Quantitative Genomics and Genetics

BTRY 4830/6830; PBSB.5201.03

Lecture 14: Introduction to Quantitative Genetic Inference

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March 14, 2023 (T) 8:05-9:20

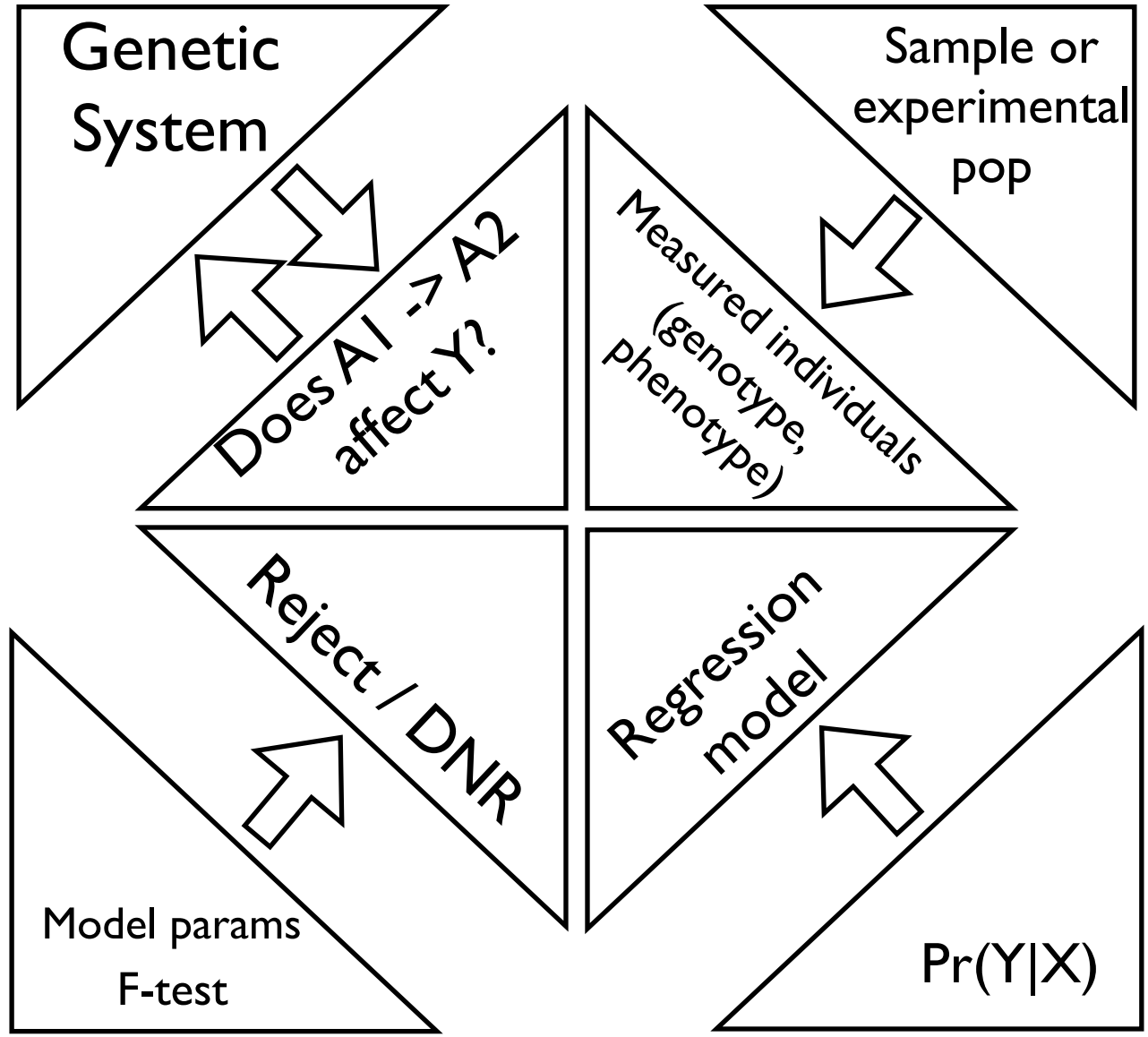
Announcements

- Office hours will be rescheduled for this Fri (March 17) from 12-2PM (!!) I will announce this by Piazza post / email as we get closer
- Homework #4 will be posted later today / this evening (this is your last homework!)
- For those in NYC, we need to permanently switch the Thurs lab time (we probably will go with 5:30-6:30) - please stay tuned for more information

Summary of lecture 14: Introduction to Genetic Inference

- Last lecture, we completed our general discussion of genetic modeling and began discussing genetic inference
- Today, we will (almost) complete our initial discussion of genetic inference!

Conceptual Overview



Review: Genetic system

- **causal mutation** - a position in the genome where an experimental manipulation of the DNA would produce an effect on the phenotype under specifiable conditions
- Formally, we may represent this as follows:

$$A_1 \rightarrow A_2 \Rightarrow \Delta Y | Z$$

- Note: that this definition considers "under specifiable" conditions" so the change in genome need not cause a difference under every manipulation (just under broadly specifiable conditions)
- Also note the symmetry of the relationship
- Identifying these is the core of quantitative genetics/genomics (why do we want to do this!?)
- What is the perfect experiment?
- Our experiment will be a statistical experiment (sample and inference!)

Review: The statistical model I

- As with any statistical experiment, we need to begin by defining our sample space
- In the most general sense, our sample space is:

$$\Omega = \{ \text{ Possible Individuals } \}$$

- More specifically, each individual in our sample space can be quantified as a pair of sample outcomes so our sample space can be written as:

$$\Omega = \{\Omega_g \cap \Omega_P\}$$

- Where Ω_g is the genotype sample space at a locus and Ω_P is the phenotype sample space
- Note that genotype $g_i = A_j A_k$ is the set of possible genotypes, where for a diploid, with two alleles:

$$\Omega_g = \{A_1A_1, A_1A_2, A_2A_2\}$$

- For the phenotype, this can be any type of measurement (e.g. sick or healthy, height, etc.)

Review: The statistical model II

- Next, we need to define the probability model on the sigma algebra of the sample space ($\mathcal{F}_{\{g,P\}}$):

$$Pr(\mathcal{F}_{\{g,P\}})$$

- Which defines the probability of each possible genotype and phenotype pair:

$$Pr\{g, P\}$$

- We will define two (types) or random variables (* = state does not matter):

$$Y : (*, \Omega_P) \rightarrow \mathbb{R}$$

$$X : (\Omega_g, *) \rightarrow \mathbb{R}$$

- Note that the probability model induces a (joint) probability distribution on this random vector (these random variables):

$$Pr(Y, X)$$

Review: The statistical model III

- The goal of quantitative genomics and genetics is to identify cases of the following relationship:

$$Pr(Y \cap X) = Pr(Y, X) \neq Pr(Y)Pr(X)$$

- Remember that, regardless of the probability distribution of our random vector, we can define the expectation:

$$\mathrm{E}\left[Y, X\right] = \left[\mathrm{E}Y, \mathrm{E}X\right]$$

- and the variance:

$$Var\left[Y, X\right] = \begin{bmatrix} Var(Y) & Cov(Y, X) \\ Cov(Y, X) & Var(X) \end{bmatrix}$$

- The goal of quantitative genomics can be rephrased as assessing the following relationship:

$$Cov(Y, X) \neq 0$$

Review: The genetic probability model I

- The quantitative genetic model is a multiple regression model with the following independent ("dummy") variables:

$$X_a(A_1A_1) = -1, X_a(A_1A_2) = 0, X_a(A_2A_2) = 1$$

$$X_d(A_1A_1) = -1, X_d(A_1A_2) = 1, X_d(A_2A_2) = -1$$

1		A_1A_2	
-1	A_1A_1		A_2A_2
	-1	0	1

- and the following "multiple" regression equation:

$$Y = \beta_\mu + X_a\beta_a + X_d\beta_d + \epsilon$$

$$\epsilon \sim N(0, \sigma^2_\epsilon)$$

Review: The genetic probability model II

- Note that, while somewhat arbitrary, the advantage of the *X*a and *X*d coding is the parameters β_a and β_d map directly on to relationships between the genotype and phenotype that are important in genetics:
  - If $\beta_a \neq 0, \beta_d = 0$ then this is a "purely" additive case
  - If $\beta_a = 0, \beta_d \neq 0$ then this is only over- or under-dominance (homozygotes have equal effects on phenotype)
  - If both are non-zero, there are both additive and dominance effects
  - If both are zero, there is no effect of the genotype on the phenotype (the genotype is not causal!)

Genetic inference I

- For our model focusing on one locus:

$$Y = \beta_\mu + X_a\beta_a + X_d\beta_d + \epsilon$$

$$\epsilon \sim N(0, \sigma^2_\epsilon)$$

- We have four possible parameters we could estimate:

$$\theta = \left[\beta_\mu, \beta_a, \beta_d, \sigma^2_\epsilon\right]$$

- However, for our purposes, we are only interested in the genetic parameters and testing the following null hypothesis:

$$H_0 : Cov(X_a, Y) = 0 \cap Cov(X_d, Y) = 0$$
$$H_A : Cov(X_a, Y) \neq 0 \cup Cov(X_d, Y) \neq 0$$

OR

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$
$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

Genetic inference II

- Recall that inference (whether estimation or hypothesis testing) starts by collecting a sample and defining a statistic on that sample
- In this case, we are going to collect a sample of *n* individuals where for each we will measure their *phenotype* and their *genotype* (i.e. at the locus we are focusing on)
- That is an individual *i* will have phenotype y_i and genotype $g_i = A_j A_k$ (where we translate these into x_a and x_d)
- Using the phenotype and genotype we will construct both an *estimator* (a statistic!) and we will additionally construct a *test statistic*
- Remember that our regression probability model defines a sampling distribution on our sample and therefore on our estimator and test statistic (!!)

Matrix Basics

$$\mathbf{v} = \vec{v} = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \qquad \mathbf{M}_1 = \bar{M}_1 = \begin{bmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{bmatrix} \qquad \mathbf{M}_2 = \bar{M}_2 = \begin{bmatrix} a & d \\ b & e \\ c & f \end{bmatrix}$$

We will also follow statistics convention where the first subscript will index rows and the second will index columns (note this is usually reversed in mathematics literature).

Matrix sum: $\mathbf{M}_1 + \mathbf{M}_1 = \begin{bmatrix} m_{11} + m_{11} & m_{12} + m_{12} \\ m_{21} + m_{21} & m_{22} + m_{22} \end{bmatrix}$

Matrix transpose: $\mathbf{M}_2^{\mathrm{T}} = \begin{bmatrix} a & b & c \\ d & e & f \end{bmatrix}$

Scalar times a matrix: $c\mathbf{M}_1 = \begin{bmatrix} cm_{11} & cm_{12} \\ cm_{21} & cm_{22} \end{bmatrix}$

Matrix multiplication:

$$\mathbf{M}_1\mathbf{M}_1 = \begin{bmatrix} m_{11}m_{11} + m_{12}m_{21} & m_{11}m_{12} + m_{21}m_{22} \\ m_{21}m_{11} + m_{22}m_{21} & m_{21}m_{12} + m_{22}m_{22} \end{bmatrix} \quad \mathbf{M}_2\mathbf{M}_1 = \begin{bmatrix} am_{11} + dm_{21} & am_{12} + dm_{22} \\ bm_{11} + em_{21} & bm_{12} + em_{22} \\ cm_{11} + fm_{21} & cm_{12} + fm_{22} \end{bmatrix}$$

$$\mathbf{v}\mathbf{v}^{\mathrm{T}} = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix}\begin{bmatrix} v_1 & v_2 \end{bmatrix} = \begin{bmatrix} v_1v_1 & v_1v_2 \\ v_2v_1 & v_2v_2 \end{bmatrix}, \quad \mathbf{v}^{\mathrm{T}}\mathbf{v} = \begin{bmatrix} v_1 & v_2 \end{bmatrix}\begin{bmatrix} v_1 \\ v_2 \end{bmatrix} = v_1v_1 + v_2v_2$$

If the following holds: $\mathbf{v}_1^{\mathrm{T}}\mathbf{v}_2 = \begin{bmatrix} v_1 & v_2 \end{bmatrix}\begin{bmatrix} v_3 \\ v_4 \end{bmatrix} = 0$ then $\mathbf{v}_1$ and $\mathbf{v}_2$ are orthogonal.

The identity matrix is defined as follows: $\mathbf{I} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$, i.e. diagonal elements are “1” and all other elements are “0”.

The inverse of a matrix $\mathbf{M}^{-1}$ has a structure such that is satisfies the following relationship (for a “square”, *k* x *k* matrix): $\mathbf{M}\mathbf{M}^{-1} = \mathbf{I}$ and $\mathbf{M}^{-1}\mathbf{M} = \mathbf{I}$.

Genetic inference III

- For notation convenience, we are going to use vector / matrix notation to represent a sample:

$$y_i = \beta_\mu + x_{i,a}\beta_a + x_{i,d}\beta_d + \epsilon_i$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} \beta_\mu + x_{1,a}\beta_a + x_{1,d}\beta_d + \epsilon_1 \\ \beta_\mu + x_{2,a}\beta_a + x_{2,d}\beta_d + \epsilon_2 \\ \vdots \\ \beta_\mu + x_{n,a}\beta_a + x_{n,d}\beta_d + \epsilon_n \end{bmatrix}$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & x_{1,a} & x_{1,d} \\ 1 & x_{2,a} & x_{2,d} \\ \vdots & \vdots & \ddots \\ 1 & x_{n,a} & x_{n,d} \end{bmatrix} \begin{bmatrix} \beta_\mu \\ \beta_a \\ \beta_d \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix}$$

$$\mathbf{y} = \mathbf{x}\beta + \epsilon$$

Genetic estimation I

- We will define a MLE for our parameters:

$$\beta = [\beta_\mu, \beta_a, \beta_d]$$

- Recall that an MLE is simply a statistic (a function that takes a sample in and outputs a number that is our estimate)

- In this case, our statistic will be a vector valued function that takes in the vectors that represent our sample

$$T(\mathbf{y}, \mathbf{x}_a, \mathbf{x}_d) = \hat{\beta} = [\hat{\beta}_\mu, \hat{\beta}_a, \hat{\beta}_d]$$

- Note that we calculate an MLE for this case just as we would any case (we use the likelihood of the fixed sample where we identify the parameter values that maximize this function)

- In the linear regression case (just as with normal parameters) this has a closed form:

$$MLE(\hat{\beta}) = (\mathbf{x}^{\mathrm{T}}\mathbf{x})^{-1}\mathbf{x}^{\mathrm{T}}\mathbf{y}$$

Genetic estimation II

- Let's look at the structure of this estimator:

$$\mathbf{y} = \mathbf{x}\beta + \epsilon$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & x_{1,a} & x_{1,d} \\ 1 & x_{2,a} & x_{2,d} \\ \vdots & \vdots & \ddots \\ 1 & x_{n,a} & x_{n,d} \end{bmatrix} \begin{bmatrix} \beta_\mu \\ \beta_a \\ \beta_d \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix}$$

$$MLE(\hat{\beta}) = (\mathbf{x}^{\mathrm{T}}\mathbf{x})^{-1}\mathbf{x}^{\mathrm{T}}\mathbf{y}$$

$$MLE(\hat{\beta}) = \begin{bmatrix} \hat{\beta}_\mu \\ \hat{\beta}_a \\ \hat{\beta}_d \end{bmatrix}$$

Genetic hypothesis testing I

- We are going to test the following hypothesis:

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$

$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

- To do this, we need to construct the following test statistic (for which we know the distribution!):

$$T(\mathbf{y}, \mathbf{x}_a, \mathbf{x}_d | H_0 : \beta_a = 0 \cap \beta_d = 0)$$

- Specifically, we are going to construct a likelihood ratio test (LRT)
- This is calculated using the same structure that we have discussed (i.e. ratio of likelihoods that take values of parameters maximized under the null and alternative hypothesis)
- In the case of a regression (not all cases!) we can write the form of the LRT for our null in an alternative (but equivalent!) form
- In addition, our LRT has an exact distribution for all sample sizes *n* (!!)

Genetic hypothesis testing II

- We now have everything we need to construct a hypothesis test for:

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$

$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

- This is equivalent to testing the following:

$$H_0 : Cov(X, Y) = 0$$

- For a linear regression, we use the F-statistic for our sample:

$$F_{[2,n-3]}(\mathbf{y}, \mathbf{x_a}, \mathbf{x_d}) = \frac{MSM}{MSE}$$

- We then determine a p-value using the distribution of the F-statistic under the null:

$$pval(F_{[2,n-3]}(\mathbf{y}, \mathbf{x_a}, \mathbf{x_d}))$$

Genetic hypothesis testing III

- To construct our LRT for our null, we will need several components, first the predicted value of the phenotype for each individual:

$$\hat{y}_i = \hat{\beta}_\mu + x_{i,a}\hat{\beta}_a + x_{i,d}\hat{\beta}_d$$

- Second, we need the "Sum of Squares of the Model" (SSM) and the "Sum of Squares of the Error" (SSE):

$$SSM = \sum_{i=1}^{n}(\hat{y}_i - \overline{y})^2 \qquad SSE = \sum_{n=1}^{n}(y_i - \hat{y}_i)^2$$

- Third, we need the "Mean Squared Model" (MSM) and the "Mean Square Error" (MSE) with degrees of freedom (df) $df(M) = 3 - 1 = 2$ and : $df(E) = n - 3$

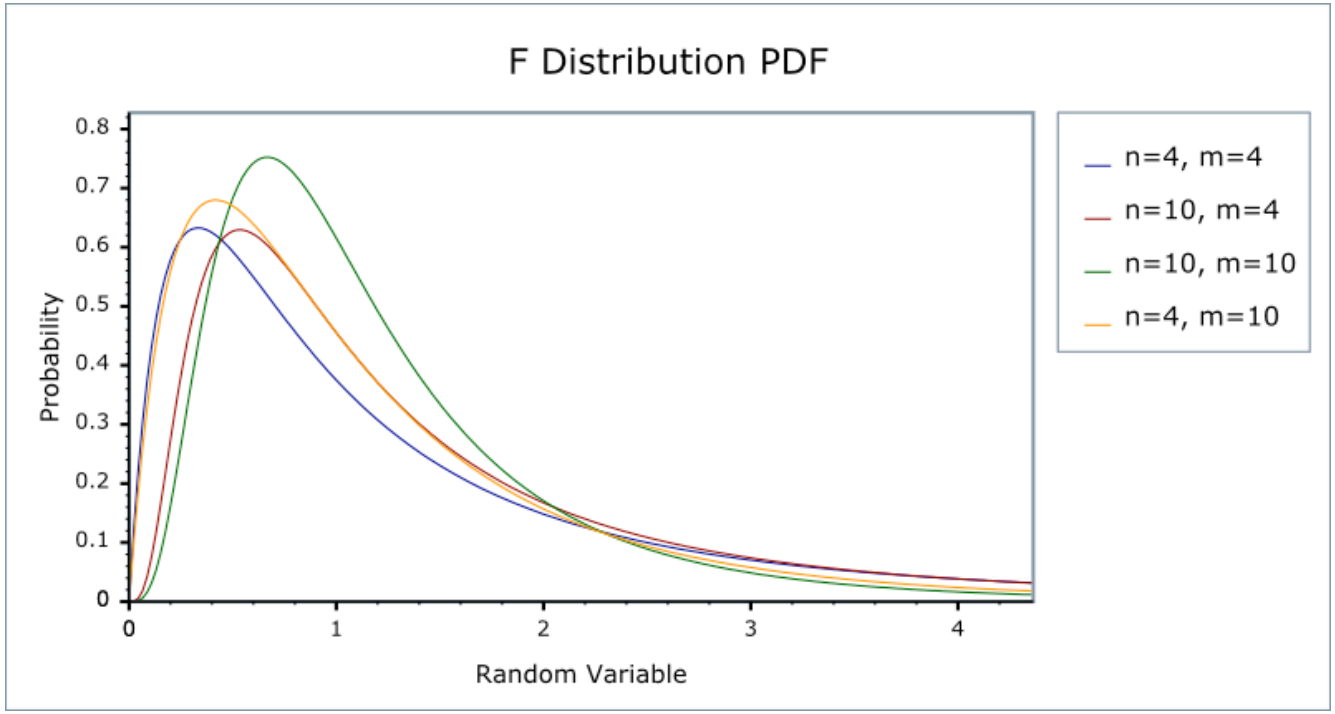
$$MSM = \frac{SSM}{df(M)} = \frac{SSM}{2} \qquad MSE = \frac{SSE}{df(E)} = \frac{SSE}{n-3}$$

- Finally, we calculate our (LRT!) statistic, the F-statistic with degrees of freedom [2, n-3]:

$$F_{[2,n-3]} = \frac{MSM}{MSE}$$

Genetic hypothesis testing IV

- In general, the F-distribution (continuous random variable!) under the H0 has variable forms that depend on d.f.:



- Note when calculating a p-value for the genetic model, we consider the value of the F-statistic we observe or more extreme towards positive infinite (!!) using the F-distribution with [2,n=3] d.f.

- However, also this is actually a two-tailed test (what is going on here (!?)

Genetic hypothesis testing V

- An F-statistic is a Likelihood Ratio Test (LRT) statistic after a simple (monotonic) transformation

$$F\text{−statistic} = f(\Lambda)$$

- Note that an F-statistic has an exact pdf under many conditions (note that we do not always produce a LRT that has an exact pdf that we can state easily)
- Also note that a t-test is actually an F-statistic (and therefore a transformed LRT) for a case where we are comparing the means of just two groups (when might this apply in genetic testing!?), similarly for a t-test of the slope of a regression)

That's it for today

- Next lecture (Thurs, March 14), we will complete our discussion of genetic inference and begin our discussion of GWAS!