Determining Risk for Families using Pedigree Analysis:

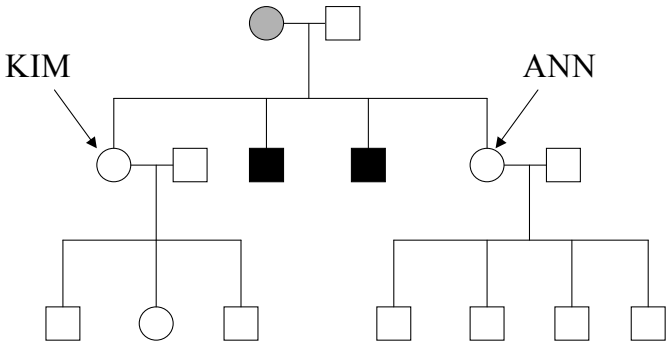
ORIGIN := 1

Pedigree Analysis:

In genetic counseling, potential parents in a family with history of a genetic disease often ask about the risk they face in deciding whether to have additional children or not. Use of Bayes' Rule (also called Bayes theorem) is standard practice in providing them with this information.

Example:

Two sisters, Kim and Ann, are in a family with a history of Hemophilia A as shown in the following pedigree. Hemophilia A is a sex-linked recessive trait (gene located on the X chromosome). Of course, given their family history, each woman wants to know her risk of being a carrier for this genetic trait.



Because brothers of both women exhibit the trait, the brothers must have received it from their mother (sex-linked). Since their mother doesn't exhibit symptoms she must be a carrier - that is, one of her X chromosomes carries the allele for Hemophilia A but it is masked by a normal allele on the other chromosome. So mother is indicated as a carrier by gray on the pedigree above.

From simple Mendelian inheritance, we know that both Kim and Ann have a 50% chance of receiving the Hemophilia A allele from their mother. We call this their common or unconditional probability of being a carrier for the trait.

However, each woman has already had children whose traits we can assess, so we know something more that is specific for each. We call this their conditional probability of being a carrier given knowledge about their children.

So we have all the information we need to perform a Bayesian analysis.

Using Bayes' Rule:

KIM

$$P\left(\frac{B_i}{A}\right) = \frac{P\left(\frac{A}{B_i}\right) \cdot P(B_i)}{\sum_i P\left(\frac{A}{B_i}\right) \cdot P(B_i)}$$

unconditional probabilities ("prior"):

$P_{B1} := 0.5$ **< probability she *is* a carrier**

$P_{B2} := 0.5$ **< probability she is *not* a carrier**

conditional probabilities

$P_{AgivenB1} := 0.5^2$ **< probability her *two* sons are normal given that she's a carrier (her condition is B_1) and her two sons are event A (a test). Each son has (0.5) probability of being normal for the trait. Inheritance for the two sons are independent events. Therefore, the combined probability that two sons are normal is (0.5)·(0.5) or $(0.5)^2$.**

$P_{AgivenB2} := 1.0$ **< probability her *two* sons are normal given she's NOT a carrier (her condition is B_2). Given the mother is not a carrier, each son has (1.0) probability of being normal. Therefore, the combined probability that the two sons are normal is $(1.0)^2 = 1$.**

Bayes' rule:

$$P_{B1givenA} := \frac{P_{AgivenB1} \cdot P_{B1}}{P_{AgivenB1} \cdot P_{B1} + P_{AgivenB2} \cdot P_{B2}} \qquad P_{B1givenA} = 0.2$$ **< $P(B_1|A)$**

^ posterior probability KIM is a carrier given her *two* normal sons

ANN

$$P\left(\frac{B_i}{A}\right) = \frac{P\left(\frac{A}{B_i}\right) \cdot P(B_i)}{\sum_i P\left(\frac{A}{B_i}\right) \cdot P(B_i)}$$

unconditional probabilities ("prior"):

$P_{B1} := 0.5$ **< probability she *is* a carrier**

$P_{B2} := 0.5$ **< probability she is *not* a carrier**

conditional probabilities

$P_{AgivenB1} := 0.5^4$ **< probability her *four* sons are normal given that she's a carrier (her condition is B_1) and her *four* sons are event A (a test). Each son has (0.5) probability of being normal for the trait. Inheritance for the *four* sons are independent events. Therefore, the combined probability that *four* sons are normal is $(0.5)^4$.**

$P_{AgivenB2} := 1.0$ **< probability her *four* sons are normal given she's NOT a carrier (her condition is B_2). Given the mother is not a carrier, each son has (1.0) probability of being normal. Therefore, the combined probability that the *four* sons are normal is $(1.0)^4 = 1$.**

Bayes' rule:

$$P_{B1givenA} := \frac{P_{AgivenB1} \cdot P_{B1}}{P_{AgivenB1} \cdot P_{B1} + P_{AgivenB2} \cdot P_{B2}} \qquad P_{B1givenA} = 0.059$$ **< $P(B_1|A)$**

^ posterior probability ANN is a carrier given her *four* normal sons

So even given their common genetic history from their mother, knowledge about the children each woman has borne substantially modifies our interpretion of her risk of being a carrier!

Bayesian Analysis in Tabular Form:

The above analyses have been set up in exactly the way Bayes 'rule was presented in the previous worksheet (it's usual form). From what I understand, geneticists often present their analysis in a slightly different tabular form. Same results, but the format looks a little different:

Hemophilia A KIM:

Probability:	**Kim is a carrier**	**Kim is NOT a carrier**		*Compare with above:*	
prior:	**0.5**	**0.5**	<-	P_{B1}	P_{B2}
conditional: (two normal sons)	**0.25** = 0.5^2	**1.0**	<-	P_{AB1}	P_{AB2}
joint:	**0.125**	**0.5**	<-	$P_{AB1} \cdot P_{B1}$	$P_{AB2} \cdot P_{B2}$
posterior:	**0.125/(0.125+0.5) = 0.2 or 20%**		<-	PB1A	

For Hemophilia A: ANN

Probability:	**Ann is a carrier**	**Ann is NOT a carrier**		*Compare with above:*	
prior:	**0.5**	**0.5**	<-	P_{B1}	P_{B2}
conditional: (four normal sons)	**0.0625** = 0.5^4	**1.0**	<-	P_{AB1}	P_{AB2}
joint:	**0.03125**	**0.5**	<-	$P_{AB1} \cdot P_{B1}$	$P_{AB2} \cdot P_{B2}$
posterior:	**0.03125/(0.03125+0.5) = 0.058824 or 5.8%**		<-	PB1A	