Calculating Risk using Open Mendel

Presented on behalf of the Open Mendel Project Team
by Janet Sinsheimer PhD
David Geffen School of Medicine at UCLA

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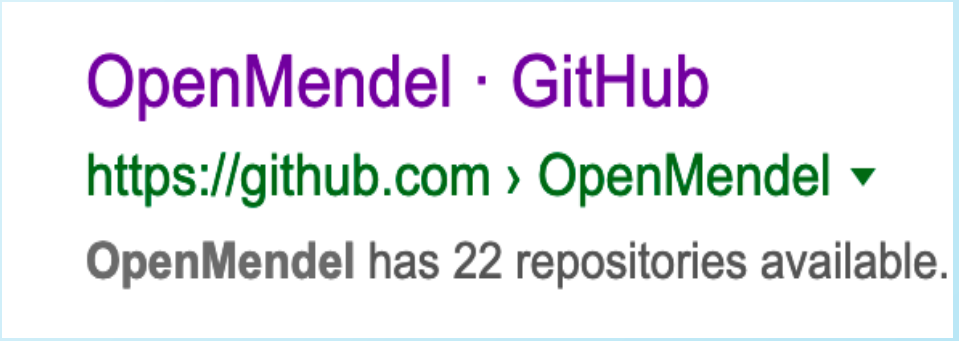
Pre-Workshop Preparation?

- Installed Julia and Open Mendel including MendelGeneticCounseling?
- If not, pair up with another who didn't have a chance
- On one computer go to: https://github.com/OpenMendel
- Or google:
- Github OpenMendel

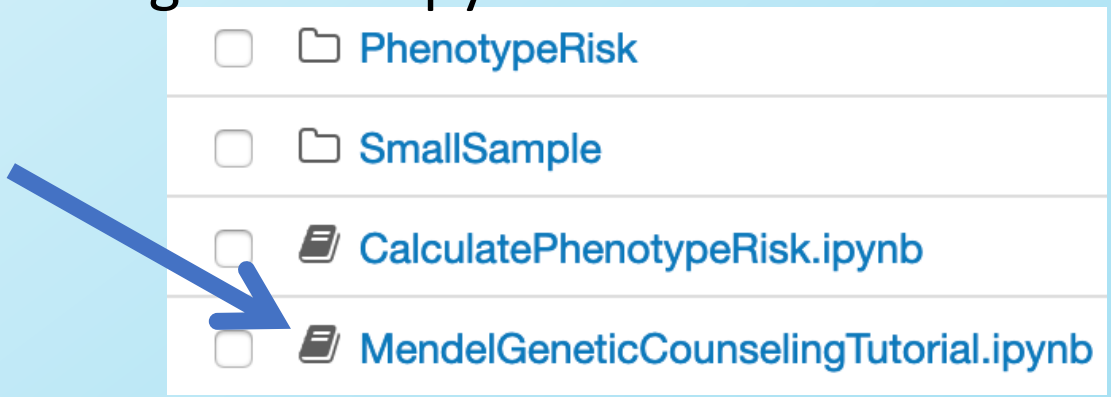


Click on **GeneticCounseling_ASHG2019**

- Go to the bottom of the webpage and click on

To Run the Tutorial

- **If you have installed Open Mendel:**
  - Launch Julia 1.2 by clicking on the app
  - Type “using IJulia”
  - Type “notebook()”
  - Go to the resulting webpage and drill down to the directory with the jupyter notebooks for this tutorial
  - Click MendelGeneticCounselingTutorial.ipynb
- **Or when Binder has Launched**
  - Click MendelGeneticCounselingTutorial.ipynb



While Binder launches – A little Background on the Open Mendel Project

- Goal: Interactive, interpretable statistical genetics software that scales to big data and aids in reproducible research.
- Started in 2016 by Profs. Kenneth Lange, Janet Sinsheimer, Eric Sobel, Jin Zhou and Hua Zhou
  - Major contributors: students, postdoctoral scholars and faculty at Jilin U., NC State, Seoul National U., U. Arizona, UCLA, UCSF, U. Wisconsin.
- Written in Julia - new computing language that "walks like python, runs like C". (https://opensourceforu.com/2016/10/julia-language/). Solves the two language problem, i.e. easily scales to big data.
- Open Mendel team want suggestions for improvements/ additions and more collaborators.
- See: H.Zhou et al. (2019) OpenMendel: a cooperative programming project for statistical genetics. *Human Genetics*.

Today's Tutorial Features MendelGeneticCounseling.jl

- See Open Mendel github site for tutorials of other modules.
- Today: How to calculate genetic risks for individuals using their family histories and covariate information via a likelihood approach to form conditional probabilities.
- MendelGeneticCounselingTutorial.ipynb, has more details and background material.
  - The version you are running is beta and should be used for research purposes only.

General Idea for Today's Tutorial:

- Assumes a single family of interest with a underlying and possibly unmeasured trait locus.
- Use already determined penetrance parameters to calculate the conditional probability that a particular individual has a heterozygous genotype given their risk factors and their families phenotypes and risk factors can include linked genetic markers.
- Conditional probability: $P(H|D) = \frac{L(H \cap D)}{L(D)}$
- where H is the individual's underlying genotype and D is all the other data (individual and family).
- Two copies of the pedigree in the pedigree file, one to calculate numerator and one to calculate denominator.

Today's Tutorial has two examples

- Example 1:
  - Uses one of the available generalized linear models, the Gamma distribution, with the link function = log.
  - Parameters estimated using MendelEstimatePenetrances.jl
  - The pedigree and cholesterol phenotypes: Schrott et al. (1972) Ann Int Med 76:711–720.
  - Determine the risk that a child (IV11) of a women with abnormally high cholesterol has a heterozygous genotype.
- Example 2:
  - Uses a penetrance file where values are stratified by sex and age.
  - The pedigree and penetrance are for BRCA1 and breast cancer and come from analyze.myvariant.org
  - Determine how probable a currently unaffected 38 year old woman (individual 18) has a heterozygous genotype.

To Run The Tutorial

- If you have installed Open Mendel:
  - Click on Julia 1.2 app
  - Type “using IJulia”
  - Type “notebook()”
  - Go to webpage and drill down to the directory with the jupyter notebooks for this tutorial
  - Click on MendelGeneticCounselingTutorial.ipynb
- If you are using Binder
  - Click on the MendelGeneticCounselingTutorial.ipynb
- **When Finished: go to File Tab and select Close and Halt**
- If extra time click on CalculatePhenotypeRisk.ipynb

Learning more about Julia and Open Mendel

On line Julia tutorials

- For Julia beginners:

https://www.youtube.com/watch?v=8h8rQyEpiZA&t=

- Links some other good online tutorials.

https://julialang.org/learning/

- statistical computing in Julia, see Prof. Hua Zhou lecture notes:

http://hua-zhou.github.io/teaching/biostatm280-2019spring/schedule.html

Open Mendel

https://github.com/OpenMendel

- Come to an Open Mendel workshop
- Wellcome course: “Genetic Analysis of Mendelian and Complex Disorders uses Open Mendel” as well as other statistical analysis programs.

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MendelGeneticCounseling ASHG Pre Workshop Installation and Checks

last update: September 18 2019, 4:09pm

As of the time of the last update to this tutorial, `Open Mendel` supports Julia versions 1.0, 1.1 and 1.2, but it is currently an unregistered package.

Download files

Download the datasets BRCA, Cholesterol and SmallSample from https://github.com/OpenMendel/GeneticCounseling_ASHG2019 (https://github.com/OpenMendel/GeneticCounseling_ASHG2019)

How to execute commands in the Jupyter notebook:'

To execute a notebook command, hold down`Shift Enter` within the box. This tutorial and corresponding modules have been checked with Julia versions 1.0, 1.1 and 1.2.

For convenience, have this notebook (OpenMendel_Instructions.ipynb) in the directory SmallSample.

NOTE: When Finished with this notebook. Go to the File tab and first select save and checkpoint to save your results. Then under the file tab, select close and halt to prevent copies of Jupyter notebook from running indefinitely in the background.

To install, press `]` to invoke the package manager mode and install these packages by typing:

```
add https://github.com/OpenMendel/SnpArrays.jl
add https://github.com/OpenMendel/MendelSearch.jl
add https://github.com/OpenMendel/MendelBase.jl
add https://github.com/OpenMendel/MendelGeneticCounseling.jl#ASHG2019
build SpecialFunctions
```

Check Julia version:

For reproducibility, check the machine information below. Please report any issues running this notebook or the module to Janet Sinsheimer PhD. (jsinshei@g.ucla.edu).

In [ ]:
```
versioninfo()
```

It is a good idea update all packages before running any analyses

In [ ]:
```
] update
```

Run a simple analysis to determine if MendelGeneticCounseling has been correctly installed.

We will now show how to set up the specific files and the options available as well as how to interpret the results during the workshop so we won't go over that information here.

Instead we will run a classic example of determining the risk of a fully penetrant disease for an individual just to make sure you can run the Open Mendel during the workshop. Make certain necessary files are available. You can invoke a shell on the mac using ";" and then typing the appropriate shell command but you can also use Julia commands.

In [ ]:
```
# Verify that you are in the appropriate directory
# ; pwd
pwd()
```

The files required for our test are PedSmall.csv, PhenoSmall.txt, LocusSmall.txt, and ControlSmallParametric.txt. If they aren't in your current directory, either move to the directory where the files are located or copy your files into the current working diretory.

If you need to change to another directory you can using the cd() command within Julia

In [ ]:
```
# on PC use "\\" instead of "\" e.g.
# cd("C:\\Users\\Janet Sinsheimer\\Documents\\Julia_files\\GeneticCounseling_ASHG2019-master")
# on Mac, the equivalent command is:
cd("/Users/janets/Documents/lap_top_janet/janet/short_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master")
```

If you needed to change directories, verify that you are indeed in the right directory using pwd() and readdir()

In [ ]:
```
pwd()
```

In [ ]:
```
readdir()
```

Now you can test the installation by running MendelGeneticCounseling. First load the module

In [ ]:
```
using MendelGeneticCounseling
```

Now run the sample files

In [ ]:
```
GeneticCounseling("ControlSmallParametric.txt")
```

Results

You should get a file with the results as well as seeing results displayed above. The correct answer is `0.03892`. If you fail to get this answer, don't get any output, or get error messages, please contact Janet Sinsheimer at jsinshei@g.ucla.edu.

NOTE: When Finished with this notebook. Go to the File tab and first select save and checkpoint to save your results. Then under the file tab, select close and halt to prevent copies of Jupyter notebook from running indefinitely in the background

MendelGeneticCounseling ASHG Workshop

last update: October 12 2019, 8pm.

The purpose of this tutorial is to demonstrate how to calculate genetic risks for individuals using their family histories and covariate information.

Installation instructions (not needed during workshop)

`MendelGeneticCounseling.jl#ASHG2019` currently supports Julia versions 1.0, 1.1 and 1.2, but it is currently an unregistered package. To install, press `]` to invoke the package manager mode and install these packages by typing:

```
add https://github.com/OpenMendel/SnpArrays.jl
add https://github.com/OpenMendel/MendelSearch.jl
add https://github.com/OpenMendel/MendelBase.jl
add https://github.com/OpenMendel/MendelGeneticCounseling.jl#ASHG2019
build SpecialFunctions
```

Be sure also to download the BRCA and Cholesterol data from https://github.com/OpenMendel/GeneticCounseling_ASHG2019 (https://github.com/OpenMendel/GeneticCounseling_ASHG2019).

NOTE: When finished with this notebook, go to the File tab and first select save and checkpoint to save your results. Then under the file tab, select close and halt to prevent copies of Jupyter notebook from running indefinitely in the background.

Navigating a Jupyter Notebook

The jupyter notebook has a menu with tabs. You can use them to insert or delete cells, change cells from coding to markdown, move up or down the notebook, and to save your notebook. For example, pressing the + button adds a new cell and the scissors deletes a cell.

Check Julia version:

For reproducibility, check the machine information below. To execute a notebook command, hold down`Shift Enter` within the box. This tutorial and corresponding modules have been checked with Julia versions 1.0, 1.1 and 1.2. Please report any issues running the tutorial or the module to Janet Sinsheimer PhD. (jsinshei@g.ucla.edu).

In [1]:
```
versioninfo()
```

```
Julia Version 1.2.0
Commit c6da87ff4b (2019-08-20 00:03 UTC)
Platform Info:
  OS: macOS (x86_64-apple-darwin18.6.0)
  CPU: Intel(R) Core(TM) i7-6567U CPU @ 3.30GHz
  WORD_SIZE: 64
  LIBM: libopenlibm
  LLVM: libLLVM-6.0.1 (ORCJIT, skylake)
```

It's a good idea to check for updates although it can take time so don't do so during the workshop. In the future remove "#" to run.

In [ ]:
```
# ] update
```

When to use MendelGeneticCounseling

`MendelGeneticCounseling.jl` is capable of calculating the risk of an underlying genotype (e.g. Homozygous_Normal, Heterozygous, Homozygous_Mutant) given a family history and individual risk factors including closely linked genetic markers. It can use parametric models or a penetrance file.

Example 1 uses a parametric model. The parametric models are currently restricted to the following generalized linear model distributions, binomial, exponential, gamma, inverse gaussian, logistic, lognormal, negative binomial, Poisson, and of course, the normal distributions but more distributions can be added to the `apply_dist.jl` function. The inverse link functions available are for the links: log, logit, cauchit, complementary log log, inverse (1/x), probit, and square root. A more experienced user can add more models to `apply_inverse_link_new.jl`. We will be adding the capability to run censored survival models soon.

`MendelGeneticCounseling.jl` is also capable of using a penetrance file that provides the probability that an individual is affected conditional their genotype and risk factors (Example 2).

This module is a prototype and features will be added. Currently we are working on models that can handle censoring, data in snp binary or vcf files, and mutation at the risk locus.

Check working directory. For convenience have the julia notebook in the same directory as your files.

In [2]:
```
pwd()
```

Out[2]:
```
"/Users/janets/Documents/lap_top_janet/janet/short_courses_2019/ASHGproposal/Gen
eticCounseling_ASHG2019-master10062019"
```

In [ ]:
```
#If you need to change directories you can use cd(). The exact syntax depends on w
hether you are using a Mac or a PC (windows).

#For the Mac an example is:  cd("/Users/janets/GeneticCounseling/Chol")

#For the PC, an example is: cd("C:\\Users\\Janet Sinsheimer\\Documents\\Julia_file
s")
```

Analysis keywords needed for a glm penetrance function.

Keyword	Default Value	Allowed value	Description
glm_mean	0.0	symbolic expression	provides the form of x^b
glm_response	"Normal"	GLM distribution	One of the following distribution choices: Binomial, exponential, gamma, inverse Gaussian, logistic, lognormal, negative binomial, Poisson, normal
glm_link	"IdentityLink"	Inverse Link Function for the appropriate GLM link	CauchitLink,CloglogLink, IdentityLink, InverseLink, LogitLink, LogLink, ProbitLink, Sqrt
glm_trait	Affected	String	Defines the column in the pedigree file that contains the trait phenotype when using a glm for the penetrance. Note: Individuals' values must be quantitative at this time
glm_scale	1.0	Positive real number	measure of the spread of the trait - in the case of the normal distribution, the standard deviation
glm_trials	1	Positive Integer	For logistic regression glm_trials = 1

Analysis keywords if using a penetrance file

Keyword	Default Value	Allowed value	Description
disease_status	""	String	Defines the column in the pedigree file that contains the trait phenotype when including a penetrance file. Values affected = 1, unaffected = 0, unknown = -1
penetrance_file	""	String	The absence of a penetrance file automatically results in a parametric penetrance file. The presence of a penetrance file results in discrete, user defined values based on risk classes

Analysis keywords - input and output common to both options.

Keyword	Default Value	Allowed value	Description
locus_file	""	String	Provides the population specific locus names, allele names and allele frequencies
output_file	Mendel_Output.txt	String	OpenMendel generated output file with table of kinship coefficients
pedigree_file	""	String	Numerator and Denominator pedigree
phenotype_file	""	String	provides genetic model for the underlying genetic locus

A list of OpenMendel keywords common to most analysis package can be found here (https://openmendel.github.io/MendelBase.jl/#keywords-table)

Example 1: Probability that an individual is heterozygous given pedigree and covariate information.

Using a gamma distribution to model the penetrance

Data used in Example 1:

The input files for all examples in this tutorial can be obtained from https://github.com/OpenMendel/GeneticCounseling_ASHG2019 (https://github.com/OpenMendel/GeneticCounseling_ASHG2019)

The data are from an example pedigree used in the Mendel version 16.0 release. The pedigree structure and phenotypes are originally from Schrott et al. (1972) Ann Int Med 76:711–720. We have used the pedigree to provide a slightly contrived example in which Mother III13, who has cholesterol value 440 at age 21 is concerned that her young son might also be affected with extreme hypercholesterolemia. This first analysis calculates the probability that person IV11 has a heterozygous genotype given his covariates and their relatives' information.

Step 1: Examine the pedigree file:

Recall what is needed in a valid pedigree structure (https://openmendel.github.io/MendelBase.jl/#pedigree-file).

'MendelGeneticCounseling.jl' calculates the conditional probability of an individual being affected given the pedigree information by calculating the joint probability of the family and the individual's affection status (numerator pedigree) divided by the probability of the family (denominator pedigree). Accordingly the user needs to provide the program with a pedigree file with a numerator pedigree that includes the genotype of the individual of interest and the denominator pedigree doesn't. In our example we have named the pedigrees Top and Bottom but the choice of two names is left to the user as long as they are distinct.

If you like using the terminnal on the Mac you can do so without leaving the notebook by typing ";". On a Mac you can view the pedigree file by typing "; cat PedChol.csv"

Here however we will use Julia commands that will work for both the Mac and the PC. The command readlines displays the contents of a file.

```
In [3]: readlines("Cholestrol/PedChol.csv")
```

```
Out[3]: 219-element Array{String,1}:
 "Pedigree,Person,Father,Mother,Sex,HC,Age ,lnChol,Chol,High_Chol"
 "  TOP ,  III11   ,  II2     ,  II1     ,2,,22,6.39,595,1"
 "  TOP ,  II16    ,  I2      ,  I1      ,1,,38,6.17,479,1"
 "  TOP ,  III56   ,  II19    ,  II18    ,2,,4,6.12,454,1"
 "  TOP ,  II18    ,  I2      ,  I1      ,2,,36,6.1,448,1"
 "  TOP ,  III13   ,  II2     ,  II1     ,2,,21,6.09,440,1"
 "  TOP ,  III50   ,  II16    ,  II17    ,2,,10,6.07,433,1"
 "  TOP ,  III7    ,  II2     ,  II1     ,1,,26,6.05,425,1"
 "  TOP ,  III1    ,  II2     ,  II1     ,1,,31,6.05,422,1"
 "  TOP ,  II29    ,  I2      ,  I1      ,1,,27,6.03,416,1"
 "  TOP ,  III58   ,  II20    ,  II21    ,1,,6,6.02,413,1"
 "  TOP ,  III55   ,  II19    ,  II18    ,1,,10,6.02,412,1"
 "  TOP ,  III15   ,  II2     ,  II1     ,1,,20,5.97,391,1"
 ⋮
 "BOTTOM,  III67   ,  II32    ,  II33    ,1,,2,5.08,160,0"
 "BOTTOM,  II8     ,,,2,,38,5.03,153,0"
 "BOTTOM,  II33    ,,,2,,19,4.97,144,0"
 "BOTTOM,  I1      ,,,2,,62,NA,NA,NA"
 "BOTTOM,  II1     ,  I2      ,  I1      ,2,,38,NA,NA,NA"
 "BOTTOM,  II10    ,,,1,,38,NA,NA,NA"
 "BOTTOM,  II26    ,,,1,,28,NA,NA,NA"
 "BOTTOM,  II5     ,  I2      ,  I1      ,1,,41,NA,NA,NA"
 "BOTTOM,  II7     ,  I2      ,  I1      ,1,,38,NA,NA,NA"
 "BOTTOM,  II9     ,  I2      ,  I1      ,2,,38,NA,NA,NA"
 "BOTTOM,  III14   ,,,1,,21,NA,NA,NA"
 "BOTTOM,  III30   ,,,1,,20,NA,NA,NA"
```

The top line provides the column names. The first 5 columns indicate the necessary pedigree information including sex. The 6th column label, HC, is the risk locus genotype, which is unknown for most individuals. The 7th column label, Age, is age in years. The 8th column label, lnChol, is log base e of the cholesterol value, the 9th column label, Chol, is total cholesterol in mg/dl, and 10th column label is a dichotomize trait where total cholesterol greater than or equal to 225 is denoted as 1 for affected and less than 225 is denoted as 0. Missing values are denoted as NA.

If you examine the file carefully you will see that all the information in the numerator pedigree is repeated in the denominator pedigree except that we specify individual IV11's genotype in the numerator pedigree but not the denominator pedigree. The likelihood of the numerator pedigree divided by the likelihood of denominator pedigree gives us $P(G_{IV11} = 1/2|\mathbf{G, Chol, Age, Sex})$, the "risk."

Step 2: Examine the control file

A control file gives specific instructions to `MendelGeneticCounseling`. We specify the dependent variable with the keyword `glm_trait`=Chol. The trait name must correspond exactly to the column name in the pedigree file.

In this example we treat the cholesterol values, which are highly right tailed, as gamma distributed. This information is specified by the keyword `glm_response` = GammaDist and `glm_link`= LogLink.

The glm_mean is the linear equation, $x^t b$.

Specifically, $f(y) = (\frac{\sigma}{\mu})^{\sigma} \frac{y^{\sigma-1} e^{\frac{-\sigma y}{\mu}}}{\Gamma(\mu)}$ where the scale $\sigma = 44.68$ and the mean, $\mu = g(x^t p) = e^{(4.691+0.562(\max(allele1,allele2))+0.00194Age+0.036Sex)}$ and g is the exponential function which is the inverse link function for $\ln$. Note that allele1/allele2 represents the current genotype presented to the penetrance function.

We specify the "normal allele" as 1 and the "mutant allele" as 2 according to their order of appearance in the locus file. By using the expression $\max(allele1, allele2)$, we are specifying that genotype $1/1$ adds 0.562, and genotype $1/2$ or $2/2$ adds 1.124 to $\ln \mu$. In other words, we are modeling the locus as dominant. Sex is coded here as 1 for males and 2 for females. Male adds 0.036 to and female adds 0.072 to $\ln \mu$. Age is measured in years; each year adds 0.00194 to $\ln \mu$. Thus a 50 year old female with genotype $1/1$ has an expected cholesterol value of $e^{(4.691+0.562+0.00194(50)+0.036(2))} = 226.3$.

The keyword `glm_trials` is ignored in this analysis. It is used when running logistic regression mean models, where `glm_response` = BinomialDist and `glm_link` = LogitLink, binomial and negative binomial models.

```
In [4]: readlines("Cholestrol/ControlParametricPenetranceExample.txt")
```

```
Out[4]: 16-element Array{String,1}:
         "#"
         "# Input and Output files."
         "#"
         "locus_file = LocusChol.txt"
         "pedigree_file = PedChol.csv"
         "phenotype_file = PhenoChol.txt"
         "output_file = CholHeterozygousRisk.txt"
         "#"
         "#  Analysis parameters for Genetic Counseling option."
         "#"
         "glm_mean = 4.691+0.562(max(allele1,allele2))+0.00194Age+0.036Sex"
         "glm_response = GammaDist"
         "glm_link = LogLink"
         "glm_trait = Chol"
         "glm_scale = 44.68"
         "glm_trials = 1"
```

Step 3: Examine the Locus and Phenotype Files.

```
In [5]: readlines("Cholestrol/LocusChol.txt")
```

```
Out[5]: 3-element Array{String,1}:
         "Locus,Allele,Chromosome,European"
         "HC,-,autosome,0.9600"
         "HC,+,autosome,0.0400"
```

```
In [6]: readlines("Cholestrol/PhenoChol.txt")
```

```
Out[6]: 4-element Array{String,1}:
          "Locus,Phenotype,Genotypes"
          "HC,Homozygous_Normal,\"-/-\""
          "HC,Homozygous_Mutant,\"+/+\""
          "HC,Heterozygous,\"+/-\""
```

The locus file provides the name of the putative disease locus. The name must match exactly the column name in the pedigree file. In this simple example, this locus is unobserved and so no one has a genotype in the pedigree file except person IV11. The locus HC has two alleles "+" and "-". The locus is on an autosomal chromosome. The "-" allele has frequency 0.96 and the "+" allele has frequency 0.04. The phenotype file provides the genetic model for this locus. The "-/-" genotype has phenotype "Homozygous_Normal", the "+/-" genotype has phenotype "Heterozygous", and the "+/+" genotype has phenotype "Homozygous_Mutant."

Step 4: Run the analysis in the Julia REPL or directly in notebook

The first command `using MendelGeneticCounseling` loads the MendelGeneticCounseling module. This command needs to be issued just once during this tutorial. The next command `GeneticCounseling` reads the control file, reads in the data and runs the analysis.

In [7]:
```
# first call of the GeneticCounseling function takes longer because of JIT compili
ng
using MendelGeneticCounseling
GeneticCounseling("Cholestrol/ControlParametricPenetranceExample.txt")
```

```
┌ Info: Recompiling stale cache file /Users/janets/.julia/compiled/v1.2/MendelGe
neticCounseling/l0fXi.ji for MendelGeneticCounseling [5eee5fa4-c0d8-5591-aecf-5d
586585de4b]
└ @ Base loading.jl:1240


     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Cholestr
ol".

Keywords modified by the user:

  control_file = Cholestrol/ControlParametricPenetranceExample.txt
  glm_link = LogLink
  glm_mean = 4.691+0.562(max(allele1,allele2))+0.00194Age+0.036Sex
  glm_response = GammaDist
  glm_scale = 44.68
  glm_trait = Chol
  glm_trials = 1
  locus_file = LocusChol.txt
  output_file = CholHeterozygousRisk.txt
  pedigree_file = PedChol.csv
  phenotype_file = PhenoChol.txt

 no penetrance file

Analyzing the data.

 The risk =  0.27557.


Mendel's analysis is finished.
```

Step 5: Interpreting the result

`MendelGeneticCounseling` should have generated a file `CholHeterozygousRisk.txt` in your local directory. The value is the conditional probability that person IV11 is heterozygous given the information provided regarding the family and the individuals' age and genotype. The probability is 0.27557.

Step 6: Test yourself.

(1) Modify the pedigree file and the control file to calculate the probability that individual IV11 has the homozygous normal genotype. Then rerun MendelGeneticCounseling with these new data. You should find the probabiity is 0.71335.

(2) Modify the pedigree file to determine the probability individual III13 has the heterozygous genotype. You should find the probability is 0.96698.

Help on modifying the jupyter notebook so you can rerun MendelGeneticCounseling without destroying your original results:

First go to the file tab and press "Save and checkpoint" then go to the insert and click "insert cell below". Then insert command to run GeneticCounseling with your new control file.

Example 2: Using a penetrance file.

In this example we illustrate how to use a penetrance file. We thank Brian Shirts for pointing us to the "Analyze My Variant" website (http://analyzemyvariant.com (http://analyzemyvariant.com)) for a realistic example. We use the penetrance classes provided for BRCA1 (http://analyzemyvariant.com/brca1-info (http://analyzemyvariant.com/brca1-info)).

BrianspedigreeMay162019.jpg

Step 1: Examine the Penetrance file

We have set up the penetrance file to have 5 columns. The first column is for the risks for homozygous wild type genotype (1/1) for each sex and risk decade (penetrance class). The second column is for the risks for heterozyous genotype (1/2) by penetrance class. The third column is for the risks for the homozygous high risk genotype (2/2) by penetrance class. The next column corresponds to the sex of the individual. The final column corresponds to the risk decade of the individual (1: $0 \leq age < 20$, 2: $20 \leq age < 30$, 3: $30 \leq age < 40$, 4: $40 \leq age < 50$, 5: $50 \leq age < 60$, 6: $60 \leq age < 70$, and 7: $70 \leq age$).

To view the file type:

```
In [8]: readlines("BRCA/PenBRCAExample.csv")
```

```
Out[8]: 15-element Array{String,1}:
          "Homozygous_Normal,Heterozygous,Homozygous_Mutant,Sex,Risk_decade"
          "0.000000885,0.001025896,0.001025896,female,1"
          "0.000040997,0.047524,0.047524,female,2"
          "0.00189916,0.18042,0.18042,female,3"
          "0.00878848,0.3736,0.3736,female,4"
          "0.0275136,0.5752,0.5752,female,5"
          "0.05646,0.6889,0.6889,female,6"
          "0.0793,0.785,0.785,female,7"
          "7.58E-08,1.07E-05,1.07E-05,male,1"
          "0.0000012,0.00017,0.00017,male,2"
          "0.000019,0.0012,0.0012,male,3"
          "0.000085,0.003,0.003,male,4"
          "0.00027,0.0062,0.0062,male,5"
          "0.00067,0.012,0.012,male,6"
          "0.0012,0.018,0.018,male,7"
```

Step 2: Examine the pedigree file

In this example we are interested in determining the probability that individual 18, a 38 year old female who is currently unaffected with breast cancer is heterozygous for a BRCA1 mutation. In this case, some members of her family have genotypes at the locus.

Like the previous example, the pedigree is present in two copies. The first copy (called Top) has the genotype of individual 18 as heterozygous. The second copy (called Bottom) has her genotype missing. The likelihood of the first pedigree divided by the likelihood of second pedigree gives us $P(G_{18} = 1/2|\mathbf{G, CancerStatus, Age, Sex})$, the "risk."

```
In [9]: readlines("BRCA/PedBRCAExample.csv")
```

```
Out[9]: 41-element Array{String,1}:
         "Pedigree,Person,Father,Mother,Sex,BRCA,Age,Risk_decade,Proband,Cancer"
         "TOP,1,0,0,male,,79,7,0,-1"
         "TOP,2,0,0,female,,78,7,0,-1"
         "TOP,3,1,2,female,Heterozygous,40,4,0,1"
         "TOP,4,1,2,female,,79,7,0,0"
         "TOP,5,1,2,female,,85,7,0,1"
         "TOP,6,1,2,female,,43,4,0,1"
         "TOP,7,0,0,male,,80,7,0,0"
         "TOP,8,7,3,male,,73,7,0,0"
         "TOP,9,7,3,male,,41,4,0,0"
         "TOP,10,0,0,female,,89,7,0,-1"
         "TOP,11,7,3,male,Heterozygous,30,3,0,0"
         "TOP,12,0,0,female,,80,7,0,0"
         ⋮
         "BOTTOM,9,7,3,male,,41,4,0,0"
         "BOTTOM,10,0,0,female,,89,7,0,-1"
         "BOTTOM,11,7,3,male,Heterozygous,30,3,0,0"
         "BOTTOM,12,0,0,female,,80,7,0,0"
         "BOTTOM,13,9,10,female,Heterozygous,41,4,0,1"
         "BOTTOM,14,9,10,male,,60,6,0,0"
         "BOTTOM,15,9,10,female,Heterozygous,50,5,0,1"
         "BOTTOM,16,9,10,female,Heterozygous,60,6,0,0"
         "BOTTOM,17,11,12,female,Heterozygous,49,4,1,1"
         "BOTTOM,18,11,12,female,,38,3,0,0"
         "BOTTOM,19,11,12,male,Heterozygous,36,3,0,0"
         "BOTTOM,20,11,12,female,Heterozygous,48,4,0,1"
```

Step 3: Examine the Locus and Phenotype File

These files are very similar to the ones we used in the first example.

```
In [10]: readlines("BRCA/LocusBRCAExample.txt")
```

```
Out[10]: 3-element Array{String,1}:
          "Locus,Allele,Chromosome,European"
          "BRCA,\"1\",Autosome,0.998"
          "BRCA,\"2\",Autosome,0.002"
```

```
In [11]: readlines("BRCA/PhenoBRCAExample.txt")
```

```
Out[11]: 4-element Array{String,1}:
          "Locus,Phenotype,Genotypes"
          "BRCA,Homz_rare,\"2/2\""
          "BRCA,Heterozygous,\"1/2\""
          "BRCA,Homz_common,\"1/1\""
```

Step 4: Examine the control file

This control file has some of the same features as parametric ones but it doesn't need to specify the GLM values because there is a penetrance file. Besides the input and output file names, the only needed information is the name of the Column in the pedigree that contains the information regarding breast cancer status.

In [12]:
```
readlines("BRCA/ControlBRCAExample.txt")
```

Out[12]:
```
10-element Array{String,1}:
 "#"
 "# Input and Output files."
 "#"
 "locus_file = LocusBRCAExample.txt  "
 "pedigree_file = PedBRCAExample.csv"
 "phenotype_file = PhenoBRCAExample.txt"
 "penetrance_file = PenBRCAExample.csv"
 "output_file = BRCAExampleOut.txt"
 "#"
 "disease_status = Cancer"
```

Step 5: Running the analysis

In [13]:
```
using MendelGeneticCounseling
GeneticCounseling("BRCA/ControlBRCAExample.txt")
```

```
    Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/BRCA".

Keywords modified by the user:

  control_file = BRCA/ControlBRCAExample.txt
  disease_status = Cancer
  locus_file = LocusBRCAExample.txt
  output_file = BRCAExampleOut.txt
  pedigree_file = PedBRCAExample.csv
  penetrance_file = PenBRCAExample.csv
  phenotype_file = PhenoBRCAExample.txt

this problem has 2 factors called Symbol[:Sex, :Risk_decade]

Analyzing the data.

 The risk =  0.45091.


Mendel's analysis is finished.
```

Step 6: Interpreting the Result

Again you should get a file with the results. The probability of that individual 18 is heterozygous is 0.45091.

Step 7: Test yourself.

(1) Modify the pedigree file and the control file to calculate the probability that individual 18 has the homozygous normal genotype. Then rerun MendelGeneticCounseling with these new files.

(2) How would the risk change if individual 18 were 20 years old instead 38 years old? What if she were 68 years old? (To determine, change her risk decade in the pedigrees and rerun the analysis).

Final Comments

The Julia version of Mendel, provides an opportunity for the user to easily modify the code to suit their own needs. All the source code is provided and Julia is both accessible and very fast.

Reference

For publication please cite:

OPENMENDEL: a cooperative programming project for statistical genetics. Zhou H, Sinsheimer JS, Bates DM, Chu BB, German CA, Ji SS, Keys KL, Kim J, Ko S, Mosher GD, Papp JC, Sobel EM, Zhai J, Zhou JJ, Lange K. Hum Genet. 2019 Mar 26. doi: 10.1007/s00439-019-02001-z

NOTE: When Finished with this notebook. Go to the File tab and first select save and checkpoint to save your results. Then under the file tab, select close and halt to prevent copies of Jupyter notebook from running indefinitely in the background

MendelGeneticCounseling ASHG Workshop - creating your own functions to calculate risk of disease.

last update: October 12 2019, 4pm.

The purpose of this tutorial is to demonstrate how to use the probabilities of the genotypes calculated in the MendelGeneticCounseling tutorial to calculate the probability of the phenotype. To accomplish this we create a function that can calculate a risk of a phenotype using results of genotype prediction, thus also showing how to write simple functions in Julia.

NOTE: When finished with this notebook, go to the File tab and first select 'save and checkpoint' to save your results. Then under the File tab, select 'close and halt' to prevent copies of Jupyter notebook from running indefinitely in the background.

Check the version of Julia you will be using:

For reproducibility, check the machine information below. To execute a notebook command, hold down`Shift Enter` within the box. This tutorial and corresponding modules have been checked with Julia versions 1.0, 1.1 and 1.2. Please report any issues running the tutorial or the module to Janet Sinsheimer PhD. (jsinshei@g.ucla.edu).

In [1]:
```
versioninfo()
```

```
Julia Version 1.2.0
Commit c6da87ff4b (2019-08-20 00:03 UTC)
Platform Info:
  OS: macOS (x86_64-apple-darwin18.6.0)
  CPU: Intel(R) Core(TM) i7-6567U CPU @ 3.30GHz
  WORD_SIZE: 64
  LIBM: libopenlibm
  LLVM: libLLVM-6.0.1 (ORCJIT, skylake)
```

This tutorial uses the Julia modules: Distributions, LinearAlgebra, CSV, DataFrames and Delimiteed Files. To add them use the package manager type

] add Distributions, LinearAlgebra, CSV, DataFrames and Delimiteed Files

In [2]:
```
using Distributions, LinearAlgebra, CSV, DataFrames, DelimitedFiles
```

Check your working directory. For convenience have the julia notebook in the same directory as your files.

In [3]:
```
pwd()
```

Out[3]:
```
"/Users/janets/Documents/lap_top_janet/janet/short_courses_2019/ASHGproposal/Gen
eticCounseling_ASHG2019-master10062019"
```

In [ ]:
```
#If you need to change directories you can use cd(). The exact syntax depends on w
hether you are using a Mac or a PC (windows).

#For the Mac an example is:  cd("/Users/janets/GeneticCounseling/Chol")

#For the PC, an example is: cd("C:\\Users\\Janet Sinsheimer\\Documents\\Julia_file
s")
```

Example 1: Calculate the risk when a penetrance file is provided

This example is very simple but it serves to introduce the concepts. The example calculates the probability that a woman is affected with Breast Cancer at or before a specified age (in this example before or during her sixties). It uses the probabilities of an individual's genotypes given their covariates and their family's information as calculated by MendelGeneticCounseling.jl. The example uses the same breast cancer data provided in the MendelGeneticCounselingTutorial.iynb. In particular use the cumulative penetrance classes provided for BRCA1 (http://analyzemyvariant.com/brca1-info (http://analyzemyvariant.com/brca1-info))

We thank Brian Shirts for pointing us to the "Analyze My Variant" website (http://analyzemyvariant.com (http://analyzemyvariant.com)) for a realistic example.

BrianspedigreeMay162019.jpg

Step 1: Calculate the probability that individual 18 has each of the three possible underlying genotypes.

Change the pedigree file by changing the genotype for individual 18 in the top pedigree in order to calculate

$P(G_{18} = 1/1|\mathbf{G, CancerStatus, Age, Sex})$,

$P(G_{18} = 1/2|\mathbf{G, CancerStatus, Age, Sex})$,

and

$P(G_{18} = 2/2|\mathbf{G, CancerStatus, Age, Sex})$,

In the example ControlBRCAExample.txt individual 18 is heterozygous in the top pedigree. You will need to change the pedigree file and change the pedigree and outfile names in the control file. Then run MendelGeneticCounseling three times, once with each of the three pedigree files.

In [4]:
```
using MendelGeneticCounseling
GeneticCounseling("PhenotypeRisk/ControlBRCAHZNExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlBRCAHZNExample.txt
  disease_status = Cancer
  locus_file = LocusBRCAExample.txt
  output_file = BRCAExampleHZNOut.txt
  pedigree_file = PedBRCAHZNExample.csv
  penetrance_file = PenBRCAExample.csv
  phenotype_file = PhenoBRCAExample.txt

this problem has 2 factors called Symbol[:Sex, :Risk_decade]

Analyzing the data.

 The risk =  0.54887.


Mendel's analysis is finished.
```

In [5]:
```
GeneticCounseling("PhenotypeRisk/ControlBRCAExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlBRCAExample.txt
  disease_status = Cancer
  locus_file = LocusBRCAExample.txt
  output_file = BRCAExampleOut.txt
  pedigree_file = PedBRCAExample.csv
  penetrance_file = PenBRCAExample.csv
  phenotype_file = PhenoBRCAExample.txt

this problem has 2 factors called Symbol[:Sex, :Risk_decade]

Analyzing the data.

 The risk =  0.45091.


Mendel's analysis is finished.
```

In [6]:
```
GeneticCounseling("PhenotypeRisk/ControlBRCAHZMExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlBRCAHZMExample.txt
  disease_status = Cancer
  locus_file = LocusBRCAExample.txt
  output_file = BRCAExampleOut.txt
  pedigree_file = PedBRCAHZMExample.csv
  penetrance_file = PenBRCAExample.csv
  phenotype_file = PhenoBRCAExample.txt

this problem has 2 factors called Symbol[:Sex, :Risk_decade]

Analyzing the data.

 The risk =  0.00021.


Mendel's analysis is finished.
```

To summarize, we find that

$P(G_{18} = 1/1|\mathbf{G, CancerStatus, Age, Sex}) = 0.54887,$

$P(G_{18} = 1/2|\mathbf{G, CancerStatus, Age, Sex}) = 0.45091,$

and

$P(G_{18} = 2/2|\mathbf{G, CancerStatus, Age, Sex}) =$0.00021.

Step 2: Examine the penetrance file

We have set up the penetrance file to have 5 columns. The first column is for the risks for homozygous wild type genotype (1/1) for each sex and risk decade (penetrance class). The second column is for the risks for heterozyous genotype (1/2) by penetrance class. The third column is for the risks for the homozygous high risk genotype (2/2) by penetrance class. The next column corresponds to the sex of the individual. The final column corresponds to the risk decade of the individual (1: $0 \leq age < 20$, 2: $20 \leq age < 30$, 3: $30 \leq age < 40$, 4: $40 \leq age < 50$, 5: $50 \leq age < 60$, 6: $60 \leq age < 70$, and 7: $70 \leq age$).

Read the file into a data frame and then extract the penetrances for women age 60 or greater but less than 70 into a vector.

In [7]:
```
BRCApen=CSV.read("PhenotypeRisk/PenBRCAExample.csv",;header=1)
```

Out[7]: 14 rows × 5 columns

	Homozygous_Normal	Heterozygous	Homozygous_Mutant	Sex	Risk_decade
	Float64	Float64	Float64	String	Int64
1	8.85e-7	0.0010259	0.0010259	female	1
2	4.0997e-5	0.047524	0.047524	female	2
3	0.00189916	0.18042	0.18042	female	3
4	0.00878848	0.3736	0.3736	female	4
5	0.0275136	0.5752	0.5752	female	5
6	0.05646	0.6889	0.6889	female	6
7	0.0793	0.785	0.785	female	7
8	7.58e-8	1.07e-5	1.07e-5	male	1
9	1.2e-6	0.00017	0.00017	male	2
10	1.9e-5	0.0012	0.0012	male	3
11	8.5e-5	0.003	0.003	male	4
12	0.00027	0.0062	0.0062	male	5
13	0.00067	0.012	0.012	male	6
14	0.0012	0.018	0.018	male	7

In [8]:
```
pen = (BRCApen[6,1],BRCApen[6,2],BRCApen[6,3])
```

Out[8]: (0.05646, 0.6889, 0.6889)

Step 3: Write a function that calculates the risk given the penetrance file, risk factors, and genotype probabilities

Note that once the genotypes of individual 18 is specified the cumulative penetrance doesn't depend on their families genotypes or phenotypes. This function is quite simple but it illustrates how to write a function.

In [9]:
```
function risknon(probgeno::Tuple,data::Tuple)where T<:Float64
        probpheno=probgeno[1]*data[1]+probgeno[2]*data[2]+probgeno[3]*data[3]
        return probpheno
end
risknon #uses the cumulative penetrances and the conditional probabilies of the ge
notypes
```

Out[9]: risknon (generic function with 1 method)

Genotype probabilities:

In [10]:
```
prob1 = 0.54887
prob2 = 0.45091
prob3 = 0.00021
probgeno = (prob1, prob2, prob3)
```

Out[10]: (0.54887, 0.45091, 0.00021)

In [11]:
```
risknon(probgeno, pen)
```

Out[11]: 0.3417657682

Conclusion

We find that individual 18 has a probability of approximately 34% of developing breast cancer on or before her sixties.

Example 2: Calculate the risk that individual IVII will have a cholesterol value of 300 or greater at age 20.

Data used in Example 2:

The input files for all examples in this tutorial can be obtained from https://github.com/OpenMendel/GeneticCounseling_ASHG2019 (https://github.com/OpenMendel/GeneticCounseling_ASHG2019)

The data are from an example pedigree used in the Mendel version 16.0 release. The pedigree structure and phenotypes are originally from Schrott et al. (1972) Ann Int Med 76:711–720. We have used the pedigree to provide a slightly contrived example in which Mother III13, who has cholesterol value 440 at age 21 is concerned that her young son might also be affected with extreme hypercholesterolemia.

Step 1: Calculate the probability of each of the possible genotypes using MendelGeneticCounseling

This tutorial assumes you have already worked with the MendelGeneticCounseling module previously. If not, please the see the tutorial MendelGeneticCounselingtutorial.ipynb.

Run MendelGeneticCounseling three times.

Using your favorite editor, alter the pedigree file by changing person IV11's genotype in the top pedigree. Also change the control file to use the new pedigree file and save the result in a new file. Then run MendelGeneticCounseling three times. The first time, determine the probability that individual IV11 has genotype -/-, the second time determine the probability that individual IV11 ahs genotype -/+, and the third time determine the probability that individual IV11 has genotype +/+

In [12]:
```
# first call of the GeneticCounseling function takes long because of JIT compiling
# homozygous wild type genotype
# if running only this example remove the `#` from the next line
# using MendelGeneticCounseling
GeneticCounseling("PhenotypeRisk/ControlParametricPenetranceHZNExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlParametricPenetranceHZNExample.txt
  glm_link = LogLink
  glm_mean = 4.691+0.562(max(allele1,allele2))+0.00194Age+0.036Sex
  glm_response = GammaDist
  glm_scale = 44.68
  glm_trait = Chol
  glm_trials = 1
  locus_file = LocusChol.txt
  output_file = CholHomozygous_NormalRisk.txt
  pedigree_file = PedCholHZN.csv
  phenotype_file = PhenoChol.txt

 no penetrance file

Analyzing the data.

 The risk =  0.71335.


Mendel's analysis is finished.
```

In [13]:
```
# heterozygous genotype
GeneticCounseling("PhenotypeRisk/ControlParametricPenetranceExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlParametricPenetranceExample.txt
  glm_link = LogLink
  glm_mean = 4.691+0.562(max(allele1,allele2))+0.00194Age+0.036Sex
  glm_response = GammaDist
  glm_scale = 44.68
  glm_trait = Chol
  glm_trials = 1
  locus_file = LocusChol.txt
  output_file = CholHeterozygousRisk.txt
  pedigree_file = PedChol.csv
  phenotype_file = PhenoChol.txt

 no penetrance file

Analyzing the data.

 The risk =  0.27557.


Mendel's analysis is finished.
```

In [14]:
```
# homozygous mutant genotype
GeneticCounseling("PhenotypeRisk/ControlParametricPenetranceHZMExample.txt")
```

```
     Welcome to OpenMendel's
 Genetic Counseling Analysis Option


Reading the data.

The current working directory is "/Users/janets/Documents/lap_top_janet/janet/sh
ort_courses_2019/ASHGproposal/GeneticCounseling_ASHG2019-master10062019/Phenotyp
eRisk".

Keywords modified by the user:

  control_file = PhenotypeRisk/ControlParametricPenetranceHZMExample.txt
  glm_link = LogLink
  glm_mean = 4.691+0.562(max(allele1,allele2))+0.00194Age+0.036Sex
  glm_response = GammaDist
  glm_scale = 44.68
  glm_trait = Chol
  glm_trials = 1
  locus_file = LocusChol.txt
  output_file = CholHomozygous_MutantRisk.txt
  pedigree_file = PedCholHZM.csv
  phenotype_file = PhenoChol.txt

 no penetrance file

Analyzing the data.

 The risk =  0.01108.


Mendel's analysis is finished.
```

Summarizing, we have calculated that:

$P(G_{IV11} = -/- | \mathbf{G, Chol, Age, Sex}) = 0.71335$

$P(G_{IV11} = -/+ | \mathbf{G, Chol, Age, Sex}) = 0.27557$

and

$P(G_{IV11} = +/+ | \mathbf{G, Chol, Age, Sex}) = 0.01108$

We will use these values to calculate the risk that individual IV11 will have a cholesterol value greater than 300 at age 20. Note that in this simple example, once we have these estimates of for the genotypes, the family members' data are no longer needed to calculate the risk.

Step 2: Create a simple Julia function to calculate the risk by summing over the penetrances.

This function calculates the probability that an individual will have a phenotype value greater than a specified value of X (the threshold) given their known risk factors and the probability of underlying genotypes. Note as written here this function is specific to gamma distributed traits.

In [15]:
```
function riskgamma(A::T,S::T,X::T,sex::T,probgeno::Tuple,coef::Tuple,geno::Tuple)w
here T<:Float64
         mean_HZN = exp(coef[1]+coef[2]*geno[1]+coef[3]*A+coef[4]*sex)/S
         mean_HZM = exp(coef[1]+coef[2]*geno[2]+coef[3]*A+coef[4]*sex)/S
         mean_Het = exp(coef[1]+coef[2]*geno[3]+coef[3]*A+coef[4]*sex)/S
         p_HZN=1.0-cdf.(Gamma(S,mean_HZN),X)
         p_HZM=1.0-cdf.(Gamma(S,mean_HZM),X)
         p_Het = 1.0-cdf.(Gamma(S,mean_Het),X)
         probrisk=probgeno[1]*p_HZN+probgeno[2]*p_Het+probgeno[3]*p_HZM
         return probrisk
  end
riskgamma #uses cdf to calculate risk of a value higher than stated value for the
individual
# if the relevant risk is when a value falls below a threhold then change 1-cdf. t
o cdf.
# if an interval is relevant, e.g. X_1 to X_2 then use cdf.(...,X_2) - cdf.(..., X
_1)
# modify mean function to fit the number of environmental covariates.
# change distribution to suit application
```

Out[15]:
```
riskgamma (generic function with 1 method)
```

Step 3: Specify the input information and run the function.

In [16]:
```
Age = 20.0
sex = 1.0
Threshold = 300.0

prob1=0.71335
prob2 = 0.27557
prob3 = 0.01108
probgeno = (prob1,prob2,prob3)

geno = (1.0, 2.0, 2.0)
coef = (4.691,0.562,0.00194,0.036)
Scale = 44.68
```

Out[16]:
```
44.68
```

In [17]:
```
risk = riskgamma(Age,Scale,Threshold,sex,probgeno,coef,geno)
```

Out[17]:
```
0.2533785208203602
```

Conclusion

We find that individual IV11 has an approximate 25% probability of having a total cholesterol level greater than 300 at age 20.

This very simple function can be made more general with more covariates or a user specified distribution but it gives you an idea of how easy it is to program in Julia.

Final Comments

The Julia version of Mendel, provides an opportunity for the user to easily modify the code to suit their own needs. All the source code is provided and Julia is both accessible and very fast.

Reference

For publication please cite:

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NOTE: When Finished with this notebook. Go to the File tab and first select save and checkpoint to save your results. Then under the file tab, select close and halt to prevent copies of Jupyter notebook from running indefinitely in the background