases of containers, focusing on real data analysis, are provided in the usecases folder.

The history of changes is available in the CHANGELOG.md file.

If you would like to contribute to developing these containers, please see the CONTRIBUTING file.

Additional tools are available in separate repositories:

- https://github.com/comorment/ldsc - LD score regression
- https://github.com/comorment/mixer - cross-trait MiXeR analysis
- https://github.com/comorment/popcorn - cross-ancestry genetic correlations
- https://github.com/comorment/magma - MAGMA, LAVA, lava-partitioning tools
- https://github.com/comorment/HDL - High-Definition Likelihood
- https://github.com/comorment/ldpred2_ref - reference files for LDpred2. The tool itself is included in r.sif (more info).
1.1.1 Project status

1.1.2 Installation

See the INSTALL.md file for installation instructions.

1.1.3 Legacy

Earlier version (prior to April 2021) of all containers and reference data was distributed on Google Drive. This is no longer the case, the folder on Google drive is no longer maintained. All containers and reference data are released through this repository.

1.1.4 Source files

The source files for configuring and building the container files provided here are found in the docker directory. See the corresponding README file therein for details.

1.1.5 Online documentation

The online documentation hosted at cosgap.rtfd.io can be built locally using Sphinx in a conda environment as

```
cd sphinx-docs/source  # documentation source/config directory
conda env create -f environment.yml  # creates environment "sphinx"
conda activate sphinx
make html  # make html-documentation in $PWD/_build/html/
```

The resulting file(s) $PWD/_build/html/index.html can be viewed in any web browser.

In order to make a pdf with the documentation, issue

```
make pdflatex
```

and open $PWD/_build/latex/cosgap.pdf in a pdf viewer.
2.1 hello.sif container

2.1.1 Description

You may use hello.sif container to familiarize yourself with Singularity (https://sylabs.io/docs/), and the way it works on your secure HPC environment (TSD, Bianca, Computerome, or similar). This singularity container is intended as a demo. It only contains Plink 1.9 (http://zzz.bwh.harvard.edu/plink/) software.

2.1.2 Getting Started

• Download hello.sif from here
• Download chr21.[bed,bim,fam] files from here
• Import these files to your secure HPC environment
• Run singularity exec --no-home hello.sif plink --help, to validate that you can run singularity. This command is expected to produce the standard plink help message, starting like this:

```
PLINK v1.9b6.18 64-bit (16 Jun 2020) www.cog-genomics.org/plink/1.9/
(C) 2005-2020 Shaun Purcell, Christopher Chang GNU General Public License v3
```

2.1.3 Helpful links to singularity documentation

It’s good idea to familiarize with basics of the singularity, such as these:

• “singularity shell” options
• Bind paths and mounts.
2.1.4 Installing Docker and Singularity on your local machine

While you’re getting up to speed with singularity, it might be reasonable to have it install on your local machine (laptop or desktop), and try out containers locally before importing them to your HPC environment.

To install singularity on Ubuntu follow steps described here: https://sylabs.io/guides/3.7/user-guide/quick_start.html
Note that sudo apt-get can give only a very old version of singularity, which isn’t sufficient. Therefore it’s best to build singularity locally. Note that singularity depends on GO, so it must be installed first. If you discovered more specific instructions, please submit an issue or pull request to update this documentation.

2.1.5 Mapping your data to singularity containers

There are several ways to give singularity container access to your data. Here are few examples:

1. singularity exec --home $PWD:/home hello.sif plink --bfile chr21 --freq --out chr21 - this command will map your current folder ($PWD) into /home folder within container, and set it as active working directory. In this way in your plink command you can refer to the files as if they are in your local folder, i.e. chr21 without specifying the path. The command will then use plink to calculate allele frequencies, and save the result in current folder.

2. singularity exec --home $PWD:/home hello.sif plink --bfile /home/chr21 --freq --out /home/chr21 Same as above command, but more explicitly refer to /home/chr21 files, without relying on it being the active working directory. Here you can also choose to use --bind argument instead of --home, which allow to map multiple folders if needed (comma-separated).

3. Now, let’s assume that instead of downloading chr21.[bim/bed/fam] files and hello.sif container you’ve cloned the entire github repo (git clone git@github.com:comorment/containers.git), and have transferred it to your HPC environment. Then change your folder to the root of the containers repository, and run these commands:

   ```bash
   mkdir out_dir && singularity exec --bind reference/:/ref:ro, out_dir:/out:rw
   singularity/hello.sif plink --bfile /ref/hapgen/chr21 --freq --out /out/chr21
   ```

   Note that input paths are relative to the current folder. Also, we specified ro and rw access, to have reference data as read-only, but explicitly allow the container to write into /out folder (mapped to out_dir on the host).

4. Run singularity shell --home $PWD:/home -B $(pwd)/data:/data hello.sif to usesingularity in interactive mode. In this mode you can interactively run plink commands. Note that it will consume resources of the machine where you currently run the singularity command (i.e., most likely, the login node of your HPC cluster).

2.1.6 Running as SLURM job

• Run singularity container within SLURM job scheduler, by creating a hello_slurm.sh file (by adjusting the example below), and running sbatch hello_slurm.sh:

   ```bash
   #!/bin/bash
   #SBATCH --job-name=hello
   #SBATCH --account=p697
   #SBATCH --time=00:10:00
   #SBATCH --cpus-per-task=1
   #SBATCH --mem-per-cpu=8000M
   module load singularity/3.7.1
   singularity exec --no-home hello.sif plink --help
   singularity exec --home $PWD:/home hello.sif plink --bfile chr21 --freq --out chr21
   ```
Please let us know if you face any problems.

### 2.1.7 TSD-specific instructions

The official documentation for singularity on TSD is available [here](#). Here are more important notes about singularity on TSD:

- `module load singularity/2.6.1` is going to be deprecated soon; instead, there will be a local installation of singularity on each Colossus node.

- Singularity might be unavailable on some of the interactive nodes. For example, in `p33` project it is recommended to run singularity on `p33-app-normont01` node. You may also find it in `p33-submit` nodes.

- You may want to run `module purge`, to make sure you use locally installed singularity. It is a good idea to run `which singularity` to validate this.

- Use `singularity --version` to find the version of singularity.

- Generally, it is a good idea to add `--no-home` argument to your singularity commands, to make sure that that scripts such as `.bashrc` do not interfere with singularity container. This also applies if you have custom software installed in your home folder. For other options that control isolation of the containers (i.e. `--containall` option) see [here](#).

- If you are a developer, and you would like to generate a singularity container, you may want to do it outside of TSD, and then bring just a `.sif` file to TSD. Also, building singularity containers is much easier by building a Docker container first (using `Dockerfile`), and converting such Docker container to a singularity container.

### 2.1.8 Software

List of software included in the container:

<table>
<thead>
<tr>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>ubuntu</td>
<td>20.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>plink¹</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
<td>GPLv3</td>
</tr>
</tbody>
</table>

References

CHAPTER THREE

INSTALLATION

We recommend to clone this entire repository using `git clone`. However, you need to install the Git LFS extension. This is done by downloading and unpacking the GitLFS package, adding `git-lfs` binary to a folder that is in your `PATH`, and running `git lfs install` command.

```
mkdir ~/bin
export PATH="/home/$USER/bin:$PATH"  # good idea to put this in your ~/.bashrc or ~/.bash_profile
wget https://github.com/git-lfs/git-lfs/releases/download/v2.13.2/git-lfs-linux-amd64-v2.13.2.tar.gz
tar -xzvf git-lfs-linux-amd64-v2.13.2.tar.gz
cp git-lfs /home/$USER/bin
git lfs install
```

Now you're all set to clone this repository (note that adding `--depth 1` to your command as shown below will limit the amount of data transfered from github to your machine):

```
git clone --depth 1 https://github.com/comorment/containers.git
```

At this point you may want to run the following find&grep command to check that all git-lfs files were downloaded successfully (i.e. you got an actual content of each file, and not just its git-lfs reference). The command searches for and lists all files within $COMORMENT folder which contain a string like oid sha, likely indicating that git-lfs file hasn't been downloaded. If the following commands doesn't find any files that you're good to go. Otherwise you may want to re-run your `git clone` commands or investigate why the're failing to download the actual file.

```
find $COMORMENT -type f -not -path '*/.*' -exec sh -c 'head -c 100 "{}"' | if grep -H "oid sha"; then echo {}; fi ' \; | grep -v "oid sha256"
```

For TSD system, a read-only copy of $COMORMENT containers is maintained at these locations (please read github/README.md file before using these copies):

```
# for p33 project
export COMORMENT=/cluster/projects/p33/github/comorment

# for p697 project
export COMORMENT=/ess/p697/data/durable/s3-api/github/comorment
```

Once you have a clone of this repository on your system, you may proceed with docs/singularity/hello.md example. Take a look at the README file in the docs/singularity folder, as well as detailed use cases in usecases.

To simplify instructions throughout this repository we use certain variables (it's a good idea to include them in your `.bashrc` or similar):
• $COMORMENT refers to a folder with comorment and reference subfolders, containing a clone of the containers and reference repositories from GitHub. Cloning reference repository is optional, and it’s only needed for internal work within the CoMorMent project - for normal use you may proceed without it.

• $SIF refers to $COMORMENT/containers/singularity folder, containing singulairty containers (the .sif files)

• SINGULARITY_BIND="$COMORMENT/containers/reference:/REF:ro,$COMORMENT/reference:/REF2:ro" defines default bindings within container (/REF, /REF2). If you don’t have access to private reference, try out commands without mapping $COMORMENT/reference:/REF2:ro - most (if not all) of the exmples don’t require private reference data.

• We assume that all containers run with --home $PWD:/home, mounting current folder mounted as /home within container

• We also recommend using --contain argument to better isolate container from the environment in your host machine. If you choose not to mount --home $PWD:/home, you may want to add --no-home argument.

• You can choose to exclude passing environment variables from the host into the container with the --cleanenv option. Read more about it here.
4.1 **gwas.sif container**

### 4.1.1 Description

The *gwas.sif* container file has multiple tools related to imputation and GWAS analysis, as summarized in the *Software* table below.

Note that some specific tools (e.g. `bolt`) are added to the path directly from their `/tools` folder (e.g. `/tools/bolt`) due to hard-linked dependencies. Either way, all tools can be invoked by their name, as listed above. For example:

```bash
> singularity exec gwas.sif regenie
```

<table>
<thead>
<tr>
<th>REGENIE v2.0.2.gz</th>
</tr>
</thead>
</table>

Copyright (c) 2020 Joelle Mbatchou and Jonathan Marchini.
Distributed under the MIT License.
Compiled with Boost Iostream library.
Using Intel MKL with Eigen.

ERROR: You must provide an output prefix using `--out`
For more information, use option `--help` or visit the website: https://rgcgith.web.˓→

### 4.1.2 Software

List of software included in the container:

<table>
<thead>
<tr>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>ubuntu</td>
<td>20.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>bcftools</td>
<td>1.19</td>
<td>MIT/Expat/GPLv3</td>
</tr>
<tr>
<td>bedtools</td>
<td>2.31.1</td>
<td>MIT</td>
</tr>
<tr>
<td>beagle</td>
<td>22Jul22.46e</td>
<td>GPLv3</td>
</tr>
<tr>
<td>bgenix</td>
<td>1.1.7</td>
<td>Boost</td>
</tr>
<tr>
<td>bolt</td>
<td>v2.4.1</td>
<td>GPLv3</td>
</tr>
<tr>
<td>cat-bgen</td>
<td>same version as bgenix</td>
<td>Boost</td>
</tr>
</tbody>
</table>
### Table 1 – continued from previous page

<table>
<thead>
<tr>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>duohmm</td>
<td>95bd395</td>
<td>MIT</td>
</tr>
<tr>
<td>eagle</td>
<td>v2.4.1</td>
<td>GPLv3</td>
</tr>
<tr>
<td>edit-bgen</td>
<td>same version as bgenix</td>
<td>Boost</td>
</tr>
<tr>
<td>flashpca_x86-64</td>
<td>2.0</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gcta64</td>
<td>1.94.1</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gctb</td>
<td>2.0.4.3</td>
<td>MIT</td>
</tr>
<tr>
<td>GWAMA</td>
<td>2.2.2</td>
<td>BSD-3-Clause</td>
</tr>
<tr>
<td>HTSlib</td>
<td>1.19.1</td>
<td>MIT/Expat/Modified-BSD</td>
</tr>
<tr>
<td>king</td>
<td>2.3.2</td>
<td>permissive</td>
</tr>
<tr>
<td>ldak</td>
<td>5.2</td>
<td>GPLv3</td>
</tr>
<tr>
<td>liftOver</td>
<td>latest</td>
<td>permissive</td>
</tr>
<tr>
<td>metal</td>
<td>2020-05-05</td>
<td>-</td>
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<tr>
<td>minimac4</td>
<td>v4.1.6</td>
<td>GPLv3</td>
</tr>
<tr>
<td>plink</td>
<td>v1.90b7.2 64-bit (11 Dec 2023)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>plink2</td>
<td>v2.00a5.10LM 64-bit Intel (5 Jan 2024)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>plink2_avx2</td>
<td>v2.00a5.10LM AVX2 Intel (5 Jan 2024)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>PRSice_linux</td>
<td>2.3.5</td>
<td>GPLv3</td>
</tr>
<tr>
<td>qctool</td>
<td>2.2.2, revision e5723df2c0e85959</td>
<td>Boost</td>
</tr>
<tr>
<td>regenie</td>
<td>v3.4</td>
<td>MIT/Boost</td>
</tr>
<tr>
<td>samtools</td>
<td>v1.19.2</td>
<td>MIT/ExpatD</td>
</tr>
<tr>
<td>shapeit4</td>
<td>4.2.2</td>
<td>MIT</td>
</tr>
<tr>
<td>shapeit5</td>
<td>v5.1.1</td>
<td>MIT</td>
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<tr>
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<td>MIT</td>
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<tr>
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<td>MIT</td>
</tr>
<tr>
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<td>v0.9.4</td>
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<tr>
<td>snptest</td>
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<td>switchError</td>
<td>6e688b1</td>
<td>MIT</td>
</tr>
<tr>
<td>vcftools</td>
<td>0.1.17 (git SHA: d511f469e)</td>
<td>GPLv3</td>
</tr>
</tbody>
</table>

### 4.2 python3.sif container

#### 4.2.1 Description

python3.sif container runs Python packaged by Conda-forge, and has many useful python modules already installed, including pandas, numpy, scipy, matplotlib, jupyter and few others (see here for full details). Basic usage is very simple:

```bash
> singularity exec --contain --home $PWD:/home python3.sif python
Python 3.10.6 | packaged by conda-forge | (main, Aug 22 2022, 20:35:26) [GCC 10.4.0] on ...
linux
Type "help", "copyright", "credits" or "license" for more information.
```

You may also use jupyter notebook like this:

---

1 Petr Danecek, James K Bonfield, Jennifer Liddle, John Marshall, Valeriu Ohan, Martin O Pollard, Andrew Whitwham, Thomas Keane, Shane A McCarthy, Robert M Davies, Heng Li, Twelve years of SAMtools and BCFtools, GigaScience, Volume 10, Issue 2, February 2021, giab008,
singularity exec --container --home $PWD:/home $SIF/python3.sif jupyter notebook --no-browser --port 8890

The port is optional, but you may want to specify it if you'd like to run jupyter on a remote server - in which case you need to enable port forwarding as described here. This also works if you connect from Windows using Putty as described here.

python3.sif container has few additional tools installed:

- /tools/ukb/ukb_helper.py - https://github.com/precimed/ukb/
- /tools/python_convert - https://github.com/precimed/python_convert

https://doi.org/10.1093/gigascience/giab008


5 https://enkre.net/cgi-bin/code/bgen/wiki?name=bgenix


7 https://enkre.net/cgi-bin/code/bgen/wiki?name=cat-bgen


10 https://enkre.net/cgi-bin/code/bgen/wiki?name=edix-bgen


15 James K Bonfield, John Marshall, Petr Danecek, Heng Li, Valeriu Ohan, Andrew Whitwham, Thomas Keane, Robert M Davies, HTSlib: C library for reading/writing high-throughput sequencing data, GigScience, Volume 10, Issue 2, February 2021, giab007, https://doi.org/10.1093/gigascience/giab007


19 Shing Wan Choi, Paul F O’Reilly, PRSice-2: Polygenic Risk Score software for biobank-scale data, GigScience, Volume 8, Issue 7, July 2019, giz082, https://doi.org/10.1093/gigascience/giz082

20 https://code.enkre.net/qctool


22 https://genome.sph.umich.edu/wiki/Minimac4


24 https://www.cog-genomics.org/plink/2.0/

25 Shing Wan Choi, Paul F O’Reilly, PRSice-2: Polygenic Risk Score software for biobank-scale data, GigScience, Volume 8, Issue 7, July 2019, giz082, https://doi.org/10.1093/gigascience/giz082


28 https://github.com/precimed/simu

29 https://www.cbg.ox.ac.uk/~gav/snptest/#download


• *ldpred* - https://github.com/bvilhjal/ldpred is installed via pip, simply run ‘ldpred –help’ to get started

### 4.2.2 Software

List of software in the container:

<table>
<thead>
<tr>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>ubuntu</td>
<td>20.04 (LTS)</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>Ldpred</td>
<td>1.0.11</td>
<td>MIT</td>
</tr>
<tr>
<td>plink</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>python3</td>
<td>python 3.10.6 + numpy, pandas, etc.</td>
<td>PSF</td>
</tr>
<tr>
<td>python_convert</td>
<td>github commit bcde562</td>
<td>GPLv3</td>
</tr>
</tbody>
</table>

### 4.3 r.sif container

#### 4.3.1 Description

The *r.sif* container has multiple genomics tools related based on R. Please confer the *Software* table below for the more complete list.

In addition several standard R packages are also included (e.g. data.table, ggplot2, rmarkdown, etc.)

Please report an issue if you encounter errors that have not been reported.

For GSRR, the example data (http://cnsgenomics.com/software/gsmr/static/test_data.zip) is available in $COMORIENT/containers/reference/example/gsmr folder. You may start the container like this:

```bash
cd $COMORIENT/containers/reference/examples/gsmr
singularity shell --home $PWD:/home $SIF/r.sif
```

and then follow the official tutorial https://cnsgenomics.com/software/gsmr/. Note that gcta64 tool is also include in r.sif container, as the tutorial depends on it.

#### 4.3.2 Software

List of software in the container:

<table>
<thead>
<tr>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>r.sif</td>
<td>ubuntu</td>
<td></td>
</tr>
<tr>
<td>r.sif</td>
<td>R</td>
<td>4.0.5 (2021-03-31) + data.table, ggplot, etc.</td>
</tr>
<tr>
<td>r.sif</td>
<td>gcta64</td>
<td>1.94.1</td>
</tr>
<tr>
<td>r.sif</td>
<td>GenomicSEM</td>
<td>GenomicSEM/GenomicSEM@bcbbaff</td>
</tr>
<tr>
<td>r.sif</td>
<td>GSMR</td>
<td>v1.0.9</td>
</tr>
<tr>
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<td>rareGWAMA</td>
<td>dajiangliu/rareGWAMA@72e962d</td>
</tr>
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<td>seqminer</td>
<td>zhanxw/seqminer@142204d</td>
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<td>MRCIEU/TwoSampleMR@c174107</td>
</tr>
<tr>
<td>r.sif</td>
<td>snpStats</td>
<td>v1.40.0</td>
</tr>
</tbody>
</table>
4.4 ldsc.sif container

LD score regression. For details, see github.com/comorment/ldsc.

4.5 HDL.sif container

High-Definition Likelihood. For details, see github.com/comorment/HDL.

4.6 MAGMA.sif container

MAGMA, LAVA, and LAVA-partitioning tools. For details, see github.com/comorment/MAGMA.

4.7 MiXeR.sif container

Causal Mixed Effect Models for Cross-Trait and Cross-Ancestry Analysis. For details, see github.com/comorment/MiXeR.

4.8 References
5.1 Genotype data spec

We expect imputed genotype data, which may be split into multiple cohorts at each site. For example, MoBa imputed genotype data is currently split into three cohorts, one per genotype array: GSA, OMNI and HCE. In this context, a cohort is a unit of GWAS analysis, and we do not make distinction between studies (i.e. TOP, DemGENE, HUNT, MoBa), and sub-cohorts within each study. If you have multiple studies, each with a set of sub-cohorts, we suggest to organize it into folders as follows <STUDY>_<COHORT> (for example, MOBA_GSA, MOBA_OMNI, MOBA_HCE, TOP, DemGENE, HUNT).

We expect the data to be in plink format (.bed/.bim.fam), split per chromosomes, organized for example as follows:

```
<BASEPATH>/<COHORT>/chr@[bed,bim,fam] # hard calls in plink format (@ indicates chr label)
<BASEPATH>/<COHORT>/chr@[vcf.gz,vcf.gz.tbi] # dosages (either compressed .vcf files, or .bgen format)
<BASEPATH>/<COHORT>/chr@[bgen,sample]
```

It is recommended (but not required) that all genetic data within cohort is placed into its own folder. A strict requirement is that within each cohort the files are only different by chromosome label, so it is possible to specify them by a single prefix with @ symbol indicating the location of a chromosome label. If your data is organized differently, we recommend to use symbolic links, rather than making a full copy of the data. We also recommend to set the data as read-only using `chmod 0444 $BASEPATH/$COHORT/chr*` command.

Many analyses use only plink files. However, dosage files are required for some analysis, for example SAIGE. For each analysis you need to provide dosage data in a compatible format (but we will provide a set of scripts or examples to help converting data between different formats). For example, SAIGE recognize either compressed .vcf.gz files (with corresponding .vcf.gz.tbi index), or .bgen/.sample formats. For .vcf.gz, please note that they should be compressed with bgzip (see here)

```
bgzip -c file.vcf > file.vcf.gz
```

In the .fam files, we require IID column to be globally unique (not just unique within families). Currently there is no need to provide family annotations, sex information, or phenotype information in .fam files, this information is currently not used in the downstream analysis. In the future we will consider adding a separate file to add pedigree information, to accomodate more complex family structures than what is feasible with .fam file. Currently we do not require IID values to be unique across cohorts.

At of now, we only support the analysis for autosomes (chr 1…22). Support for other chromosomes will came later. We expect the same set of individuals across all autosomes (chr 1…22).
5.1.1 Change log

- v0.9 - first version of this document

5.2 Phenotypes and covariates spec

For phenotypes and covariates, we expect the data to be organized in a single delimiter-separated file (hereinafter referred to as phenotype file), with rows corresponding to individuals, and columns corresponding to relevant variables of interest or covariates. By default the delimiter is expected to be a comma, but also can be tab, semicolon, space, or a white-space delimited file. Phenotype file should be accompanied by a data dictionary file, as described below. We expect a single phenotype file and a single data dictionary file for each cohort:

```<BASEPATH>/<COHORT>/pheno.csv
<BASEPATH>/<COHORT>/pheno.dict```

Off note: when we run GWAS analysis on a given cohort, we use subjects that has both genetic and phenotype data available, thus it’s fine to include subjects without genetic data in the phenotype file. If you have sub-cohorts of the same study, it is OK to re-use one phenotype file containing information for all sub-cohorts, as long all subjects have a unique IID across cohorts.

The phenotype file must include a subject IID column, containing identifiers that matches the IID in genetic data (i.e. the IID column in plink .fam files). If FID column is included in the phenotype file it will be simply ignored. All subjects should be uniquely identified by their IID. This is against plink specification for the .fam file, however other software may not support subject identification through a pair of (FID, IID). Because of this we require all subject IIDs to be unique across families.

The phenotype file must contain all covariates needed for GWAS analysis, including age, sex, principal genetic components, and other confounders such as genetic batch or plate, if needed. Column names in the phenotype file must be unique. It is OK to include other relevant columns in the phenotype file - a GWAS analysis can be customized to use a subset of columns, as well as a subset of subjects.

Missing values should be encoded by empty string (see example below). It is allowed to use # to comment out first lines. Columns required in phenotype file: IID and SEX (note that use of IID, not ID, to match plink nomenclature).

Phenotype file should be accompanied by a data dictionary file, which define whether each variable is a binary (case/control), nominal (a discrete set of values) or continuous. The data dictionary should be a file with two columns, one row per variable (listed in the first column), with second column having values BINARY, NOMINAL, ORDINAL, CONTINUOUS or IID. Exactly one column must be marked with IID type. The file may have other optional columns, i.e. description of each variable. The file should have column names, first two columns must have names FIELD and TYPE.

The purpose of the pheno.dict file is to allow scripts to choose correct analysis: for example, if target variable is continuous, we can run GWAS with linear regression mode, while if target variable is binary, we will run logistic regression; similarly, if a nominal variable is used as covariate, then it will be included as factor.

Binary variables must be encoded as 1 (cases) and 0 (controls). This is default in regenie. For plink, such coding can be used with --1 argument. If you have a binary variable such as SEX and you want to keep the actual labels (e.g. “male” and “female”), then you should mark it as “NOMINAL” in the dictionary file.

Example MoBa/pheno.csv file. Subject IID=3 have missing values for SEX and MDD.

```# optional comments or description
IID,SEX,MDD,PC1,PC2,PC3
1,M,0,0.1,0.2,0.3
2,F,1,0.4,0.5,0.6```

(continues on next page)
Example MoBa/pheno.dict file:

<table>
<thead>
<tr>
<th>FIELD</th>
<th>TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IID,IID</td>
<td>Identifier</td>
<td></td>
</tr>
<tr>
<td>SEX</td>
<td>NOMINAL</td>
<td>Sex (M - male, F - female)</td>
</tr>
<tr>
<td>MDD</td>
<td>BINARY</td>
<td>Major depression diagnosis</td>
</tr>
<tr>
<td>PC1</td>
<td>CONTINUOUS</td>
<td>First principal component</td>
</tr>
<tr>
<td>PC2</td>
<td>CONTINUOUS</td>
<td>2nd principal component</td>
</tr>
<tr>
<td>PC3</td>
<td>CONTINUOUS</td>
<td>3rd principal component</td>
</tr>
</tbody>
</table>

5.2.1 Change log

- v0.9 - first version of this document
- v0.9.1 - specify case/control coding and rename COLUMN->FIELD in the dictionary file

5.3 Summary statistics spec

The results of GWAS are represented as summary statistics, with the following columns:

- **SNP** - marker name, for example rs#.
- **CHR** - chromosome label
- **BP** - base-pair position
- **A1** - effect allele for Z and BETA columns
- **A2** - other allele
- **N** - sample size
- **CaseN, ControlN** - sample size for cases and controls (logistic regression only)
- **FRQ** - frequency of A1 allele
- **Z** - z-score (or t-score) of association
- **BETA** - effect size; for logistic regression, this contains log(OR)
- **SE** - standard error of the BETA column
- **L95, U95** - lower and upper 95% confidence interval of the BETA.
- **P** - p-value

For SNP, CHR, BP, A1 and A2 columns the scripts/gwas/gwas.py script will simply copy over the information from the genetic file, i.e. from .bgen or .bim files. This means that SNP is likely to be dbSNP rs#, or some other form of identified such as CHR:BP:A1:A2. For CHR and BP, there we don’t enforce a specific genomic build - it all depends on what build was used by the genotype data. Finally, A1 and A2 are not guarantied to be minor or major alleles, but A1 will be used as an effect allele for signed summary statistics (i.e. Z and BETA columns).
The sample size $N$ is as reported by the software (plink2 or regenie). For case-control traits, this appears to be a sum of cases and controls (not the effective sample size which would take into account imbalance between cases and controls).

L95 and U95 columns are only provided for plink2 results. CaseN and ControlN columns are only provided for plink2 results for logistic regression. If you need these columns for regenie analysis consider also running plink2 analysis, and copy over the columns into your regenie output.

### 5.3.1 Comparison of columns names

- **CoMorMent**: this file
- **LDSC**: https://github.com/precimed/ldsc/blob/master/munge_sumstats.py
- **BioPsyk**: https://github.com/BioPsyk/cleansumstats/blob/dev/assets/schemas/cleaned-sumstats.yaml
- **NORMENT**: https://github.com/precimed/python_convert/blob/master/sumstats_utils.py

<table>
<thead>
<tr>
<th>CoMorMent</th>
<th>daner</th>
<th>LDSC</th>
<th>BioPsyk</th>
<th>NORMENT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>missing</td>
<td>?</td>
<td>missing</td>
<td>0</td>
<td>missing</td>
<td>good idea to provide this column and referencing a line in .bim file</td>
</tr>
<tr>
<td>CHR</td>
<td>CHR</td>
<td>CHR</td>
<td>CHR</td>
<td>CHR</td>
<td>OK</td>
</tr>
<tr>
<td>BP</td>
<td>BP</td>
<td>BP</td>
<td>POS</td>
<td>BP</td>
<td>keep BP which is more informative (“POS” could also stand for genomic position)</td>
</tr>
<tr>
<td>SNP</td>
<td>SNP</td>
<td>SNP</td>
<td>RSID</td>
<td>SNP</td>
<td>keep SNP which makes more sense as we copy over marker name from genetic file</td>
</tr>
<tr>
<td>A1</td>
<td>A1</td>
<td>A2</td>
<td>EffectAllele</td>
<td>A1</td>
<td>keep A1 for consistency with LDSC even thought EffectAllele is more informative</td>
</tr>
<tr>
<td>A2</td>
<td>A2</td>
<td>A2</td>
<td>OtherAllele</td>
<td>A2</td>
<td>keep A2 for consistency with LDSC even though OtherAllele is more informative</td>
</tr>
<tr>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>PVAL</td>
<td>OK</td>
</tr>
<tr>
<td>SE</td>
<td>SE</td>
<td>SE</td>
<td>SE</td>
<td>SE</td>
<td>OK</td>
</tr>
<tr>
<td>L95</td>
<td>?</td>
<td>missing</td>
<td>ORL95</td>
<td>missing</td>
<td>keep “L95” as confidence interval may also be for the BETA or LOG(OR)</td>
</tr>
<tr>
<td>U95</td>
<td>?</td>
<td>missing</td>
<td>ORU95</td>
<td>missing</td>
<td>keep “U95”</td>
</tr>
<tr>
<td>N</td>
<td>?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>OK</td>
</tr>
<tr>
<td>CaseN</td>
<td>Nca</td>
<td>N_CA</td>
<td>CaseN</td>
<td>NCA</td>
<td>OK</td>
</tr>
<tr>
<td>ControlN</td>
<td>Nco</td>
<td>N_CO</td>
<td>ControlN</td>
<td>NCONTROL</td>
<td>OK</td>
</tr>
<tr>
<td>INFO</td>
<td>INFO</td>
<td>INFO</td>
<td>INFO</td>
<td>INFO</td>
<td>OK</td>
</tr>
<tr>
<td>Direction</td>
<td>Direction</td>
<td>missing</td>
<td>Direction</td>
<td>DIRECTION</td>
<td>OK</td>
</tr>
<tr>
<td>BETA</td>
<td>BETA or OR</td>
<td>BETA</td>
<td>BETA or OR</td>
<td>keep “BETA” for consistency with LDSC (and also BETA is more informative)</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>OK</td>
</tr>
<tr>
<td>FRQ</td>
<td>FRQ_A_N</td>
<td>FRQ</td>
<td>EAF</td>
<td>FRQ</td>
<td>keep “FRQ” which makes more sense for non-EUR populations</td>
</tr>
<tr>
<td>missing</td>
<td>?</td>
<td>missing</td>
<td>EAF_1K</td>
<td>missing</td>
<td>not needed</td>
</tr>
</tbody>
</table>
5.3.2 Change log

• v0.9 - first version of this document
Reference data descriptions should go here.

6.1 openSNP example data

This project relies on data from openSNP, a platform for sharing personal genomics data. This public data is licensed under the CC0.

To obtain the datas for use in various examples provided here, see detailed instructions at https://github.com/comorment/opensnp.

6.2 Summary statistics

This folder contains summary statistics that we use in use cases throughout containers.

If you use this data you must comply with requirements established by the authors of these datasets. The links and a summary of these requirements is provided below.

- `clozuk_pgc2.meta.sumstats.txt.gz`, obtained from https://walters.psycm.cf.ac.uk/


  DISCLAIMER: These data are provided "as is", and without warranty, for scientific and educational use only. If you download these data, you acknowledge that these data will be used only for non-commercial research purposes; that the investigator is in compliance with all applicable state, local, and federal laws or regulations and institutional policies regarding human subjects and genetics research; that secondary distribution of the data without registration by secondary parties is prohibited; and that the investigator will cite the appropriate publication in any communications or publications arising directly or indirectly from these data. You also acknowledge that yourself
or any member of your research team will never attempt to identify any participant in these studies.

- SavageJansen_2018_intelligence_metaanalysis.txt.gz, obtained from https://ctg.cnrc.nl/software/summary_statistics (original file named SavageJansen_IntMeta_sumstats.zip, extracted and re-packed into .gz)


Please cite this reference when using the summary statistics.

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (https://creativecommons.org/licenses/by-nc-sa/4.0/). In addition, when downloading the sumstats you agree not to attempt to identify individual participants and not to use the sumstats for projects that may lead to stigmatizing individuals or groups of individuals.

- Morningness_sumstats_Jansenetal.txt.gz, obtained from https://ctg.cnrc.nl/software/summary_statistics (original file named Morningness_sumstats_Jansenetal.txt.gz, extracted and re-packed into .gz)


Please cite this reference when using the summary statistics.

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (https://creativecommons.org/licenses/by-nc-sa/4.0/). In addition, when downloading the sumstats you agree not to attempt to identify individual participants and not to use the sumstats for projects that may lead to stigmatizing individuals or groups of individuals.
CHAPTER
SEVEN

SCRIPTS

Documentation of helper scripts provided with this project

7.1 GWAS

For in-depth explanation of the gwas.py and config.yaml codes provided here, please see the usecases:

- gwas_demo
- gwas_real

7.2 LDpred2

The files in this directory exemplifies how to run the LDpred2 analysis using the bigsnpr R library, using ldpred2.R script developed by Andreas Jangmo, Espen Hagen and Oleksandr Frei. The script is based on this tutorial. The LDpred2 method is explained in the publication:


7.2.1 Prerequisites

This README assumes the following two repositories are cloned using git:

- http://github.com/comorment/containers
- https://github.com/comorment/ldpred2_ref
- https://github.com/comorment/opensnp

We also assume the following commands are executed from the current folder (the one containing createBackingFile.R and ldpred2.R scripts).
Note on help functions

The main R scripts contained in this directory (ldpred2.R, createBackingFile.R, imputeGenotypes.R, complementSum) are set up using the argparse package for parsing command line arguments. The help output from each script can be printed to the terminal, issuing:

```
export SIF=$COMORMENT/containers/singularity
export RSCRIPT="singularity exec --home=$PWD:/home $SIF/r.sif Rscript"
# invoke ldpred2.R input options:
$RSCRIPT ldpred2.R --help
```

yielding:

```
   [--sumstats SUMSTATS] [--out OUT] [--out-merge-ids
LD-FILE] [--ld-meta-file LD-META-FILE] [--chr2use CHR2USE]
COL-N] [--stat-type STAT-TYPE] [--effective-sample-size
EFFECTIVE-SAMPLE-SIZE] [--n-cases N-CASES] [--n-controls
N-CONTROLS] [--name-score NAME-SCORE] [--hyper-p-length
HYPER-P-LENGTH] [--hyper-p-max HYPER-P-MAX] [--ldpred-mode
LDPPRED-MODE] [--cores CORES] [--set-seed SET-SEED]
   [--genomic-build GENOMIC-BUILD] [--tmp-dir TMP-DIR]
```

Calculate polygenic scores using ldpred2

flags:
- h, --help show this help message and exit
 -out-merge Merge output with existing file.
 -geno-impute-zero Set missing genotypes to zero.
...

Note on filtering of genotype data

The current version of these scripts performs no filtering of genotype data (e.g., minor allele frequency, imputation quality) prior to calculating linkage disequilibrium or polygenic scores. This should be done for polygenic score analyses intended for publication.

Note on missing genotypes

If genotypes are missing LDpred2 will stop and return an error (Error: You can't have missing values in 'X'). One can either pass --geno-impute-zero to replace missing genotypes with zero or impute with any other tool such as plink, or use imputeGenotypes.R that works for bigSNPR (.rds/.bk) files. Currently, only “simple” imputation with mode, mean, random or zero is supported by this script. For documentation on these methods see snp_fastImputeSimple.

First, note that using --geno-impute-zero is costly in computational time so it’s better to impute prior to running ldpred2.R. Second, imputeGenotypes.R does not create a copy of the genotypes, thus the imputation performed persists. If you wish to keep the original .rds/.bk files you should copy these prior to imputing.
An example use of `imputeGenotypes.R`:

```
# Convert from plink format to bigSNPR .rds/.bk files
$RSCRIPT createBackingFile.R --file-input <fileGeno>.nomiss.bed --file-output <fileGeno>.nomiss.rds

# Copy these files if you wish to leave the original files unchanged
cp <fileGeno>.rds <fileGeno>.nomiss.rds
cp <fileGeno>.bk <fileGeo>.nomiss.bk

$RSCRIPT imputeGenotypes.R --impute-simple mean0 --geno-file-rds <fileGeno>.nomiss.rds
```

Another option is to use PLINK's `--fill-missing-a2` option, and re-run `createBackingFile.R`:

```
export PLINK="singularity exec --home=$PWD:/home $SIF/gwas.sif plink"
$PLINK --bfile /REF/examples/prsice2/EUR --fill-missing-a2 --make-bed --out EUR.nomiss
$RSCRIPT createBackingFile.R --file-input EUR.nomiss.bed --file-output EUR.nomiss.rds

$RSCRIPT ldpred2.R --geno-file-rds EUR.nomiss.rds ...
```

### Note on genomic builds

By default, the LDpred2 scripts assume that the genotype data and summary statistics use build GRCh37/hg19, but there are no explicit checks for consistent builds across input files. If the genotype data and summary statistics file use another build, the `--genomic-build <build>` flag should be used to specify build version, parsing either `hg18`, `hg19` or `hg38` as an argument. As of now, setting this argument will affect the loading of LD metadata only, but not the genotype data or summary statistics. A symptom of using the wrong build is that the script will match only a small fraction of variants between the genotype data, summary statistics file and/or LD reference data.

### Optional: Estimating linkage disequilibrium (LD)

LDpred2 uses the LD structure when calculating polygenic scores. By default, the LDpred2.R script uses LD structure based on European samples provided by the LDpred2 authors. Instead of calculating LD on your own, the `calculateLD.R` script can be used. The output from this script can then be used as input to LDpred2.R (with the optional `--ld-file` flag).

It should be noted that creating these LD matrixes may require several steps that are dependent on what type of genotypic data you have. These are not covered in detail here, but a first step is to ensure that you filter out related individuals, and use a reasonably sized set of genotyped or well-imputed SNPs. How to restrict individuals and SNPs is covered below.

First, to use `calculateLD.R` you need to download genetic maps from 1000 genomes in order to convert each SNPs physical position to genomic position. If you don’t provide these files, LDpred2 will try to download these automatically which will cause an error without an internet connection. To prevent this behavior, these should be downloaded manually and the folder where they are stored should be passed to the LDpred2-script using the flag `--dir-genetic-maps`.

Two parameters that can be passed to `calculateLD.R` and affect the LD estimation are `--window-size` (region around index SNP in base pairs) and `--thres-r2` (threshold for including a SNP correlation in the LD). The default for `--thres-r2` is 0 in `bigsnpr::snp_cor`, but `calculateLD.R` has a default of 0.01.

The example script below will output one file per chromosome (output/1d-chr-1.rds, output/1d-chr-2.rds, ...) and a “map” indicating the SNPs used in LD estimation (output/map.rds). The flag `--sumstats` can be used to filter SNPs to use where the first argument is the file and the second the column name or position of the RSID of the SNP (ie it does not need to be a proper sumstats file). The `--extract` argument does similar but expects a file that is just a list of RSIDs. These arguments can be combined and the SNPs used will then be limited to those that overlap in both files.
By a similar principle, `--extract-individuals` can be used together with `--sample-individuals` to limit the set of individuals (e.g., unrelated only), and then to draw a sample from this set.

```bash
# point to input/output files
export fileGeno=/REF/examples/ldpred2/g1000_eur_chr21to22_hm3rnd1.bed
export fileGenoRDS=g1000_eur_chr21to22_hm3rnd1.rds
export filePheno=/REF/examples/ldpred2/simu.pheno
export fileSumstats=/REF/examples/ldpred2/trait1.sumstats.gz
export fileOutLD=ld-chr-@.rds
export fileOutLDMap=ld-map.rds

# set environmental variables. Replace "<path/to/comorment>" with
# the full path to the folder containing cloned "containers" and "ldpred2_ref" repositories
export COMORMENT=<path/to/comorment>
export SIF=$COMORMENT/containers/singularity
export REFERENCE=$COMORMENT/containers/reference
export LDPRED2_REF=$COMORMENT/ldpred2_ref
export SINGULARITY_BIND=$REFERENCE:/REF,${LDPRED2_REF}:/ldpred2_ref
export RSCRIPT="singularity exec --home=$PWD:/home $SIF/r.sif Rscript"

# convert genotype to LDpred2 format
$RSCRIPT createBackingFile.R --file-input $fileGeno --file-output $fileGenoRDS

# create genetics maps directory, download and process
mkdir -p 100genomes/maps
$RSCRIPT calculateLD.R --geno-file-rds $fileGenoRDS
   --dir-genetic-maps 100genomes/maps
   --chr2use 21 22 --sumstats $fileSumstats SNP
   --file-ld-blocks $fileOutLD --file-ld-map $fileOutLDMap

Note that “bad” LD matrixes may result in optimization failures as these when running the LDpred2 scoring:

```
Running LDpred2 auto model
Error in { : task 1 failed - "L-BFGS-B needs finite values of 'fn'">
Calls: snp_ldpred2_auto -> %dorng% -> do.call -> <Anonymous> -> <Anonymous>
```

The LDpred2 creators recommend creating independent LD blocks in these matrixes. The `splitLD.R` script can be used for this purpose. The setup is the same as the example above, but we add a modified `$RSCRIPT [...]` statement using the outputted matrixes from `calculateLD.R` as input to `splitLD.R`. There are several parameters to this script that will affect the “shape” of these blocks (thus subsequent performance in LDpred2). Consult `splitLD.R` and `bigsnpr::snp_ldsplit` for details.

```
$RSCRIPT splitLD.R --file-ld-blocks $fileOutLD
   --file-ld-map $fileOutLDMap
   --file-output-ld-blocks ld-blocked-chr@.rds
```

The script `analyzeLD.R` can be used to visualize these matrixes and provide summary statistics. We don’t cover its use in detail here, but if you experience issues with LD matrixes one way may be to compare plots and statistics between your matrixes and those provided by by the LDpred2 creators. `Rscript analyzeLD.R --help` provides an overview of usage.
7.2.2 Running LDpred2 analysis

**Effective sample-size**

LDpred2 requires information on effective sample size. There are three ways to provide this to LDpred2:

- As a column in the summary statistics, defaulting to column N. If it is a different column, provide with argument `--col-n`.
- Manually calculated by providing this number with `--effective-sample-size`.
- Manually specified by providing the number of cases and controls with arguments `--n-cases` and `--n-controls`.

Specifying the effective sample size manually will override any sample size column in the sumstats. Providing both `--effective-sample-size` and `--n-cases`/`--n-controls` will throw an error.

**Summary statistics**

LDpred2 requires chromosome number, effective allele (eg A1), reference allele (eg A2, A0), and either SNP ID (RSID) or genomic position. If the summary statistics lack any of this information, the software will not run. Commonly, output from meta-analysis software such as metal do not contain this information. The `complementSumstats.R` script can be used to add these columns. In the example below, this script is used to append this information in a set of gzipped files inside a directory, and output these as gzipped files:

```bash
# set environmental variables. Replace "<path/to/comorment>" with
# the full path to the folder containing cloned "containers" and "ldpred2_ref"
  ...repositories
export COMORMENT=<path/to/comorment>
export SIF=$COMORMENT/containers/singularity
export REFERENCE=$COMORMENT/containers/reference
export SINGULARITY_BIND=$REFERENCE:/REF,${LDPRED2_REF}:/ldpred2_ref
export RSCRIPT="singularity exec --home=$PWD:/home $SIF/r.sif Rscript"

# Directory with possibly gzipped sumstat files
dirSumstats=directory/sumstats
# Directory to direct output
dirOutput=directory/sumstats/processed
if [ ! -d $dirOutput ]; then mkdir $dirOutput; fi;

for fileSumstats in `ls $dirSumstats`; do
  echo "Processing file $fileSumstats"
  $RSCRIPT $COMORMENT/containers/LDpred2/complementSumstats.R --col-sumstats-snp-id
  ...MarkerName --sumstats $dirSumstats/$fileSumstats --file-output $dirOutput/$fileSumstats
gzip $dirOutput/$fileSumstats
done
```

When working within the container, the `--reference` argument can be omitted, but can be replaced with anything else along with `--col-reference-snp-id` to set the SNP ID column in the reference file. The argument `--columns-append` controls which columns to append and default to the `#CHROM` and `POS` which are the columns of chromosome and position in the HRC reference data (default of `--reference` argument). This script will fail if there are duplicate SNPs in any of these files that are matched. In the example below, output is piped to gzip. To write directly to a file the arguments `--file-output <output file>` and `--file-output-col-sep` controls the location of the output file and the column separator used (defaults to tab, "\t").
NOTE: In case the summary statistics file (or any other file used by the scripts) is outside the working directory, make sure to append its directory to the SINGULARITY_BIND environment variable as above, and refer to the file accordingly - otherwise the running container won’t see the file.

Synthetic example (chr21 and chr22)

The following set of commands gives an example of how to apply LDpred2 on a synthetic example generated here. This only uses chr21 and chr22, so it runs much faster than the previous example. This example requires only map_hm3_plus.rds, ldref_hm3_plus/LD_with_blocks_chr21.rds, and ldref_hm3_plus/LD_with_blocks_chr22.rds files from the ldpred2_ref repository, so you may download them separately rather than clone the entire repo.

```
# point to input/output files
export fileGeno=/REF/examples/ldpred2/g1000_eur_chr21to22_hm3rnd1.bed
export fileGenoRDS=g1000_eur_chr21to22_hm3rnd1.rds
export fileSumstats=/REF/examples/ldpred2/trait1.sumstats.gz
export fileOut=simu

# set environmental variables. Replace "<path/to/comorment>" with
# the full path to the folder containing cloned "containers" and "ldpred2_ref"
export COMORMENT=<path/to/comorment>
export SIF=$COMORMENT/containers/singularity
export REFERENCE=$COMORMENT/containers/reference
export LDPRED2_REF=$COMORMENT/ldpred2_ref
export SINGULARITY_BIND=$REFERENCE:/REF,${LDPRED2_REF}:/ldpred2_ref

export RSCRIPT="singularity exec --home=$PWD:/home $SIF/r.sif Rscript"

# convert genotype to LDpred2 format
$RSCRIPT createBackingFile.R --file-input $fileGeno --file-output $fileGenoRDS

# run LDpred2 infinitesimal mode
$RSCRIPT ldpred2.R --ldpred-mode inf \  
  --chr2use 21 22 \  
  --geno-file-rds $fileGenoRDS \  
  --sumstats $fileSumstats \  
  --out $fileOut.inf

# run LDpred2 automatic mode
$RSCRIPT ldpred2.R --ldpred-mode auto \  
  --chr2use 21 22 \  
  --geno-file-rds $fileGenoRDS \  
  --sumstats $fileSumstats \  
  --out $fileOut.auto
```
Optional: Append score to existing file

It is possible to merge the calculated score to an existing file. For example, you might have a file looking like this:

```
FID IID SEX PC1 ...
1 1 M 1.1 ...
2 2 F 0.3 ...
```

By replacing the `$fileOut.inf` and `$fileOut.auto` argument above with `<myfile>` and using the options `--name-score myScoreInf` for the `--ldpred-mode inf` statement and `--name-score myScoreAuto` for the other, and add the flag `--out-merge` you end up with these scores in the existing file.

```
FID IID SEX PC1 ... myScoreInf myScoreAuto
1 1 M 1.1 ... 0.3 0.4
2 2 F 0.3 ... -0.2 0.1
```

Note that by default, merging is based on the columns IID and FID in the output file. If these columns are named differently the option `--out-merge-ids <FID column> <IID column>` should be used to specify their names.

Height example

The following set of commands gives an example of how to apply LDpred2 on genetic data from the OpenSNP project, and a height GWAS sumstats file. This example requires the opensnp_hm3.* and UKB_NEALELAB_2018_HEIGHT.GRCh37.hm3.gz files from the opensnp repository, so you may download them separately rather than clone the entire repo, and place them according to the paths in the script below.

```
# Set environmental variables. Replace "<path/to/comorment>" with
# the full path to the folder containing cloned "containers" and "ldpred2_ref"

export COMORMENT=<path/to/comorment>
export SIF=$COMORMENT/containers/singularity
export REFERENCE=$COMORMENT/containers/reference
export LDPRED2_REF=$COMORMENT/ldpred2_ref
export OPENSNP=$COMORMENT/opensnp
export SINGULARITY_BIND=$REFERENCE:/REF,${LDPRED2_REF}:/ldpred2_ref,${OPENSNP}:/opensnp

# Point to LDpred2.R input/output files
export fileGeno=/opensnp/imputed/opensnp_hm3.bed
export fileGenoRDS=opensnp_hm3.rds
export fileSumstats=/opensnp/gwas/UKB_NEALELAB_2018_HEIGHT.GRCh37.hm3.gz
export fileOut=Height

export RSCRIPT="singularity exec --home=$PWD:/home $SIF/r.sif Rscript"

# convert genotype to LDpred2 format
$RSCRIPT createBackingFile.R --file-input $fileGeno --file-output $fileGenoRDS

# impute
$RSCRIPT imputeGenotypes.R --impute-simple mean0 --geno-file-rds $fileGenoRDS

# Generate PGS usign LDPRED-inf
$RSCRIPT ldpred2.R
    --ldpred-mode inf
```

(continues on next page)
7.2.3 Output

The main LDpred2 output files are *Height.score.inf* and *Height.score.auto* put in this directory. The files are text files with tables formatted as

<table>
<thead>
<tr>
<th>FID</th>
<th>IID</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG00096</td>
<td>HG00096</td>
<td>-0.733896062346436</td>
</tr>
<tr>
<td>HG00097</td>
<td>HG00097</td>
<td>0.688693127521599</td>
</tr>
<tr>
<td>HG00099</td>
<td>HG00099</td>
<td>0.203279440703434</td>
</tr>
<tr>
<td>HG00100</td>
<td>HG00100</td>
<td>0.0890499485064315</td>
</tr>
</tbody>
</table>

The script will also output .bk and .rds binary files with prefix EUR in this directory.

7.2.4 Slurm job

On an HPC resource, the same analysis can be run by first writing a job script *run_ldpred2_slurm.job*. In order to run the job, first make sure that the `SBATCH_ACCOUNT` environment variable is defined:

```bash
export SBATCH_ACCOUNT=project_ID
```

where `project_ID` is the granted project that computing time is allocated. As above, `<path/to/containers` should point to the cloned containers repository. Entries like `--partition=normal` may also be adapted for different HPC resources. Then, the job can be submitted to the queue by issuing `sbatch run_ldpred2_slurm.job`. The status of running jobs can usually be enquired by issuing `squeue -u $USER`.
Redirect temporary file output

By default, the LDpred2.R script will put large file(s) in the system temporary directory (using `base::tempdir()`). For use on HPC resources, use of the designated `$SCRATCH`, `$LOCALTMP`, or `$TMPDIR` directories is recommended to avoid filling up the system temporary directory.

One can redirect the temporary file output by setting the `TMPDIR` environment variable to a mounted directory on the HPC resource, by incorporating the following lines into the job script:

```
export SINGULARITY_BIND=$REFERENCE:/REF,${LDpred2_REF}:/ldpred2_ref,$SCRATCH:/scratch
export SINGULARITYENV_TMPDIR=/scratch
```

Otherwise, the location of temporary files can be specified by the `--tmp-dir` argument to the `ldpred2.R` script.

7.3 PGS toolset

More on PGS: https://choishingwan.github.io/PRS-Tutorial/

7.3.1 Codes

- `README.md`: this file
- `pgs/pgs.py`: Python class definitions setup to create bash commands for different PGS tools (plink, PRSice2, LDpred2, etc.)
- `run_pgs_synthetic.py`: Python run script setup to run PGS tools on synthetic data provided in this repository, mainly for testing purposes.
- `run_pgs_w_QC.py`: Python run script setup to run PGS tools on data provided in this repository, mainly for testing purposes. Performs basic QC steps.
- `run_pgs_MoBa_*.py`: Python run scripts to run PGS tools on MoBa data.
- `pgs_exec.py`: `gwas.py` like command line tool that can be used to run, create bash and slurm job scripts for different PGS tools based on user input.
- `vis_pgs_synthetic.ipynb`: Jupyter notebook plotting/comparing the output PGS scores generated by the `run_pgs_synthetic.py` script.
- `vis_pgs_w_QC.ipynb`: Jupyter notebook plotting/comparing the output PGS scores generated by the `run_pgs_w_QC.py` script.
- `start_jupyter_server.py`: start a Jupyter server using the `python3.sif` container (allows jupyter notebooks within VSCode with the Jupyter extension)
- `config.yaml`: YAML file defining some parameters for Slurm jobs scripts and PGS methods
- `pgs_exec_example_*.sh`: Example bash scripts for `pgs_exec.py`
- `requirements.txt`: Python package requirements. Install with `pip install -r requirements.txt`
- `Rscripts/*.R`: misc. R scripts defining or being used by the PGS tools or optional QC steps.
- `tests/*`: directory for unit tests, executable with `py.test -v tests` in this directory
7.3.2 Requirements

The basic requirements for running these codes (sans project specific genomics data) are the same as for the rest of this project, i.e., a basic Python environment and a working Singularity/Aptainer installation.

7.3.3 Running the codes

Running these codes requires Python 3.8+ (tested/developed mainly using Python 3.9+) and a working Singularity/Aptainer installation.

Input files

To work with these codes, some input files are required. These are:

Summary statistics

GWAS summary files formatted according to the sumstats specification

Phenotypic data

Phenotypic data formatted according to the phenotype specification

Genotypic data

Genotypic data formatted according to the genotype specification

Covariate data

Covariate data formatted according to the covariate specification

Output files

The output will be written to a user-specified output/ directory, which is created if it does not exist. The output directory will contain subdirectories for each PGS method, e.g., output/PGS_synthetic_plink/ as specified in the runtime scripts.

PGS scores

The individ level output file shared by all PGS methods is named test.score. The text file contains the PGS scores for each individual in the phenotype file. The first two columns are FID and IID. The third column score is the PGS score.

NOTE: For PLINK and PRSice-2, the score column contains the “best” PGS score, i.e., the one with the highest R2 for the tested range of p-value thresholds. The scores for each p-value threshold are also written to the output directory as separate files.
Summary statistics

The file `test_summary.txt` contains the R (generalized) linear model (LM/GLM) summary statistics for the PGS model in plain-text format, while `test_summary.csv` contains the LM/GLM summary statistics in tabular (`.csv`) format. Both the full model and the null model are reported, typically assumed to be on the form

**full model** \[ y \sim PGS_{score} + PC_1 + PC_2 + \ldots + PC_n + SEX \]

**null model** \[ y_{null} \sim PC_1 + PC_2 + \ldots + PC_n + SEX \]

**nocov model** \[ y_{nocov} \sim PGS_{score} \]

For binary traits, the GLM should use the binomial family and the logit link function to fit the model.

For binary traits, we also summarize Odds Ratios (OR) and 95% confidence intervals (CI) for the PGS models. These outputs are written to plaintext and tabular files named `test_summary.or.txt` and `test_summary.<null/full/nocov>.or.csv`, respectively.

Python runtime scripts

`run_pgs_synthetic.py`

Run PGS using PLINK, PRSice2 and LDpred2 on synthetic data provided in this repository, namely the files:

- summary statistics: `/REF/examples/ldpred2/trait1.sumstats.gz`
- phenotype data: `/REF/examples/ldpred2/simu.pheno`
- genotype data: `/REF/examples/ldpred2/g1000_eur_chr21to22_hm3rnd1.bed/bim/fam`
- covariate data: `/REF/examples/prsice2/EUR.cov`

*NOTE:* Files from a full clone of https://github.com/comorment/ldpred2_ref with LDpred2 reference data is required and should be located in a directory `ldpred2_ref` as defined in the `config.yaml` file.

Running the script:

```
$ python3 run_pgs_synthetic.py
environment variables in use:
    ROOT_DIR: /nrec/space/espenh
    CONTAINERS: /nrec/space/espenh/containers
...
# A tibble: 1 × 12
  r.squared adj.r.squ...1 sigma stati...2 p.value df logLik AIC BIC devia...3
<dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
1 0.765 0.762 0.494 201. 3.47e-150 8 -354. 728. 770. 120.
# ... with 2 more variables: df.residual <int>, nobs <int>, and abbreviated
# variable names 1adj.r.squared, 2statistic, 3deviance
[1] "R2 (null model): 0.0250978564710413"
[1] "R2 (full model): 0.765387984851408"
```

*NOTE:* The script may require other packages than Python builtins, such as pandas and pyyaml. Install these by issuing pip install <package> in the current Python environment. There is also pip install -r requirements.txt.

The output will be added to the output/PGS_synthetic_<method>/ directories.
run_pgs_w_QC.py

Run PGS using PLINK, PRSice2 and LDpred2 on tutorial data provided in this repository, including some basic QC steps on the data based on suggestions from this tutorial.

The main input files are:

- summary statistics: /REF/examples/prsice2/Height.gwas.txt.gz
- phenotype data: /REF/examples/prsice2/EUR.height
- genotype data: /REF/examples/prsice2/EUR.bed/bim/fam
- covariates: /REF/examples/prsice2/EUR.cov
- eigenvectors: /REF/examples/prsice2/EUR.eigenvec

**NOTE:** Files from a full clone of https://github.com/comorment/ldpred2_ref with LDpred2 reference data is required and should be located in a directory ldpred2_ref as defined in the config.yaml file.

Running the script:

```
python3 run_pgs_w_QC.py
```

run_pgs_MoBa_.py

Run basic PGS for height using PLINK, PRSice2 and LDpred2, respectively on MoBa child sample data (only on TSD p697).

pgs_exec.py command line tool

Run, create bash and slurm job scripts for different PGS tools

Get a list of options:

```
$ python3 pgs_exec.py --help

A pipeline for PGS analysis

positional arguments:
  {plink,prsice2,ldpred2-inf,ldpred2-auto}

optional arguments:
  -h, --help                    show this help message and exit
  --method {plink,prsice2,ldpred2-inf,ldpred2-auto} Method for PGS
  --config CONFIG               config YAML file
  --sumstats-file SUMSTATS_FILE summary statistics file
  --pheno-file PHENO_FILE       phenotype file
```

(continues on next page)
--phenotype PHENOTYPE
phenotype name (must be a column header in``pheno_file``)

--phenotype-class {CONTINUOUS,BINARY}
phenotype class

--geno-file-prefix GENO_FILE_PREFIX
file path to .bed, .bim, .fam, etc. files

--output-dir OUTPUT_DIR
Output file directory

--runtype {sh,slurm,subprocess}
operation mode

Example w. PRSice2 as subprocess on synthetic dataset (pgs_exec_example_1.sh):

```bash
python3 pgs_exec.py \
  --sumstats-file /REF/examples/ldpred2/trait1.sumstats.gz \
  --pheno-file /REF/examples/ldpred2/simu.pheno \
  --phenotype trait1 \
  --phenotype-class CONTINUOUS \
  --geno-file-prefix /REF/examples/ldpred2/g1000_eur_chr21to22_hm3rnd1 \
  --output-dir output/PGS_synthetic_prsice2 \
  --runtype subprocess \
  prsice2 \
  --covariate-file /REF/examples/prsice2/EUR.cov \
  --eigenvec-file output/PGS_synthetic_prsice2/g1000_eur_chr21to22_hm3rnd1.eigenvec
```

**NOTE:** The last two lines will override settings for method: prsice2 in config.yaml file, being parsed to the PRSice2.r script

Example w. LDpred2-inf via shell (sh) script on synthetic dataset (pgs_exec_example_2.sh):

```bash
python3 pgs_exec.py \
  --sumstats-file /REF/examples/ldpred2/trait1.sumstats.gz \
  --pheno-file /REF/examples/ldpred2/simu.pheno \
  --phenotype trait1 \
  --phenotype-class CONTINUOUS \
  --geno-file-prefix /REF/examples/ldpred2/g1000_eur_chr21to22_hm3rnd1 \
  --output-dir output/PGS_synthetic_LDpred2_inf \
  --runtype sh \
  ldpred2-inf \
  --covariate-file /REF/examples/prsice2/EUR.cov \
  --eigenvec-file output/PGS_synthetic_LDpred2_inf/g1000_eur_chr21to22_hm3rnd1.eigenvec \
  --file-geno-rds output/PGS_synthetic_LDpred2_inf/g1000_eur_chr21to22_hm3rnd1.rds \
  file-keep-snps /REF/hapmap3/w_hm3.justrs \
  chr2use 21,22
```

Which generates a shell script that can be run as

```bash
bash bash_scripts/ldpred2-inf-230918-12:26:35.sh  # YYMMDD-HH:MM:SS is appended to file name
```

**NOTE** Replacing ``--runtype 'sh' with `--runtype 'slurm' and 'ldpred2-inf' by 'ldpred2-auto' generates a slurm jobscript using LDpred2-auto which can be submitted by issuing bash slurm_job_scripts/ldpred2-auto.job (cf. pgs_exec_example_3.sh)
7.3.4 Config file

The config.yaml file defines some parameters for Slurm jobscripts, job environment, and PGS methods in a YAML file. The parameters defined throughout the file are:

**parameters to pass for SLURM jobs**

Entries that will be put in the SLURM job scripts. These are:

```yaml
slurm:
  job_name: pgs  
  account: p697_norment  
  time: "00:30:00"  
  cpus_per_task: 4  
  mem_per_cpu: 4000MB  
  partition: normal

# list of modules to load in SLURM jobs
module_load:
  - singularity/3.7.3  
# cf. the output of: "module spider singularity"
```

**environment variables (edit as necessary)**

Control where the PGS tools are located, where the reference data is located, etc. These are:

```yaml
environ:
  # mandatory root directory containing all inferred directories (edit as necessary).
  ROOT_DIR: "/nrec/space/espenh"

# dependent environment variables (edit as necessary)
# NB: "SIF" is mandatory
environ_inferred:
  # folder containing full clone of https://github.com/comorment/containers
  CONTainers: "$ROOT_DIR/containers"
  # reference data within containers repo
  REFERENCE: "$CONTainers/reference"
  # directory with singularity containers (.sif files)
  SIF: "$CONTainers/singularity"
  # folder containing full clone of https://github.com/comorment/ldpred2_ref with...
  LDpred2 reference data
  LDPRED2_REF: "$ROOT_DIR/ldpred2_ref"
  # folder containing LDpred2 R scripts
  LDPRED2_SCRIPTS: "$CONTainers/scripts/pgs/LDpred2"

# for SINGULARITY_BIND variable to set in job scripts
# NB! will be set as "export SINGULARITY_BIND=value0:/key0,value1:/key1,..."
# NB! Also mandatory
SINGULARITY_BIND:
  REF: "$REFERENCE"
  ldpred2_ref: "$LDPRED2_REF"
  ldpred2_scripts: "$LDPRED2_SCRIPTS"
```
Parameters specific to each PGS calculating tool

Refer class documentation of each tool for details

**Plink**

used by class PGS\_PLINK

```r
plink:
    clump\_p1: 1
    clump\_r2: 0.1
    clump\_kb: 250
    range\_list: [0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1]
    strat\_indep\_pairwise: [250, 50, 0.25]
    nPCs: 6
    score\_columns: [SNP, A1, BETA]
    threads: 4
```

**PRSice-2**

used by class PGS\_PRSice2

```r
prsice2:
    MAF: 0.01
    INFO: 0.8
    nPCs: 6
    thread: 4
```

**LDpred2**

used by class PGS\_LDpred2

```r
ldpred2:
    nPCs: 6
    cores: 4
```
The following use cases illustrate applications of CoMorMent containers:

- `gwas_demo.md` describes how to run a demo GWAS analysis with `plink2` and `regenie` following the `CoMorMent specifications`.
- `gwas_real.md` illustrates usage of `gwas.py` analysis on MoBa height and depression phenotypes
- `meta_simu.md` describe use cases related to meta-analysis
- `bolt-lmm_demo.md` describes how to run bolt-lmm
- `scripts/pgs/LDpred2/README.md` describes how to run PRS analyses using LDpred2
9.1 gwas.py

class gwas.ActionAppendDeprecated (option_strings, dest, nargs=None, const=None, default=None, type=None, choices=None, required=False, help=None, metavar=None)

Methods

__call__ (parser, namespace, values[...]) Call self as a function.

format_usage

class gwas.ActionStoreDeprecated (option_strings, dest, nargs=None, const=None, default=None, type=None, choices=None, required=False, help=None, metavar=None)

Methods

__call__ (parser, namespace, values[...]) Call self as a function.

format_usage

class gwas.LoadFromFile (option_strings, dest, nargs=None, const=None, default=None, type=None, choices=None, required=False, help=None, metavar=None)
Methods

__call__(parser, namespace, values[, ...])
Call self as a function.

class gwas.Logger(fh, mode)
Lightweight logging.

Methods

error(msg)
Print to log file, error file and stdout with a single command.

log(msg)
Print to log file and stdout with a single command.

class gwas.NumpyEncoder(*, skipkeys=False, ensure_ascii=True, check_circular=True, allow_nan=True,
sort_keys=False, indent=None, separators=None, default=None)

Methods

default(obj)
Implement this method in a subclass such that it returns a serializable object for o, or calls the base implementation (to raise a TypeError).

encode(o)
Return a JSON string representation of a Python data structure.

iterencode(o[, _one_shot])
Encode the given object and yield each string representation as available.

default(obj)
Implement this method in a subclass such that it returns a serializable object for o, or calls the base implementation (to raise a TypeError).

For example, to support arbitrary iterators, you could implement default like this:

def default(self, o):
    try:
        iterable = iter(o)
    except TypeError:
        pass
    else:
gwas.sec_to_str(t)

Convert seconds to days:hours:minutes:seconds

9.2 pgs.pgs

class pgs.pgs.BasePGS(sumstats_file='/REF/examples/prsice2/Height.gwas.txt.gz',
    pheno_file='/REF/examples/prsice2/EUR.height', phenotype='Height',
    phenotype_class='CONTINUOUS', geno_file_prefix='/REF/examples/prsice2/EUR',
    output_dir='qc-output', **kwargs)

Base PGS object declaration with some shared properties for subclassing

Parameters

    sumstats_file: str
        summary statistics file (.gz)

    pheno_file: str
        phenotype file (for instance, .height)

    phenotype: str or None
        if not None, phenotype name (must be a column header in pheno_file)

    phenotype_class: str
        phenotype class, either CONTINUOUS or BINARY

    geno_file_prefix: str
        path to QC’d .bed, .bim, .fam files (w.o. file ending) (<ENV/path/to/data/file>)

    output_dir: str
        path for output files (<path>)

**kwargs

Attributes

    data_prefix: str
        file name prefix of .bed, .bim, etc. files

Methods

    get_str: abstract method for returning string with commands

    abstract get_str()

Required public method

class pgs.pgs.PGS_LDpred2(sumstats_file='/REF/examples/prsice2/Height.gwas.txt.gz',
    pheno_file='/REF/examples/prsice2/EUR.height', phenotype='Height',
    phenotype_class='CONTINUOUS',
    geno_file_prefix='/REF/examples/prsice2/EUR', output_dir='PGS_ldpred2_inf',
    method='auto', file_geno_rds='PGS_ldpred2_inf/EUR.rds', **kwargs)

9.2. pgs.pgs
Helper class for setting up LDpred2 PRS analysis. Inherited from class BasePGS

**Parameters**

- **sumstats_file**: str
  summary statistics file (.gz)

- **pheno_file**: str
  phenotype file (for instance, .height)

- **phenotype**: str or None
  if not None, phenotype name (must be a column header in pheno_file)

- **phenotype_class**: str
  phenotype class, either ‘CONTINUOUS’ or ‘BINARY’

- **geno_file_prefix**: str
  path to QC’d .bed, .bim, .fam files (w.o. file ending) (<ENV/path/to/data/file>)

- **output_dir**: str
  path for output files (<path>)

- **method**: str
  LDpred2 method, either “auto” (default) or “inf” for infinitesimal

- **file_geno_rds**: str
  base name for .rds file output

**kwargs

dict of additional keyword/arguments pairs parsed to the $LDPRED2_SCRIPTS/ldpred2.R script (see file for full set of options). If the option is only a flag without value, set value as None-type or empty string.

**Methods**

- **generate_eigenvec_eigenval_files(nPCs=6)**
  Return string which can be included in job script for generating .eigenvec and .eigenval files in the output directory using PLINK

  **Parameters**

  - **nPCs**: int
    number of PCs to account for

- **get_model_evaluation_str(eigenvec_file=None, nPCs=None, covariate_file=None)**
  Return callable string for fitting a simple linear model between PGS score and phenotype data using R stats::lm, printing stats::lm.fit.summary output to file

  **Parameters**

  - **eigenvec_file**: path
    path to file with PCs (no header, columns FID, IID, PC1, PC2, …)
nPCs: int
number of PCs to account for
covariate_file: path
path to file with covariates (header, columns FID, IID, <covariate>)

Returns
str
get_str(create_backing_file=True)
Public method to create commands

Parameters
create_backing_file: bool
if True (default), prepend statements for running the $LDPRED2_SCRIPTS/
createBackingFile.R script, generating file_geno_rds

Returns
list of str
list of command line statements for analysis run

class pgs.pgs.PGS_PRSice2(sumstats_file='/REF/examples/prsice2/Height.gwas.txt.gz',
pheno_file='/REF/examples/prsice2/EUR.height', phenotype='Height',
phenotype_class='CONTINUOUS',
geno_file_prefix='/REF/examples/prsice2/EUR', output_dir='PGS_prsice2',
covariate_file='/REF/examples/prsice2/EUR.cov',
eigenvec_file='/REF/examples/prsice2/EUR.eigenvec', nPCs=6, MAF=0.01,
INFO=0.8, **kwargs)

Helper class for setting up PRSice-2 PRS analysis. Inherited from class BasePGS

Parameters
sumstats_file: str
summary statistics file (.gz)
pheno_file: str
phenotype file (for instance, .height)
phenotype: str or None
if not None, phenotype name (must be a column header in pheno_file)
phenotype_class: str
phenotype class, either CONTINUOUS or BINARY
geno_file_prefix: str
path to QC'd .bed, .bim, .fam files (w.o. file ending) (<ENV/path/to/data/file>)
output_dir: str
path for output files (<path>)
covariate_file: str or None
path to covariate file (.cov)
eigenvec_file: str or None
path to eigenvec file (.eig) with PCs
nPCs: int
number of Principal Components (PCs) to include in covariate generation
MAF: float
base-MAF upper threshold value (0.01)

INFO: float
base-INFO upper threshold value (0.8)

**kwargs
dict of additional keyword/arguments pairs parsed to the Rscripts/PRSice.R script (see file for full set of options). If the option is only a flag without value, set value as None-type or empty string.

Attributes

data_prefix: str
file name prefix of .bed, .bim, etc. files

Methods

get_model_evaluation_str()
Return callable string for fitting a simple linear model between PGS score and phenotype data using R stats::lm, printing stats::lm.fit.summary output to file

Returns
str

get_str()
Public method to create commands

Returns
list of str
list of command line statements for analysis run

class pgs.pgs.PGS_Plink(sumstats_file=/REF/examples/prsice2/Height.gwas.txt.gz, pheno_file=/REF/examples/prsice2/EUR.height', phenotype='Height', phenotype_class=CONTINUOUS', geno_file_prefix='QC_data/EUR', output_dir='PGS_plink', covariate_file=/REF/examples/prsice2/EUR.cov', eigenvec_file=/REF/examples/prsice2/EUR.eigenvec', clump_p1=1, clump_r2=0.1, clump_kb=250, clump.snp_field='SNP', clump_field='P', range_list=None, strat_indep_pairwise=None, nPCs=6, score_columns=None, **kwargs)

Helper class for setting up Plink PRS analysis. Inherited from class BasePGS

Parameters

sumstats_file: str
summary statistics file (.gz)

pheno_file: str
phenotype file (for instance, .height)

phenotype: str or None
if not None, phenotype name (must be a column header in pheno_file)

phenotype_class: str
phenotype class, either CONTINUOUS or BINARY
**geno_file_prefix**: str
   path to QC’d .bed, .bim, .fam files (w.o. file ending) (</ENV/path/to/data/file>)

**output_dir**: str
   path for output files (<path>)

**covariate_file**: str
   path to covariance file (.cov)

**eigenvec_file**: str or None
   None, or path to eigenvec file (.eigenvec)

**clump_p1**: float
   plink –clump-p1 parameter value (default: 1)

**clump_r2**: float
   plink –clump-r2 parameter value (default: 0.1)

**clump_kb**: float
   plink –clump-r2 parameter value (default: 250)

**clump.snp_field**: str
   plink –clump-snp-field parameter value (default: ‘SNP’)

**clump_field**: str
   plink –clump-field parameter value (default: ‘P’)

**range_list**: list of floats
   list of p-value ranges for plink –q-score-range arg. (default: [0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5])

**strat_indep_pairwise**: list of scalars
   plink –indep-pairwise parameters for stratification describing window size (kb), step size (variant ct), r^2 threshold (default: [250, 50, 0.25])

**nPCs**: int
   plink –pca parameter value (default: 6)

**score_columns**: list of str
   for plink’s –score, column names in sumstats_file. Requires header. Default: ['SNP', 'A1', 'BETA']

**kwargs**

**Attributes**

**data_prefix**: str
   file name prefix of .bed, .bim, etc. files
Methods

get_model_evaluation_str()

Return callable string for fitting a simple linear model between PGS score and phenotype data using R stats::lm, printing stats::lm.fit.summary output to file

Parameters

mode: str
'basic' or 'stratification'

update_effect_size: bool
if True, compute PGS using OR

get_str(mode='basic', update_effect_size=False)

Parameters

mode: str
'basic' or 'stratification'

update_effect_size: bool
if True, compute PGS using OR


Helper class for common GWAS QC. Inherited from class BasePGS

Based on the tutorial https://choishingwan.github.io/PRS-Tutorial/target/#qc-of-target-data

Use with caution. This class is not fully tested.

Parameters

sumstats_file: str
summary statistics file (.gz)

pheno_file: str
phenotype file (for instance, .height)

geno_file_prefix: str
path to (raw) .bed, .bim, .fam files (w.o. file ending) (<ENV/path/to/data/file>)

output_dir: str
path for output files (<path>)

phenotype: str
default: 'Height'

data_postfix: str
default: '.QC'

QC_target_kwargs: dict
default: {‘maf’: 0.01, ‘hwe’: 1e-6, ‘geno’: 0.01, ‘mind’: 0.01}

QC_prune_kwargs: dict
default: {‘indep-pairwise’: [200, 50, 0.25]}
QC_relatedness_prune_kwargs: dict
  defaultL: {'rel-cutoff': 0.125}

**kwargs

Methods

get_str()

Standard GWAS QC

pgs.pgs.convert_dict_to_str(d, key_prefix='--')

Parameters

- **d**: dict
  - key, value pairs

- **key_prefix**: str
  - string prefix for key names. Default: "--"

Returns

- str
  - string formatted as "--key0 value0 --key1 value1 ...". In case values are iterable, it will be formatted as "--key0 value0[0] value0[1] ... --key0"

pgs.pgs.df_columns_to_file(source_file, output_file, usecols=None, delim_whitespace=True, delimiter=None, **kwargs)

Extract columns from dataframe (.csv) on file to output_file

Parameters

- **source_file**: file path
  - .csv (or similar) input file read by pandas.read_csv.

- **output_file**: file path
  - output file to be written

- **usecols**: list of str or None
  - columns to read and write

- **delim_whitespace**: bool
  - parsed to df.read_csv. Default: True

- **delimiter**: None or str
  - delimiter. Default: None

- **kwargs**: keyword arguments parsed to pd.read_csv()

pgs.pgs.post_run_plink(output_dir, data_prefix, best_fit_file='best_fit_prs.csv', score_file='test.score')

Read best-fit predictions and export standardized test.score file to output_dir from class PGS_Plink output

Parameters

- **output_dir**: path
  - path to output directory
data_prefix: str
standard file name prefix (for .bed, .bim, .fam, etc.)

best_fit_file: str
.csv file in output_dir with best fit Threshold value. Default: ‘best_fit_prs.csv’

score_file: str
test score file in output_dir. Default: ‘test.score’

pgs.pgs.post_run_prsice2(output_dir, data_prefix, score_file='test.score')

Read best-fit predictions and export standardized test.score file to output_dir from class PGS_PRSice2 output

Parameters

output_dir: path
path to output directory

data_prefix: str
standard file name prefix (for .bed, .bim, .fam, etc.)

score_file: str
test score file in output_dir. Default: ‘test.score’

pgs.pgs.run_call(call)
run subprocess call

pgs.pgs.set_env(config)
Function to set environment variables from config.yaml

TODO: add defaults

Parameters

config: dict
config dictionary from config.yaml (or similar file)
Thanks for considering contributing! Please read this document to learn the various ways you can contribute to this project and how to go about doing it.

10.1 Bug reports and feature requests

10.1.1 Did you find a bug?

First, do a quick search to see whether your issue has already been reported. If your issue has already been reported, please comment on the existing issue.

Otherwise, open a new GitHub issue. Be sure to include a clear title and description. The description should include as much relevant information as possible. The description should explain how to reproduce the erroneous behavior as well as the behavior you expect to see. Ideally you would include a code sample or an executable test case demonstrating the expected behavior.

10.1.2 Do you have a suggestion for an enhancement or new feature?

We use GitHub issues to track feature requests. Before you create a feature request:

- Make sure you have a clear idea of the enhancement you would like. If you have a vague idea, consider discussing it first on a GitHub issue.
- Check the documentation to make sure your feature does not already exist.
- Do a quick search to see whether your feature has already been suggested.

When creating your request, please:

- Provide a clear title and description.
- Explain why the enhancement would be useful. It may be helpful to highlight the feature in other libraries.
- Include code examples to demonstrate how the enhancement would be used.
10.2 Making a pull request

When you’re ready to contribute code to address an open issue, please follow these guidelines to help us be able to review your pull request (PR) quickly.

1. **Initial setup** (only do this once)

   If you haven’t already done so, please fork this repository on GitHub. Then clone your fork locally with

   ```
   git clone https://github.com/USERNAME/containers.git
   ```

   or

   ```
   git clone git@github.com:USERNAME/containers.git
   ```

   At this point the local clone of your fork only knows that it came from your repo, `github.com/USERNAME/containers.git`, but doesn’t know anything the main repo, `https://github.com/comorment/containers.git`. You can see this by running

   ```
   git remote -v
   ```

   which will output something like this:

   ```
   origin https://github.com/USERNAME/containers.git (fetch)
   origin https://github.com/USERNAME/containers.git (push)
   ```

   This means that your local clone can only track changes from your fork, but not from the main repo, and so you won’t be able to keep your fork up-to-date with the main repo over time. Therefore you’ll need to add another “remote” to your clone that points to `https://github.com/comorment/containers.git`. To do this, run the following:

   ```
   git remote add upstream https://github.com/comorment/containers.git
   ```

   Now if you do `git remote -v` again, you’ll see

   ```
   origin https://github.com/USERNAME/containers.git (fetch)
   origin https://github.com/USERNAME/containers.git (push)
   upstream https://github.com/comorment/containers.git (fetch)
   upstream https://github.com/comorment/containers.git (push)
   ```

2. **Ensure your fork is up-to-date**

   Once you’ve added an “upstream” remote pointing to `https://github.com/comorment/containers.git`, keeping your fork up-to-date is easy:

   ```
   git checkout main  # if not already on main
   git pull --rebase upstream main
   git push
   ```

3. **Create a new branch to work on your fix or enhancement**

   Committing directly to the main branch of your fork is not recommended. It will be easier to keep your fork clean if you work on a separate branch for each contribution you intend to make.

   You can create a new branch with
4. Test your changes

Our continuous integration (CI) testing runs a number of checks for each pull request on GitHub Actions. You can run most of these tests locally, which is something you should do before opening a PR to help speed up the review process and make it easier for us.

And finally, please update the CHANGELOG with notes on your contribution in the “Unreleased” section at the top.

After all of the above checks have passed, you can now open a new GitHub pull request. Make sure you have a clear description of the problem and the solution, and include a link to relevant issues.

We look forward to reviewing your PR!

10.3 Information for developers

The list of tools included in the different Dockerfiles and installer bash scripts for each container is provided here. Please keep this up to date when pushing new container builds.

10.3.1 Sphinx

We use sphinx to generate online documentation from README.md files of this repository. This uses MyST package to generate links in the documentation. Here are few rules that we follow across .md files to make it work well:

- use full path to the file in this repository

10.3.2 Folder structure

These folders are relevant to the users:

- docs folder contain user documentation
- usecases folder contain extended examples / tutorials
- singularity folder contain pre-build containers
- reference folder contain reference data used in use-cases
- scripts folder contain pipelines such as gwas.py and pgs-toolkit, as well as other helper scripts.

These folders are relevant to developers:

- docker folder contains several Dockerfile files (container definitions) and relevant shell scripts (in docker/scripts/) used within those Dockerfile’s. Unit-tests validating functionality of the resulting containers are available in the tests folder.
- sphinx-docs provides scripts used to build sphinx documentation.
10.3.3 Note about NREC machine

We use NREC machine to develop and build containers. NREC machine has small local disk (~20 TB) and a larger external volume attached (~400 TB). If you use NREC machine, it’s important to not store large data or install large software to your home folder which is located on a small disk, using `/nrec/projects` space instead:

<table>
<thead>
<tr>
<th>Filesystem</th>
<th>Size</th>
<th>Used</th>
<th>Avail</th>
<th>Use%</th>
<th>Mounted on</th>
</tr>
</thead>
<tbody>
<tr>
<td>/dev/sda1</td>
<td>20G</td>
<td>9.6G</td>
<td>9.7G</td>
<td>50%</td>
<td>/</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol-comorment</td>
<td>393G</td>
<td>346G</td>
<td>28G</td>
<td>93%</td>
<td>/nrec/projects</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol_2-comorment_2</td>
<td>935G</td>
<td>609G</td>
<td>279G</td>
<td>69%</td>
<td>/nrec/space</td>
</tr>
</tbody>
</table>

Both docker and singularity were configured to avoid placing cached files into local file system. For docker this involves changing `/etc/docker/daemon.json` file by adding this:

```json
{
  "data-root": "/nrec/projects/docker_root"
}
```

(as described https://tienbm90.medium.com/how-to-change-docker-root-data-directory-89a39be1a70b; you may use `docker info` command to check the data-root)

For singularity, the configuration is described here https://sylabs.io/guides/3.6/user-guide/build_env.html and it was done for the root user by adding the following line into `/etc/environment`:

```bash
export SINGULARITY_CACHEDIR="/nrec/projects/singularity_cache"
```

Common software, such as git-lfs, is installed to `/nrec/projects/bin`. Therefore it’s reasonable for all users of the NREC comorment instance to add this folder to the path by changing `~/.bashrc` and `~/.bash_profile`:

```bash
export PATH="/nrec/projects/bin:$PATH"
```

A cloned version of comorment repositories is available here:

```
/nrec/projects/github/comorment/containers
/nrec/projects/github/comorment/reference
```

Feel free to change these folders and use `git pull / git push`. TBD: currently the folder is cloned as ‘ofrei’ user - I’m not sure if it will actually work to pull & push. But let’s figure this out.

10.3.4 Testing container builds

Some basic checks for the functionality of the different container builds are provided in `<containers>/tests/`, implemented in Python. The tests can be executed using the Pytest testing framework.

To install Pytest in the current Python environment, issue:

```bash
pip install pytest  # --user optional
```

New virtual environment using `conda`:

```
conda create -n pytest python=3 pytest -y  # creates env "pytest"
conda activate pytest  # activates env "pytest"
```

Then, all checks can be executed by issuing:
cd `<containers>`
py.test -v tests  # with verbose output

Checks for individual containers (e.g., `gwas.sif`) can be executed by issuing:

```
py.test -v tests/test_<container-prefix>.py
```

Note that the proper container files (*.sif files) corresponding to the different test scripts must exist in `<containers>/singularity/`, not only git LFS pointer files.

### 10.3.5 Git clone ignoring LFS

See stackoverflow.com/questions/42019529/how-to-clone-pull-a-git-repository-ignoring-lfs

```
GIT_LFS_SKIP_SMUDGE=1 git clone git@github.com:comorment/containers.git
```
All notable changes to this project will be documented in this file.
The format is based on Keep a Changelog, and this project adheres to Semantic Versioning.

Note that CoMorMent containers are organized using several GitHub repositories:

- https://github.com/comorment/containers - .sif files, public reference data, documentation, common scripts
- https://github.com/comorment/reference - private reference data with access restricted to CoMorMent collaborator

All of the above repositories are covered by this CHANGELOG. They will have the same version tags on github. In addition, we have repositories containing specific tools, e.g. https://github.com/comorment/HDL, which will be covered by their own CHANGELOG.md file.

To identify the version of a .sif file, run `md5sum <container>.sif` command and find the MD5 checksum in the list below. If MD5 sum is not listed for a certain release then it means that the container hasn’t been changed from the previous release.

### 11.1 [Unreleased]

#### 11.1.1 Added

- Additions go here

#### 11.1.2 Updated

- Change LDpred2 usage example to use the OpenSNP based datasets
- Bundle of sphinx documentation build updates/restructures
- Refer to the project as “COSGAP-containers”
- Minor changes to documentation + suggestion of TOC
- migrate online documentation to cosgap.readthedocs.io
- updated documentation to reflect the new project name
- added references/urls to software tables in the documentation for hello.sif and gwas.sif
11.1.3 Fixed

- Fixes go here

11.1.4 Removed

- Removed Saige support and Saige-related files

11.1.5 Misc

- Miscellaneous goes here

11.2 [1.8.1] - 2024-03-05

11.2.1 Fixed

- Fixed parsing of IID field in pheno.dict
- Fixed issue with files with different suffixes produced by plink2 for binary phenotypes in gwas.py

11.3 [1.8.0] - 2024-02-22

11.3.1 Added

- Added scripts to analyze and filter bigSNPR LD matrixes (scripts/pgs/LDpred2/analyzeLD.R, scripts/pgs/LDpred2/splitLD.R).

11.4 [1.7.2] - 2024-02-14

11.4.1 Updated

- Rebuilt r.sif container with md5sum checksum:

```
3d69fc2168ef98d1eda3da05391cd6e4 singularity/r.sif
```

11.4.2 Added

- added CC-GWAS R package to r.sif container
11.5 [1.7.1] - 2024-02-06

11.5.1 Fixed

- Fixed parsing of `--genomic-build hg18/hg38` in `ldpred2.R`

11.6 [1.7.0] - 2024-02-02

11.6.1 Added

- Added `samtools 1.19.2, bedtools 2.31.1, liftOver (latest)` to `gwas.sif` container
- Added corresponding unit tests

11.6.2 Updated

- Updated the following binaries (not listing apt package updates) in `gwas.sif` built
  - bcf tools to 1.19
  - bolt to 2.4.1
  - gcta to 1.94.1
  - gctb to 2.04.3
  - htslib to 1.19.1
  - king to 2.3.2
  - minimac4 to 4.1.6
  - plink to v1.90b7.2 64-bit (11 Dec 2023)
  - plink2 to v2.00a5.10LM 64-bit Intel (5 Jan 2024)
  - plink2_avx2 to v2.00a5.10LM AVX2 Intel (5 Jan 2024)
  - PRSice_linux to 2.3.5
  - regenie to 3.4.1
  - vcf tools to git SHA: d511f469e87c2ac9779bcdec3670b2b51667935fe (0.1.17dev)

- Rebuilt `gwas.sif` w. md5sum checksum:

```
a775f4216b15b731471821d0c2a0da43  singularity/gwas.sif
```

- updated installer scripts
11.6.3 Fixed

- Broken `docker/scripts/build_docker.sh` script

11.7 [1.6.0] - 2023-12-12

11.7.1 Added

- Added `gdb` debugger, `ldak` and `snptest` binaries to `gwas.sif` container
- Added tests for `ldak` and `snptest` binaries in `gwas.sif` container

11.7.2 Updated

- Updated `metal` to version 2020-05-05 in `gwas.sif`
- Updated `qctool` to v2.2.2 and added related binaries `inthinnerator`, `hptest`, `ldbird` and `selfmap` to `gwas.sif`
- Rebuilt `gwas.sif` (md5 checksum b6104b58d21f862f9d61a86d9d4802a6)

11.8 [1.5.1] - 2023-10-20

11.8.1 Fixed

- Fixed broken ReadTheDocs documentation build

11.9 [1.5.0] - 2023-10-17

11.9.1 Added

- Added `<containers>/scripts/pgs/pgs_toolkit`, a Python toolkit for computing PGS using LDpred2, PRSice2 or PLINK
- Added `<containers>/docker/scripts/build_docker.sh` script replacing corresponding build statement in `Makefile`
- Added test for `gcta`

11.9.2 Updated

- Updated `r.sif` build with many additional R packages, with corresponding updates to build recipes and tests
- Use `https://packagemonitor.ritter.co/cran/__linux__/focal/2023-02-16` as main R package repo
- `r.sif` md5 checksum:

```bash
1280ba24d9964d450b2e4c4a9c00587 singularity/r.sif
```

- Updated GitHub workflow versions to current versions
11.9.3 Removed

- removed logging of docker build ... in docker/Makefile (issues with piping to tee in case of build errors)

11.10 [1.4.0] - 2023-10-17

11.10.1 Added

- Added phasing/imputation tools beagle, duohmm, eagle, shapeit5, switchError, to gwas.sif container + updated tests

11.10.2 Fixed

- Fix issue that shell script wouldn’t capture failing statements

11.10.3 Updated

- Updated gwas.sif Dockerfile and installed shell scripts (misc. dependencies updates, installing gcta version 1.93.3beta2)
- Rebuilt gwas.sif using Docker --no-cache option to fix missing minimac4 binary, w. md5 checksum:

<table>
<thead>
<tr>
<th>a1dd235221902741bf5773945a584e47</th>
</tr>
</thead>
<tbody>
<tr>
<td>singularity/gwas.sif</td>
</tr>
</tbody>
</table>

11.10.4 Removed

- Removed unused install_miniconda.sh script from src/scripts folder

11.11 [1.3.9] - 2023-10-17

11.11.1 Added

- User-set directory option for temporary files during LDpred2 runs, by default base::tempdir()

11.12 [1.3.8] - 2023-10-17

11.12.1 Fixed

- Added --genomic-build hg18/hg19/hg38 option to ldpred2.R to use correct LD reference meta file pos column name
11.13 [1.3.7] - 2023-10-17

11.13.1 Added

- Added a feature to read and convert BGEN (.bgen) files to scripts/pgs/LDpred2/createBackingFile.R

11.14 [1.3.7] - 2023-10-12

- User-set directory for temporary files during LDpred2 runs, by default base::tempdir()

11.15 [1.3.6] - 2023-08-17

11.15.1 Fixed

- Ignore LDpred2 --col-bp <column> arg in case --merge-by-rsid is used

11.16 [1.3.5] - 2023-08-17

11.16.1 Updated

- Updated LDpred2 README file

11.17 [1.3.4] - 2023-06-22

11.17.1 Updated

- Update regenie to v3.2.8

11.17.2 Fixed

- #187 - Regression in gwas.py in handling of info, maf, hwe and geno filters

11.18 [1.3.3] - 2023-06-14

11.18.1 Updated

- Removed time consuming genotype missingness check from ldpred2.R.
11.19 [1.3.2] - 2023-06-12

11.19.1 Fixed

• Fixed misc. issues with cross references in online documentation

11.20 [1.3.1] - 2023-06-07

11.20.1 Added

• Added unittest for uppercase chromosome column name in sumstats files, that may also contain chromosomes encoded as character(s)

11.20.2 Fixed

• Fixed issue with character encoding in sumstats files, in case chromosome column name is uppercase.

11.21 [1.3.0] - 2023-05-19

11.21.1 Added

• Added to ldpred2.R: Multi-threading of snp_lodsc, arguments for parameters to snp_ldpred2_auto, and alternative effective sample-size calculation through --n-cases and n-controls.

11.21.2 Fixed

• Solved error due to case-sensitive handling of --col-chr in ldpred2.R and naming of diagnostic plot when using --name-score.

11.22 [1.2] - 2023-05-11

11.22.1 Added

• Added RELEASES.md file explaining steps needed to make releases.
• Added PRSice_linux to r.sif
• Added tests for gwas.py
• Added package GWASTools to r.sif.
• Added confidence intervals to qq plots created by gwas.py using GWASTools R package.
• Added status badges and citation.cff file
11.22.2 Updated

- Updated file and folder layout, fixing minor documentation issues. Moving from m2r2 to Myst-parser for Sphinx-generated online docs.
- Rebuilt the R container
  ```
  5ebfc50f96bc6b25f61858927283e2d singularity/r.sif
  ```
- Rebuilt the R container
  ```
  23d195a10b84603b15d0e8c42df40fbd singularity/r.sif
  ```

11.22.3 Fixed

- Set version file info to 1.2.dev (was 0.1.1dev)
- Fixed bad parsing of arbitrary length list of args in usecases/LDpred2/complementSumstats.R
- Made usecases/LDpred2/complementSumstats.R write output file by default, not stdout.
- Fixed ldpred2.R script in case --file-phen0/--col-phen0/--col-phen0-from-fam args were used, by removing these options altogether.
- Use packagemanager.rstudio.com/cran/linux/focal/2023-02-16 as main R package repo
- gwas.py --variance-standardize option now throws an error when applied to columns with no variance

11.22.4 Removed

- Removed redundant usecases/LDpred2_tutorial files

11.22.5 Misc

- Python code max line length of 120 chars, ignore number of newlines between functions

11.22.6 Misc

- Python code max line length of 120 chars, ignore number of newlines between functions

11.23 [1.1] - 2022-12-01

Maintenance/feature release with the following main software incorporated into each container:

<table>
<thead>
<tr>
<th>container</th>
<th>OS/tool</th>
<th>version</th>
<th>license</th>
</tr>
</thead>
<tbody>
<tr>
<td>hello.sif</td>
<td>ubuntu</td>
<td>20.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>hello.sif</td>
<td>plink</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>ubuntu</td>
<td>20.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>container</td>
<td>OS/tool</td>
<td>version</td>
<td>license</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>plink</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>plink2</td>
<td>v2.00a3.6LM 64-bit Intel (14 Aug 2022)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>plink2_avx2</td>
<td>v2.00a3.6LM AVX2 Intel (24 Jan 2020)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>PRSice_linux</td>
<td>2.3.3 (2020-08-05)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>simu_linux</td>
<td>v0.9.4</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bolt</td>
<td>v2.4 July 22, 2022</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>gcta64</td>
<td>version 1.93.2 beta Linux</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>gctb</td>
<td>2.02</td>
<td>MIT</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>qctool</td>
<td>2.0.6, revision 18b8f17</td>
<td>Boost</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>king</td>
<td>2.2.9 - ©</td>
<td>permissive</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>metal</td>
<td>version released on 2011-03-25</td>
<td>-</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>vcftools</td>
<td>0.1.17</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bcftools</td>
<td>1.12 (using htslib 1.12)</td>
<td>MIT/Expat/GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>flashpca_x86-64</td>
<td>2.0</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>regenie</td>
<td>v2.0.2.gz</td>
<td>MIT/Boost</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>GWAMA</td>
<td>2.2.2</td>
<td>BSD-3-Clause</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>minimac4</td>
<td>v4.1.0</td>
<td>GPLv3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bgenix</td>
<td>1.1.7</td>
<td>Boost</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>cat-bgen</td>
<td>same version as bgenix</td>
<td>Boost</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>edit-bgen</td>
<td>same version as bgenix</td>
<td>Boost</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>HTSlib</td>
<td>1.12</td>
<td>MIT/Expat/Modified-BSD</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>shapeit4.2</td>
<td>v4.2.2</td>
<td>MIT</td>
</tr>
<tr>
<td>python3.sif</td>
<td>ubuntu</td>
<td>20.04 (LTS)</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>python3.sif</td>
<td>python3</td>
<td>python 3.10.6 + numpy, pandas, etc.</td>
<td>PSF</td>
</tr>
<tr>
<td>python3.sif</td>
<td>LDpred</td>
<td>1.0.11</td>
<td>MIT</td>
</tr>
<tr>
<td>python3.sif</td>
<td>python_convert</td>
<td>github commit bcde562</td>
<td>GPLv3</td>
</tr>
<tr>
<td>python3.sif</td>
<td>plink</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>r.sif</td>
<td>ubuntu</td>
<td>20.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>r.sif</td>
<td>R</td>
<td>4.0.5 (2021-03-31) + data.table, ggplot, etc.</td>
<td>misc</td>
</tr>
<tr>
<td>r.sif</td>
<td>gcta64</td>
<td>version 1.93.2 beta Linux</td>
<td>GPLv3</td>
</tr>
<tr>
<td>r.sif</td>
<td>PRSice_linux</td>
<td>2.3.3 (2020-08-05)</td>
<td>GPLv3</td>
</tr>
<tr>
<td>r.sif</td>
<td>rareGWAMA</td>
<td>dajiangliu@rareGWAMA@72e962d</td>
<td>-</td>
</tr>
<tr>
<td>r.sif</td>
<td>GenomicSEM</td>
<td>GenomicSEM/GenomicSEM@bcbbaff</td>
<td>GPLv3</td>
</tr>
<tr>
<td>r.sif</td>
<td>TwoSampleMR</td>
<td>MRCIEU/TwoSampleMR@c174107</td>
<td>unknown/MIT</td>
</tr>
<tr>
<td>r.sif</td>
<td>SMR</td>
<td>v1.0.9</td>
<td>GPLv3</td>
</tr>
<tr>
<td>r.sif</td>
<td>snpStats</td>
<td>v1.40.0</td>
<td>GPLv3</td>
</tr>
<tr>
<td>saige.sif</td>
<td>ubuntu</td>
<td>16.04</td>
<td>Creative Commons CC-BY-SA version 3.0 UK licence</td>
</tr>
<tr>
<td>saige.sif</td>
<td>SAIGE</td>
<td>version 0.43</td>
<td>GPLv3</td>
</tr>
</tbody>
</table>

Main changes since release version 1.0.0:
11.23.1 Added

- add option to append usecases/LDpred2/ldpred.R score output to an existing file
- add script usecases/LDpred2/complementSumstats.R to append chromosome and position to summary statistics
- add polygenic score output tests for usecases/LDpred2/ldpred.R
- add usecases/LDpred2/imputeGenotypes.R for imputing genotypes using R-package bigSNPR
- add usecases/LDpred2/calculateLD.R for calculation LD using R-package bigSNPR.
- add autobuilt online documentation from repository sources at https://comorment-containers.readthedocs.io/en/latest/
- add R libraries for LDpred2 analysis to r.sif + corresponding example.
- add tests for metal and qctool in gwas.sif build
- add basic GitHub actions from https://github.com/precimed/container_template.git
- add FaST-LMM (version 0.6.3) to future python3.sif, and corresponding test
- add shapeit4.2 binary (shapeit4 v.4.2.2) and HTSlib (1.11) to future gwas.sif builds, and corresponding test
- add additional tests for software in gwas.sif, python3.sif builds
- add versions identifiers for all explicitly installed software across hello.sif, gwas.sif, python3.sif, r.sif, listed in docker/README.md
- replaced Ubuntu 18.04 with 20.04 (LTS) as base image for hello.sif, gwas.sif, python3.sif
- replaced src/scripts/install_miniconda3.sh by scr/scripts/install_mambaforge.sh which is now used in future python3.sif builds
- add tests for bgenix and Minimac4 software in gwas.sif, removing build-time dependencies for these from container
- add basic test that KING software runs in gwas.sif
- add Dockerfiles and install scripts for gwas.sif, hello.sif, python3.sif, r.sif, saige.sif from gwas.
- add CHANGELOG.md (this file)
- add gwas.py --analysis saige option, allowing to run SAIGE analysis
- add gwas.py --analysis figures option, using R qqman for QQ and manhattan plots
- add gwas.py --pheno-sep and --dict-sep options to specify delimiter for the phenotype file and phenotype dictionary file
- add package qqman to r.sif
- add package yaml to python3.sif
- add gctb_2.0_tutorial.zip reference files under reference/examples/gctb_2.0_tutorial
- add config.yaml file with configuration options, which can be specified via gwas.py --config option
- add --chunk-size-bp and --bim option, allowing to run SAIGE analysis in smaller chunks
- add --keep and --remove options to gwas.py, allowing to keep and remove subsets of individuals from analysis; the functions work similarly to plink2 as described here.
11.23.2 Updated

- rebuilt the following containers following version pinning in Dockerfiles, install scripts, etc. (see above additions):

```
bb7a8e0b977e29e03067d75d19803913 singularity/gwas.sif
11ac9e8fe69df07d650bd5e17cdee5 singularity/hello.sif
c78d57397471ee802d37837ca5f8b797 singularity/python3.sif
e8f26b23a8b44f15f3daf2b02623780 singularity/r.sif
a3fd8411e13cf8670551b7f334a58d singularity/saige.sif
```

11.23.3 Fixed

- usecases/LDpred2/ldpred2.R error when sumstats contain characters in chromosome column.
- use `afterok` spec instead of `afterany` in SLURM dependencies so that next steps of the pipeline don’t run if a previous step has failed (fix #26)
- use SLURM’s `cpus_per_task=1` for SAIGE step2, because it doesn’t support –nThreads (see https://github.com/saigegit/SAIGE/issues/9)

11.23.4 Removed

- removed misc. source/data files in `/tools/*` from container builds
- removed unused `libquadmath0` library from builds (affecting future `gwas.sif`, `hello.sif`, and `python3.sif` builds)
- the following command-line options are removed; instead, they can be specified via config. `yaml` file: `--slurm-job-name`, `--slurm-account`, `--slurm-time`, `--slurm-cpus-per-task`, `--slurm-mem-per-cpu`, `--module-load`, `--comorment-folder`, `--singularity-bind`. Note that `config.yaml` file is now required.
- `gwas.py --analysis loci manh qq` options as removed (fix #22)
- `--bed-fit`, `--bed-test`, `--bgen-fit`, `--bgen-test` options of `gwas.py` are removed; use new options `--geno-fit-file` and `--geno-file` instead
- remove `regenie.sif` and `regenie3.sif`, because regenie software is also included in `gwas.sif`
- remove MiXeR package from `python3.sif` container, because MiXeR is now available as a separate container (https://github.com/comorment/mixer). This is also where you will find MiXeR’s use-cases.
- MAGMA, LAVA and ldblock software is moved to https://github.com/comorment/magma. MAGMA reference files are also moved to this repository.
- `enigma-cnv.sif` and `enigma-cnv.sif` is moved to https://github.com/comorment/iPsychCNV enigma-cnv.sif is also available here: in https://github.com/ENIGMA-git/ENIGMA-CNV/tree/main/CNVCalling/containers
- `tryggve_query.sif` is moved to https://github.com/comorment/Tryggve_psych
- `matlabruntime.sif` container is moved to https://github.com/comorment/matlabruntime. pleioFDR reference files are also moved to this repository.
11.24 [1.0.0] - 2020-10-20

11.24.1 Added

- initial release of the following containers:

<table>
<thead>
<tr>
<th>container</th>
<th>tool</th>
<th>version</th>
</tr>
</thead>
<tbody>
<tr>
<td>enigma-cnv.sif</td>
<td>plink</td>
<td>v1.90b6.18 64-bit (16 Jun 2020)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>plink2</td>
<td>v2.00a2.3LM 64-bit Intel (24 Jan 2020)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>plink2_avx2</td>
<td>v2.00a2.3LM AVX2 Intel (24 Jan 2020)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>PRSice_linux</td>
<td>2.3.3 (2020-08-05)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>simu_linux</td>
<td>Version v0.9.4</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bolt</td>
<td>v2.3.5 March 20, 2021</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>gcta64</td>
<td>version 1.93.2 beta Linux</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>gctb</td>
<td>GCTB 2.02</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>qctool</td>
<td>version: 2.0.6, revision 18b8f17</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>king</td>
<td>KING 2.2.6 - ©</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>metal</td>
<td>version released on 2011-03-25</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>vcftools</td>
<td>VCFtools (0.1.17)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bcftools</td>
<td>Version: 1.12 (using htslib 1.12)</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>flashpca_x86-64</td>
<td>flashpca 2.0</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>regenie</td>
<td>REGENIE v2.0.2.gz</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>GWAMA</td>
<td>GWAMA_v2.2.2.zip</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>magma</td>
<td>magma_v1.09a_static.zip</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>shapeit2</td>
<td>Version: v2.904</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>impute4</td>
<td>impute4.1.2_r300.3</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>minimac4</td>
<td>Version: 1.0.2; Built: Fri Sep 3 13:25:51</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>bgenix</td>
<td>version: 1.1.7, revision</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>cat-bgen</td>
<td>same version as bgenix</td>
</tr>
<tr>
<td>gwas.sif</td>
<td>edit-bgen</td>
<td>same version as bgenix</td>
</tr>
<tr>
<td>python3.sif</td>
<td>python3</td>
<td>python 3.10 + standard packages (numpy, pandas, etc)</td>
</tr>
<tr>
<td>python3.sif</td>
<td>ldpred</td>
<td>?</td>
</tr>
<tr>
<td>python3.sif</td>
<td>mixer</td>
<td>mixer v1.3</td>
</tr>
<tr>
<td>python3.sif</td>
<td>python_convert</td>
<td>github commit bcede562f0286f3f271dbb54d486d4ca1d40ae36</td>
</tr>
<tr>
<td>r.sif</td>
<td>R</td>
<td>version 4.0.3 + standard packages (data.table, ggplot, etc)</td>
</tr>
</tbody>
</table>

Here is the list of tools available in prebuilt containers:
<table>
<thead>
<tr>
<th>container</th>
<th>tool</th>
<th>version</th>
</tr>
</thead>
<tbody>
<tr>
<td>r.sif</td>
<td>seqminer</td>
<td>?</td>
</tr>
<tr>
<td>r.sif</td>
<td>rareGWAMA</td>
<td>?</td>
</tr>
<tr>
<td>r.sif</td>
<td>GenomicSEM</td>
<td>?</td>
</tr>
<tr>
<td>r.sif</td>
<td>TwoSampleMR</td>
<td>?</td>
</tr>
<tr>
<td>r.sif</td>
<td>GSMR</td>
<td>v1.0.9</td>
</tr>
<tr>
<td>r.sif</td>
<td>LAVA</td>
<td>?</td>
</tr>
<tr>
<td>r.sif</td>
<td>LAVA partitioning</td>
<td>?</td>
</tr>
<tr>
<td>saige.sif</td>
<td>SAIGE</td>
<td>version 0.43</td>
</tr>
<tr>
<td>enigma-cnv.sif</td>
<td>PennCNV</td>
<td>version 1.0.5</td>
</tr>
<tr>
<td>ldsc.sif</td>
<td>LDSC</td>
<td>version 1.0.1</td>
</tr>
<tr>
<td>ipsychcnv.sif</td>
<td>???</td>
<td>missing Dockerfile</td>
</tr>
<tr>
<td>matlabruntime.sif</td>
<td>???</td>
<td>work in progress</td>
</tr>
<tr>
<td>regenie.sif</td>
<td>???</td>
<td>?</td>
</tr>
<tr>
<td>regenie3.sif</td>
<td>???</td>
<td>?</td>
</tr>
</tbody>
</table>
12.1 Docker

Build recipes for containers using Docker and Singularity.

12.1.1 Software versions

Please confer and update accordingly the software version tables in the respective singularity files for each container.

12.1.2 Feedback

If you face any issues, or if you need additional software, please let us know by creating an issue.

12.1.3 Note about NREC machine

We use NREC machine to develop and build containers. NREC machine has small local disk (~20 TB) and a larger external volume attached (~400 TB). If you use NREC machine, it’s important to not store large data or install large software to your home folder which is located on a small disk, using /nrec/projects space instead:

<table>
<thead>
<tr>
<th>Filesystem</th>
<th>Size</th>
<th>Used</th>
<th>Avail</th>
<th>Use%</th>
<th>Mounted on</th>
</tr>
</thead>
<tbody>
<tr>
<td>/dev/sda1</td>
<td>20G</td>
<td>9.6G</td>
<td>9.7G</td>
<td>50%</td>
<td>/</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol-comorment</td>
<td>393G</td>
<td>346G</td>
<td>28G</td>
<td>93%</td>
<td>/nrec/projects</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol_2-comorment_2</td>
<td>935G</td>
<td>609G</td>
<td>279G</td>
<td>69%</td>
<td>/nrec/space</td>
</tr>
</tbody>
</table>

Both docker and singularity were configured to avoid placing cached files into local file system. For docker this involves changing /etc/docker/daemon.json file by adding this:

```json
{
    "data-root": "/nrec/projects/docker_root"
}
```

(as described https://tienbm90.medium.com/how-to-change-docker-root-data-directory-89a39be1a70b ; you may use docker info command to check the data-root)

For singularity, the configuration is described here https://sylabs.io/guides/3.6/user-guide/build_env.html and it was done for the root user by adding the following line into /etc/environment

---

CHAPTER

TWELVE

INTERNAL USAGE

Miscellaneous notes for internal usage.

12.1 Docker

Build recipes for containers using Docker and Singularity.

12.1.1 Software versions

Please confer and update accordingly the software version tables in the respective singularity files for each container.

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<table>
<thead>
<tr>
<th>Filesystem</th>
<th>Size</th>
<th>Used</th>
<th>Avail</th>
<th>Use%</th>
<th>Mounted on</th>
</tr>
</thead>
<tbody>
<tr>
<td>/dev/sda1</td>
<td>20G</td>
<td>9.6G</td>
<td>9.7G</td>
<td>50%</td>
<td>/</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol-comorment</td>
<td>393G</td>
<td>346G</td>
<td>28G</td>
<td>93%</td>
<td>/nrec/projects</td>
</tr>
<tr>
<td>/dev/mapper/nrec_extvol_2-comorment_2</td>
<td>935G</td>
<td>609G</td>
<td>279G</td>
<td>69%</td>
<td>/nrec/space</td>
</tr>
</tbody>
</table>

Both docker and singularity were configured to avoid placing cached files into local file system. For docker this involves changing /etc/docker/daemon.json file by adding this:

```json
{
    "data-root": "/nrec/projects/docker_root"
}
```

(as described https://tienbm90.medium.com/how-to-change-docker-root-data-directory-89a39be1a70b ; you may use docker info command to check the data-root)

For singularity, the configuration is described here https://sylabs.io/guides/3.6/user-guide/build_env.html and it was done for the root user by adding the following line into /etc/environment

---

CHAPTER

TWELVE

INTERNAL USAGE

Miscellaneous notes for internal usage.

12.1 Docker

Build recipes for containers using Docker and Singularity.

12.1.1 Software versions

Please confer and update accordingly the software version tables in the respective singularity files for each container.

12.1.2 Feedback

If you face any issues, or if you need additional software, please let us know by creating an issue.

12.1.3 Note about NREC machine

We use NREC machine to develop and build containers. NREC machine has small local disk (~20 TB) and a larger external volume attached (~400 TB). If you use NREC machine, it’s important to not store large data or install large software to your home folder which is located on a small disk, using /nrec/projects space instead:

<table>
<thead>
<tr>
<th>Filesystem</th>
<th>Size</th>
<th>Used</th>
<th>Avail</th>
<th>Use%</th>
<th>Mounted on</th>
</tr>
</thead>
<tbody>
<tr>
<td>/dev/sda1</td>
<td>20G</td>
<td>9.6G</td>
<td>9.7G</td>
<td>50%</td>
<td>/</td>
</tr>
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<td>/dev/mapper/nrec_extvol-comorment</td>
<td>393G</td>
<td>346G</td>
<td>28G</td>
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<td>/nrec/projects</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Both docker and singularity were configured to avoid placing cached files into local file system. For docker this involves changing /etc/docker/daemon.json file by adding this:

```json
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}
```

(as described https://tienbm90.medium.com/how-to-change-docker-root-data-directory-89a39be1a70b ; you may use docker info command to check the data-root)

For singularity, the configuration is described here https://sylabs.io/guides/3.6/user-guide/build_env.html and it was done for the root user by adding the following line into /etc/environment

---
Common software, such as git-lfs, is installed to /nrec/projects/bin. Therefore it's reasonable for all users of the NREC comorment instance to add this folder to the path by changing ~/.bashrc and ~/.bash_profile.

```
export PATH="/nrec/projects/bin:$PATH"
```

A cloned version of comorment repositories is available here:

```
/nrec/projects/github/comorment/containers
/nrec/projects/github/comorment/reference
```

Feel free to change these folders and use git pull / git push. TBD: currently the folder is cloned as ‘ofrei’ user - I’m not sure if it will actually work to pull & push. But let’s figure this out.

### 12.1.4 Testing container builds

Some basic checks for the functionality of the different container builds are provided in `<containers>/tests/`, implemented in Python. The tests can be executed using the Pytest testing framework.

To install Pytest in the current Python environment, issue:

```
pip install pytest  # --user optional
```

New virtual environment using conda:

```
conda create -n pytest python=3 pytest -y  # creates env "pytest"
conda activate pytest  # activates env "pytest"
```

Then, all checks can be executed by issuing:

```
cd <containers>
py.test -v tests  # with verbose output
```

Checks for individual containers (e.g., gwas.sif) can be executed by issuing:

```
py.test -v tests/test_<container-prefix>.py
```

Note that the proper container files (*.sif files) corresponding to the different test scripts must exist in `<containers>/singularity/`, not only git LFS pointer files.

### 12.1.5 Git clone ignoring LFS

See stackoverflow.com/questions/42019529/how-to-clone-pull-a-git-repository-ignoring-lfs

```
GIT_LFS_SKIP_SMUDGE=1 git clone git@github.com:comorment/containers.git
```
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