Appendix to Hanley and McNeil Radiology paper "A Method of Comparing the Areas under ROC curves derived from same cases."

PS (JH 2002.09.17): This was a first (? rough) step in the early 1980's. The method of ***DeLong ER, DeLong DM, Clarke-Pearson DL Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988 Sep;44(3):837-45*** is more elegant and less parametric. They implemented it using a SAS macro. The paper by ***Hanley JA, Hajian-Tilaki KO. Sampling variability of nonparametric estimates of the areas under receiver operating characteristic curves: an update. Acad Radiol. 1997 Jan;4(1):49-58*** shows how to implement the DeLong et al. method by spreadsheet (or by a simple SAS program available on the website http://www.epi.mcgill.ca/hanley/)

Appendix

Calculation of r

Let $\hat{Area}_x$ and $\hat{Area}_y$ represent estimates of the ROC areas $Area_x$ and $Area_y$. Then the correlation r between $\hat{Area}_x$ and $\hat{Area}_y$ can be expressed as

$$r = \frac{Cov(\hat{Area}_x, \hat{Area}_y)}{SE(\hat{Area}_x)SE(\hat{Area}_y)} \qquad (1)$$

Calculation of Denominator in (1)

From our first paper (4), the variance, or square of the standard error, is given by

$$Var(\hat{Area}) = \frac{Area(1 - Area) + (n - 1)(Q_1 + Q_2 - 2\ Area^2)}{n^2}$$

where

n = number of abnormals [= number of normals, for simplification]

Q_1 = probability that a randomly chosen abnormal will appear more abnormal than each of two randomly chosen normals

Q_2 = probability that two randomly chosen abnormals will each appear more abnormal than one randomly chosen normal

The area of the quantities Q_1 and Q_2 can be thought of as follows: let the "degree of abnormality" of a randomly chosen abnormal be represented by

x_A, with mean μ_A and variance σ_A^2. Similarly, let the degree of abnormality for a randomly chosen normal be X_N, with mean μ_N and variance σ_N^2. Then the area is the probability that an X_A and an X_N will be correctly ranked i.e.

$$\text{Area} = \text{Prob}(X_A > X_N) = \text{Prob}(X_A \quad X_N > 0)$$

which is simply the probability that an observation $V = X_A - X_N$ which follows a distribution with mean $\mu_A - \mu_N$ and variance $\sigma_A^2 + \sigma_N^2$ will have a value greater than zero. If X_A and X_N are taken to be Gaussian, then the area equals the proportion of the standardized normal distribution to the left of $(\mu_A - \mu_N)/\sqrt{\sigma_A^2 + \sigma_N^2}$.

In order to translate Q_1 and Q_2 into numerical terms, let X_{A1}, X_{A2}, X_{N1}, X_{N2} represent the values for two randomly chosen abnormals and two randomly chosen normals respectively, and again assume that X_A's and X_N's follow overlapping Gaussian distributions.

Then

$$Q_1 = \text{Probability } (X_{A1} > X_{N1} \text{ and } X_{A1} > X_{N2},$$

which can be calculated instead as

$$Q_1 = \text{Prob}(X_{A1} - X_{N1} > 0 \text{ and } X_{A1} - X_{N2} > 0).$$

If we define two new variables

$$V_1 = X_{A1} - X_{N1} \text{ and } V_2 = X_{A1} - X_{N2},$$

Q_1 becomes the probability mass in the right upper quadrant of the bivariate (V_1, V_2) Gaussian distribution with means

$$\mu_{V_1} = \mu_A - \mu_N \qquad \mu_{V_2} = \mu_A - \mu_N ,$$

variances

$$\sigma^2_{V_1} = \sigma^2_A + \sigma^2_N \qquad \sigma^2_{V_2} = \sigma^2_A + \sigma^2_N ,$$

and covariance

$$\mathrm{Cov}(V_1 , V_2) = \sigma^2_A .$$

This quantity Q_1 can be obtained for various values of σ^2_A, σ^2_N and Area by IMSL subroutine MDBNOR (9) or other equivalent programs. The quantity Q_2 is obtained in a similar way, being the probability in the right upper quadrant of a bivariate Gaussian distribution with the same means and variances but with covariance σ^2_N .

<u>Calculation of Numerator in (1)</u>

To do this, we express each area estimate in its equivalent Wilcoxon-statistic formulation.

$$\mathrm{Area}_x = \sum_k \sum_\ell S^{(x)}_{ij} / n^2$$

$$\mathrm{Area}_y = \sum_k \sum_\ell S^{(y)}_{k\ell} / n^2$$

where

$$S_{ij}^{(x)} = \begin{cases} 1 \text{ if the } i^{th} \text{ chosen abnormal is regarded as more abnormal} \\ \text{than the } j^{th} \text{ chosen normal, when both are imaged with} \\ \text{modality } x, \; 0 \text{ if the ranking is reversed.} \end{cases}$$

$S_{k\ell}^{(y)}$ = 1 or 0, according to a similar rule, for the pair of images obtained with modality y.

Then using E as expected value or long run average over many samples,

$$\mathrm{Cov}(\hat{Area}_x, \hat{Area}_y) = E(\hat{Area}_x \hat{Area}_y) - E(\hat{Area}_x)E(\hat{Area}_y)$$

$$= \frac{1}{n^4} \sum_i \sum_j \sum_k \sum_\ell E(S_{ij}^{(x)} S_{k\ell}^{(y)}) - Area_x Area_y ,$$

$$= \frac{1}{n^4} \left[n^2 Q_3 + n(n^2 - n)Q_4 + n(n^2 - n)Q_5 + (n^2 - n)(n^2 - n)Area_x Areea_y \right]$$
$$- Area_x Area_y ,$$

where

Q_3 = Probability that a randomly chosen abnormal will be regarded as more abnormal than a randomly selected normal, when each of the two subjects is imaged with each of the two modalities.

Q_4 = Probability that a randomly chosen abnormal will be regarded as more abnormal than a randomly chosen normal when using modality x, and that with modality y a second randomly chosen abnormal will be ranked more abnormal than the same randomly chosen normal.

Q_5 = The reverse of Q_4, i.e. with one randomly chosen abnormal and two randomly chosen normals.

The quantities Q_3 to Q_5 are calculated in a manner somewhat similar to that used for Q_1 and Q_2. As illustration, to calculate Q_4, let (X_{A_1}, X_{N_1}) represent the degrees of abnormality in a randomly chosen (abnormal, normal) pair of subjects imaged with modality x. Let (Y_{A_2}, Y_{N_1}) represent the degree of abnormality seen when the same normal and a second abnormal are imaged with modality y. Then

$$Q_4 = \text{Prob}(V_1 = X_{A_1} - N_1 > 0 \text{ and } V_2 = Y_{N_2} - Y_{N_1} > 0)$$

Let the X's and Y's have Gaussian distributions as before, let the (X_N, Y_N) pair, corresponding to a single normal imaged by both modalities, have a correlation of ρ_N, and assume that their bivariate distribution is in fact bivariate Gaussian. Similarly, assume that the pair of observations (X_A, Y_A) for a single randomly selected abnormal have a bivariate Gaussian distribution, with correlation coefficient ρ_A. Then Q_4 becomes the probability in the right upper quadrant of the (V_1, V_2) bivariate Gaussian distribution with

$$\mu_{V_1} = \mu_{Ax} - \mu_{Nx} \qquad \mu_{V_2} = \mu_{Ay} - \mu_{Ny}$$

$$\sigma^2_{V_1} = \sigma^2_{Ax} + \sigma^2_{Nx} \qquad \sigma^2_{V_2} = \sigma^2_{Ay} + \sigma^2_{Ny}$$

Covariance (V_1, V_2) = Cov(X_N, Y_N) = $\rho_N \sigma_{Nx} \sigma_{Ny}$ and can be obtained by subroutine MDBNOR.

For Q_3 and Q_5, the correspondingly defined (V_1, V_2) pairs will have bivariate distribuitions with obvious means and variances and with

$$\text{Cov}(V_1, V_2) = \rho_A \sigma_{Ax} \sigma_{Ay} + \rho_N \sigma_{Nx} \sigma_{Ny}$$

in the case of Q_3, and

$$\text{Cov}(V_1, V_2) = \rho_N \sigma_{Ax} \sigma_{Ay}$$

in the case of Q_5.