PubH 7405:
REGRESSION ANALYSIS

INTRODUCTION TO

LOGISTIC REGRESSION

Let Y be the Dependent Variable Y taking on values 0 and 1, and:

π = Pr(Y=1)

Y is said to have the "**Bernouilli distribution**" (Binomial with n = 1).

We have:

$$E(Y) = \pi$$

$$Var(Y) = \pi(1-\pi)$$

Consider, for example, an analysis of **whether or not business firms have a daycare facility**, according to the **number of female employees**, the **size of the firm**, the **type of business**, and the **annual revenue**. The dependent variable Y in this study was defined to have two possible outcomes:

(i) Firm **has a daycare** facility (Y=1), and
(ii) Firm **does not have** a daycare facility (Y=0).

As another example, consider a study of **Drug Use among middle school kids**, as a function of **gender** and **age** of kid, **family structure** (e.g. who is the head of household), and **family income**. In this study, the dependent variable Y was defined to have two possible outcomes:

(i) Kid **uses drug** (Y=1), and
(ii) Kid **does not use** drug (Y=0).

In another example, say, a man has a physical examination; he's concerned: **Does he have prostate cancer?** The "**truth**" would be confirmed by a biopsy. But it's a very painful process (at least, could we say if he needs a biopsy?)
In this study, the dependent variable Y was defined to have two possible outcomes:

(i) Man **has prostate cancer** (Y=1), and
(ii) Man **does not have** prostate cancer (Y=0).

Possible predictors include **PSA level, age, race.**

Suppose Prostate Cancer has been confirmed, the next concern is **whether the cancer has been spread to neighboring lymph nodes**; knowledge would dictate appropriate treatment strategy. The "**truth**" would be confirmed by performing a "laparotomy" (to examine the nodes), but any surgery involves risks; the question is **whether we can** accurately predict **nodal involvement** without a surgery.

In this study, the dependent variable Y was defined to have two possible outcomes:
(i) **With nodal involvement** (Y=1), and
(ii) **Without** nodal involvement (Y=0).

Possible “predictors” include **X-ray reading**, biopsy result pathology reading (**grade**), size and location of the tumor (**stage** - by palpation with the fingers via the rectum), and **“acid phosphatase level”** (in blood serum).

The basic question is: Can we do “regression” when the dependent variable, or “response”, is **binary**?

For “binary” Dependent Variables, we run into problems with the “**Normal** Error Model” – **The distribution of Y is Bernouilli**. However, the “normal” assumption is **not very important** (i.e. “robust”); effects of any violation is quite minimal – especially if n is large!

The Mean of Y is in well-defined but it has **limited range**:

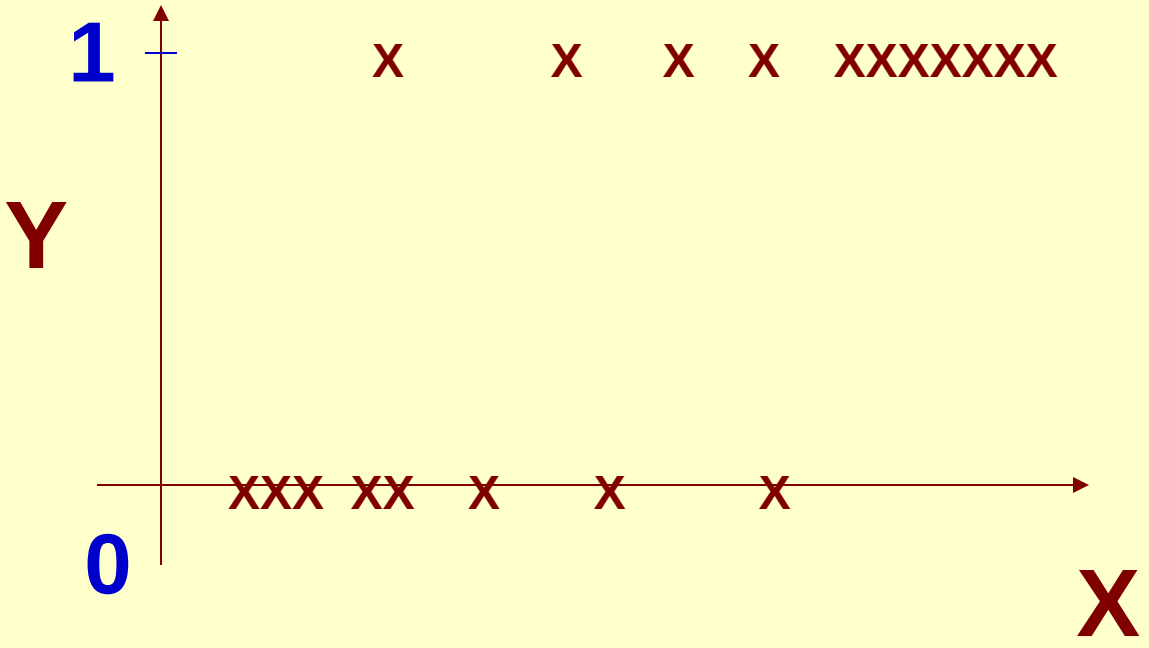
Mean of Y = Pr(Y=1) = π
$0 \leq \pi \leq 1$,

and **fitted values may fall outside of (0,1).** However, that's a **minor problem**.

The Variance (around the regression line) **is <u>not constant</u>** (a model violation that we learn in diagnostics); variance is function of the Mean π of Y (which is **a function of predictors**):

$$\sigma^2 = \pi(1- \pi)$$

More important, **the relationship is not linear**. For example, with one predictor X, we usually have:



We still can focus on "modeling the mean", in this case it is a Probability, π = Pr(Y=1), but the usual linear regression with the "normal error regression model" is definitely not applicable – all assumptions are violated, some may carry severe consequences.

<u>Conclusion</u>:
We need some transformation for Y (assumptions about Y are violated)

EXAMPLE: Dose-Response

Data in the table show the effect of different concentrations of (nicotine sulphate in a 1% saponin solution) on fruit flies; here X = log(100xDose), just making the numbers easier to read.

Dose(gm/100cc)	# of insects, n	# killed, r	x	p (%)
0.1	47	8	1.000	17.0
0.15	53	14	1.176	26.4
0.2	55	24	1.301	43.6
0.3	52	32	1.477	61.5
0.5	46	38	1.699	82.6
0.7	54	50	1.845	92.6
0.95	52	50	1.978	96.2

Proportion p is an estimate of Probability π

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p is an increasing function of x; in what way?

UNDERLYING ASSUMPTION

It is assumed that **each subject/fly has its own tolerance** to the drug. The amount of the chemical needed to kill an individual fruit fly, called "**individual lethal dose**" (ILD), cannot be measured - because **only one fixed dose is given to a group of n flies (indirect assay)**

(1) If that dose is below some particular fly's ILD, the insect survived.

(2) **Flies which died are those with ILDs below the given fixed dose.**

INTERPRETATION OF DATA

Dose	# n	# killed	X	p(%)
0.1	47	8	1.000	17.0
0.15	53	14	1.176	26.4
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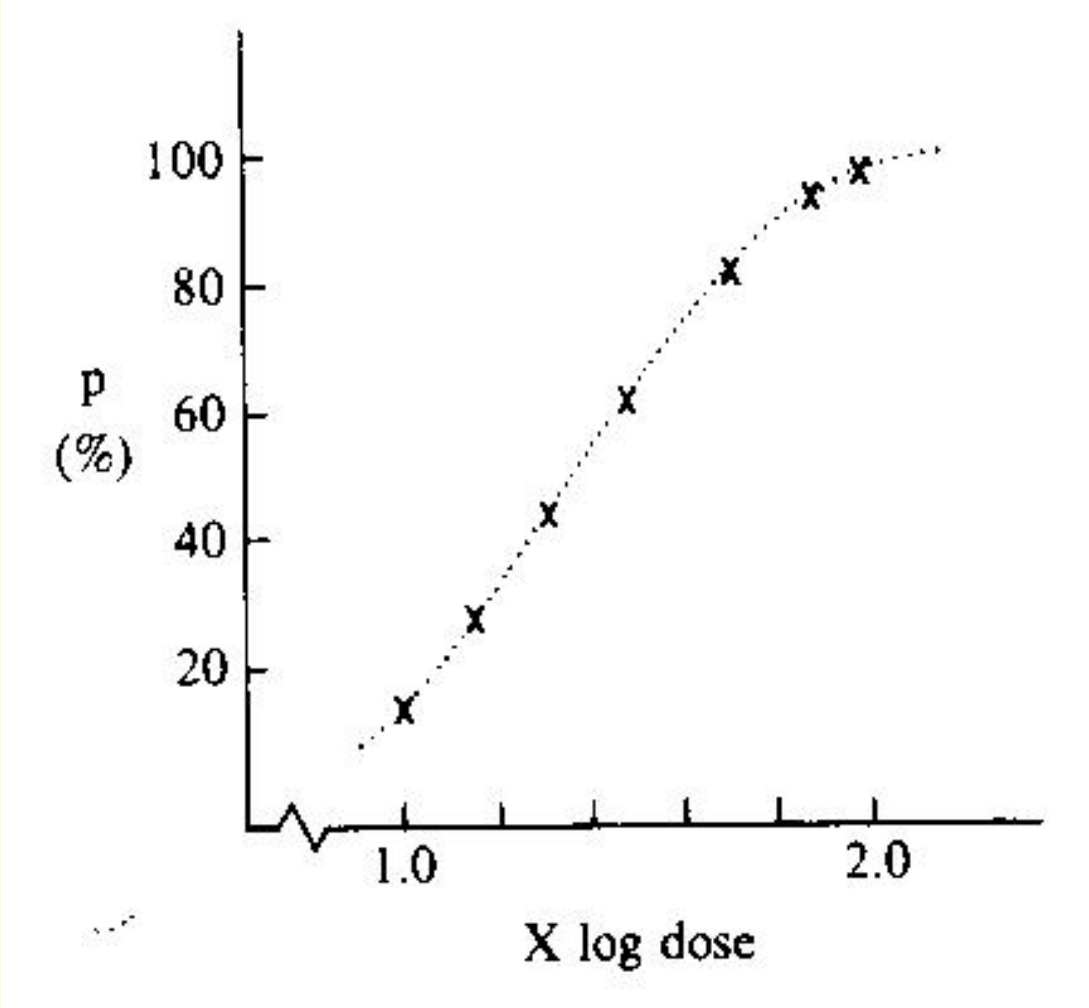
- 17% (8 out of 47) of the first group respond to dose of .1gm/100cc (x=1.0); that **means 17% of subjects have their ILDs less than .1**
- 26.4% (14 out of 53) of the 2nd group respond to dose of .15gm/100cc (X=1.176); that is **26.4% of subjects have their ILDs less than .15**

Interpretation of data:

we view each dose D (with X = log of D) as upper endpoint of an interval and p the cumulative relative frequency



A symmetric **sigmoid dose-response curve** suggests that it be seen as some **cumulative distribution function** (**cdf**).

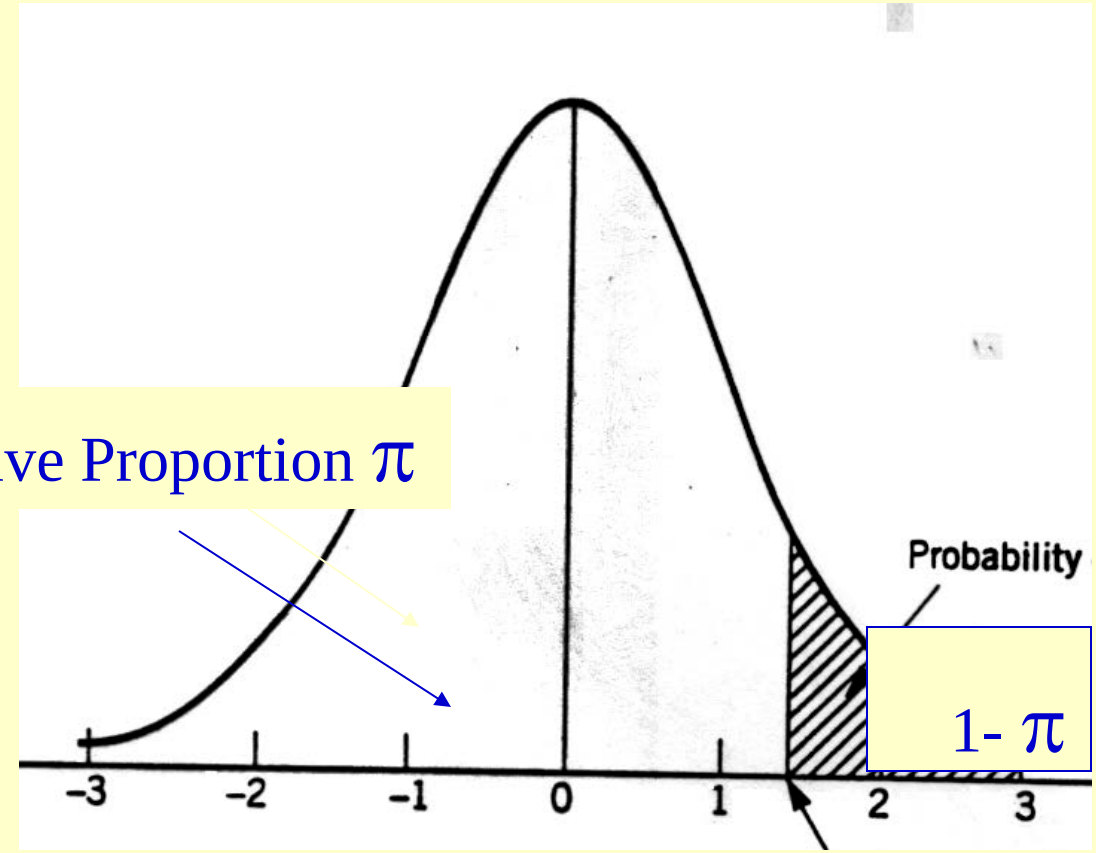
"**Empirical evidence**", i.e. data, suggest that we view **p the cumulative relative frequency**. This leads to a **"transformation" from "π" to an "upper endpoint", say Z** (which is on the continuous scale) corresponding to that cumulative frequency of some cdf. After this transformation, **the regression model is then imposed on Z, the transformed value of π.**

MODELING A PROBABILITY

Let π be the probability "to be modeled" and X a covariate (let consider only one X for simplicity). The first step in the regression modeling process is to obtain "**the transformed value Z of π**" using the following **transformation:**

$$\boldsymbol{\pi = \int_{-\infty}^{Z} f(u)du \quad or \quad \int_{Z}^{\infty} f(u)du}$$

$f(u)$ is some **probabilit y density function** .



Transformation: π to Z which is on a linear scale

As a result, the proportion π has been transformed into a new variable Z on the "**linear**" or continuous scale with **unbounded range**. We can use Z as the dependent variable in a regression model. (We now should only worry about "normality" which is not very important)

The relationship between covariate X (in the example, log of the dose) or covariates X's and Probability π (through Z) is then stipulated by the usual simple linear regression:

$$Z = \beta_0 + \beta_1 x$$

or multiple regression:

$$Z = \beta_0 + \sum_{i=1}^{k} \beta_i x_i$$

All **we need** is a "**probabilit y density function**" f(.) in order to translate π to Z through :

$$\boldsymbol{\pi = \int_{-\infty}^{Z} f(z)dz \quad or \quad \int_{Z}^{\infty} f(z)dz}$$

In theory, any probability density function can be used. We can choose one either by its **simplicity** and/or its **extensive scientific supports**. And we can check to see **if the data fit** the model (however, it's practically hard because we need lots of data to tell).

A VERY SIMPLE CHOICE

A possibilit y is "Unit Exponentia l Distributi on" with density :

$$\mathbf{f(z) = e^{-z};\ z \geq 0}$$

Result (for one covariate X) is:

$$\pi = \int_{-\beta_0 - \beta_1 x}^{\infty} e^{-z} dz$$

$$\mathbf{\ln(\pi) = \beta_0 + \beta_1 x}$$

That is to **model the "log" of the probability as a "linear function" of covariates.**

Of course, you could use

"**multiple regression**" too :

$$\ln\pi = \beta_0 + \sum_{i=1}^{k} \beta_i x_i$$

The advantage of the approach of modeling the "log" of the probability as a "linear function" of covariates, is **easy interpretation** of model parameters, the **probability is changed by a multiple constant** (i.e."**multiplicative model**" which is usually plausible)

Example : Say X_1 is binary

$$\ln \pi = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

$$x_1 = 0 \text{ (unexposed)} : \ln \pi_{unexposed} = \beta_0 + \beta_2 x_2$$

$$x_1 = 1 \text{ (exposed)} : \ln \pi_{exposed} = \beta_0 + \beta_1 + \beta_2 x_2$$

$$\beta_1 = \ln \pi_{exposed} - \ln \pi_{unexposed}$$

$$= \ln \frac{\pi_{exposed}}{\pi_{unexposed}}$$

$$= \ln(Odds)$$

REGRESSION COEFFICIENTS

- **If X_1 is binary (=0/1) representing an exposure, β_1 represents the (log of) the "odds" (of having the event represented by Y) associated with the exposure – adjusted for that of X_2**
- **If X_1 is on a continuous scale, β_1 represents the (log of) the "odds" (of having the event represented by Y) associated with one unit increase in the value of X_1 - adjusted for X_2**

The model is plausible; calculations could be simple too; after the log transformation of “p”, proceeding with usual steps in regression analysis.

this approach has a small problem: the exponential distribution is defined only on the whole positive range **and** certain choice of “x” could make the **fitted probabilities exceeding 1.0**

$$\ln \pi = \beta_0 + \beta_1 x$$

LOGISTIC TRANSFORMATION

(Standard) **Logistic Distributi on** with density :

$$f(\theta) = \frac{\exp(\theta)}{[1+\exp(\theta)]^2}$$

Result is:

$$\pi = \int_{-\infty}^{Z=\beta_0+\beta x} \frac{e^{\theta}}{[1+e^{\theta}]^2} d\theta$$

$$= \frac{\exp(\beta_0 + \beta_1 x)}{1+\exp(\beta_0 + \beta_1 x)}$$

$$= \frac{1}{1+\exp(-\beta_0 - \beta_1 x)}$$

$$\boldsymbol{\pi = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}}}$$

$$1 - \pi = \frac{1}{1 + e^{\beta_0 + \beta_1 x}}$$

$$\frac{\pi}{1 - \pi} = e^{\beta_0 + \beta_1 x}$$

$$\boldsymbol{\log \frac{\pi}{1 - \pi} = \beta_0 + \beta_1 x}$$

We refer to this as "**Logistic Regression**"

Exponential transformation leads to a linear model of "**Log of Probability**": $\ln(\pi)$;
Logistic transformation leads to a linear model of "**Log of Odds**": $\ln[\pi/(1-\pi)]$

When π is small (rare disease/event), the probability and the odds are approximately equal.

$$Odds = \frac{\pi}{1-\pi}$$

$$\pi = \frac{Odds}{1+Odds}$$

Advantages:

(1) Also very simple data transformation:

$Z = \log\{p/(1-p)\}$

(2) The **logistic density**, with **thicker tails** as compared to normal curve, may be a **better representation of real-life processes.**

A POPULAR MODEL

- Although one can use the Standard Normal density in the regression modeling process (or any density function for that purpose),
- The Logistic Regression, as a result of choosing Logistic Density remains the **most popular choice** for a number of reasons: closed form formula for π, easy computing (Proc **LOGISTIC**)
- The most important reasons: **interpretation of model parameter** and **empirical supports**!

REGRESSION COEFFICIENTS

$$\pi = \frac{\exp(\beta_0 + \beta_1 x)}{1 + \exp(\alpha + \beta x)}$$

$$\ln \frac{P}{1-P} = \beta_0 + \beta_1 x$$

β_1 represents the **log of the odds ratio** associated with X, if X is binary, or with "an unit increase" in X if X is on continuous scale; β_0 only depends on "event prevalence"**-** just like any **intercept**.

Example : Say X_1 is binary

$$\ln \frac{\pi}{1-\pi} = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

$$x_1 = 0 \text{ (unexposed)} : \ln Odds_{unexposed} = \beta_0 + \beta_2 x_2$$

$$x_1 = 1 \text{ (exposed)} : \ln Odds_{exposed} = \beta_0 + \beta_1 + \beta_2 x_2$$

$$\ln Odds_{exposed} - \ln Odds_{unexposed} = \beta_1$$

$$\frac{Odds_{exposed}}{Odds_{unexposed}} = \text{Odds Ratio} = (e^{\beta_1})$$

β_1 is the odds ratio on the log scale if X is binary

REGRESSION COEFFICIENTS

- **If X_1 is binary (=0/1) representing an exposure, β_1 represents the (log of) the "odds ratio" (of having the event represented by Y) associated with the exposure – adjusted for that of X_2**
- **If X_1 is on a continuous scale, β_1 represents the (log of) the "odds ratio" (of having the event represented by Y) associated with one unit increase in the value of X_1 - adjusted for X_2**

Logistic Regression applies in both prospective and retrospective (case-control) designs. In **prospective design**, we can calculate/estimate the **probability of an event** (for specific values of covariates). In **retrospective design**, we cannot calculate/estimate the probability of events because the “intercept” is meaningless but **relationship between event and covariates are valid**.

SUPPORTS FOR LOGISTIC MODEL

The fit and the origin of the linear logistic model could be easily traced as follows. When a dose D of an agent is applied to a pharmacological system, the fractions f_a and f_u of the system affected and unaffected satisfy the so-called "median effect principle" (Chou, 1976):

$$\frac{f_a}{f_u} = \left\{ \frac{d}{ED_{50}} \right\}^m$$

where ED_{50} is the "median effective dose" and "m" is a Hill-type coefficient; m = 1 for first-degree or Michaelis-Menten system. The median effect principle has been investigated much very thoroughly in pharmacology.

If we set " $\pi = f_a$", the **median effect principle and the logistic regression model are completely identical** with a slope $\beta_1 = m$.

Besides the Model, the other aspect where Logistic Regression, both simple and multiple, is very different from our usual approach is **the way we estimate the parameters or regression coefficients.** The obstacle is the **lack of homoscedasticity**: we cannot assume a constant variance after the logistic transformation.

$$\mathbf{Z = \log \frac{P}{1 - P}}$$

$$Var(Z) = [\frac{dZ}{dp}]^2 Var(p)$$

$$= \frac{1}{[p(1-p)]^2} Var(p)$$

$$= \frac{1}{[p(1-p)]^2} \frac{p(1-p)}{n}$$

$$= \frac{1}{np(1-p)}$$

Not constant

SOLUTION #1: WEIGHTED LS

Instead of minimizing the “sum of squares”, we minimize the “weighted sum of squares”

$$\Sigma w[z - (\alpha + \beta x)]^2$$

where the weight for the value Z is 1/Var(Z). This **can be done but much more complicated**.

In addition, Z might not be defined if p=0 or p=1

$$Z = \log \frac{P}{1 - P}$$

SOLUTION #2: MLE

Model :

$$\pi = \frac{\exp(\beta_0 + \beta_1 x)}{1 + \exp(\alpha + \beta x)}$$

Likelihood Function :

$$L = \prod_{i=1}^{n} \Pr(Y_i = y_i)$$

$$= \prod_{i=1}^{n} \pi_i^{y_i} (1 - \pi_i)^{1 - y_i}$$

$$= \prod_{i=1}^{n} \frac{\{\exp[\beta_0 + \beta_1 x_i]\}^{y_i}}{1 + \exp[\beta_0 + \beta_1 x_i]}; y_i = 0/1$$

Maximum Likelihood Estimation (MLE) process gives us estimates of all regression coefficients and their standard errors, b_i (estimate of β_i) and $SE(b_i)$

TEST FOR SINGLE FACTOR

- The **question** is: “Does the addition of one particular factor of interest add significantly to the prediction of Pr(Y=1) **over and above that achieved by other factors**?”.
- The **Null Hypothesis** for this test may stated as: "Factor X_i does not have any value added to the prediction of the probability of response over and above that achieved by other factors ". In other words,

$$H_0 : \beta_i = 0$$

TEST FOR SINGLE FACTOR

- The Null Hypothesis is $H_0 : \beta_i = 0$
- Regardless of the number of variables in the model, one simple approach is using

$$\mathbf{z = \frac{b_i}{SE(b_i)}}$$

- Refer it to the percentiles of the **standard normal distribution**, where b_i is the corresponding estimated regression coefficient and $SE(b_i)$ is the standard error of β_i , both of which are provided by any computer package**.**

ESTIMATING ODDS RATIO

- General form of 95% CI for β_i: $b_i \pm 1.96*SE(b_i)$; b_i is point estimate of β_i, provided by SAS, and $SE(b_i)$ from Information matrix, also by SAS
- Transforming the 95% confidence interval for the parameter estimates to 95% C.I. for Odds Ratios:

$$\exp\left[b_i \pm 1.96 SE(b_i)\right]$$

Logistic Model For Interaction

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

"Usual approach": use the product of individual terms to represent "interaction" – also called "effect modification"

Interaction Hypothesis

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

Testing for interaction

H_0: $\beta_3 = 0$

H_A: $\beta_3 \neq 0$

(Interaction = Effect Modification)

In summary, with "Logistic Regression", we "lost" these tools that we use with NERM:

The global F-test

R^2 and all coefficients of partial determination (there are some substitutes but not as good)

All graphs (Scatter diagram, all residual plots, and Variable-added Plot)

Least Squares method (but MLE is better)

All other methods/tools are unchanged (test for single factors, stepwise, etc…)

Indirect Assays: Dose fixed, Response random.

Depending on the "measurement scale" for the response (our random variable), we divide indirect assays into two groups:

(1) **Quantal assays**, where the response is binary: whether or not an event (like the death of the subject) occurs,

(2) Quantitative assays, where measurements for the response are on a continuous scale.

Quantal response assays belong to the class of qualitative indirect assays. They are characterized by experiments in which **each level** of a stimulus (eg. dose of a drug) is **applied to n experimental units; r of them respond** and (n-r) do not response.That is “binary” response (yes/no). The group size “n” may vary from dose to dose; in theory, some n could be 1 (so that r = 0 or 1).

From Webster International Dictionary:

"Biological Assay is the estimation of the strength of a drug by comparing its effect on biological material, as animals or animal tissue, with those of a standard product."

In other words, we (usually) can only estimate "relative potency" of an agent, not its "potency".

Quantal assays are exceptions to this definition.

QUANTAL ASSAYS VERSUS QUANTITATIVE ASSAYS

- Quantal bioassays are qualitative; we observe occurrences of an event - not obtain measurements on continuous scale.
- Because the event is well-defined, **we can estimate agent's potency.** The most popular parameter is the level of the stimulus which result in a response by 50% of individuals in a population. It is often denoted by **LD50** for median lethal dose, or **ED50** for median effective dose, or **EC50** for median effective concentration.
- However, measures of potency depend on the biological system used; the estimates of LD50's for preparations of the same system can be used to form the **relative potency** – which would be more likely **independent from the system**.

The most popular parameter LD50 (for median lethal dose), or ED50 (for median effective dose), or EC50 (for median effective concentration) is the level of the stimulus which result in a response by 50% of individuals in a population.

(1) It is a measure of the agent's potency, which could be used to form relative potency.

(2) It is chosen by a **statistical reason**; for any fixed number of subjects, one would attain greater precision as compared to estimating, say, LD90 or LD10 or any other percentiles.

THE ASSAY PROCEDURE

- The usual design consists of a series of dose levels with subjects completely randomized among/to the dose levels. The experiment may include a standard and a test preparations; or maybe just the test.
- The **dose levels** chosen should range from "**very low**" (few or no subjects would respond) to "**rather high**" (most or all subjects would respond).
- The objective is often **to estimate the LD50**; the number of observations per preparation depends on the desired level of precision of its estimate – sample size estimation is a very difficult topic.

LOG POTENCY

In the logistic the density, if we set p = .5 (or Y=0) we can obtain "log potency" (**log of LD50)**; its estimate is given by, where b_0 and b_1 are estimated intercept and slope, respectively:

$$\pi = \frac{\exp[\beta_0 + \beta_1 x]}{1 + \exp[\beta_0 + \beta_1 x]}$$

$$= .5 \Leftrightarrow \beta_0 + \beta_1 x = 0$$

$$x_{med} = M = -\frac{\beta_0}{\beta_1}$$

$$M = \log(LD50)$$

$$= -\frac{\beta_0}{\beta_1}$$

$$= \frac{\hat{b}_0}{b_1}$$

EXAMPLE AN IN VITRO EXPERIMENT

Cells from a tumor-derived cell line are deposited in wells of a cell culture dish in complete growth medium. After phase growth is established (say, 72 hrs in a typical cell line), wells are treated with **different concentrations of a test agent – including a control** (i.e. vehicle) well. **Doses are spread over a wide range from very low to very high.**

The endpoint is "cell survival" and the aim is to establish "potency parameters".

Unlike Clinical or In Vivo trials; for In Vitro trials, the number of cells at the beginning of the experiment in each well, prior to drug exposure, may be large but **unknown**; that is **why a control (i.e. vehicle) well is needed.** (same volume were deposited in wells)

Cells: ALL

Drug: Vincristine

(**Extra feature**: original and recurrent tumors from the same patient which is not needed here)

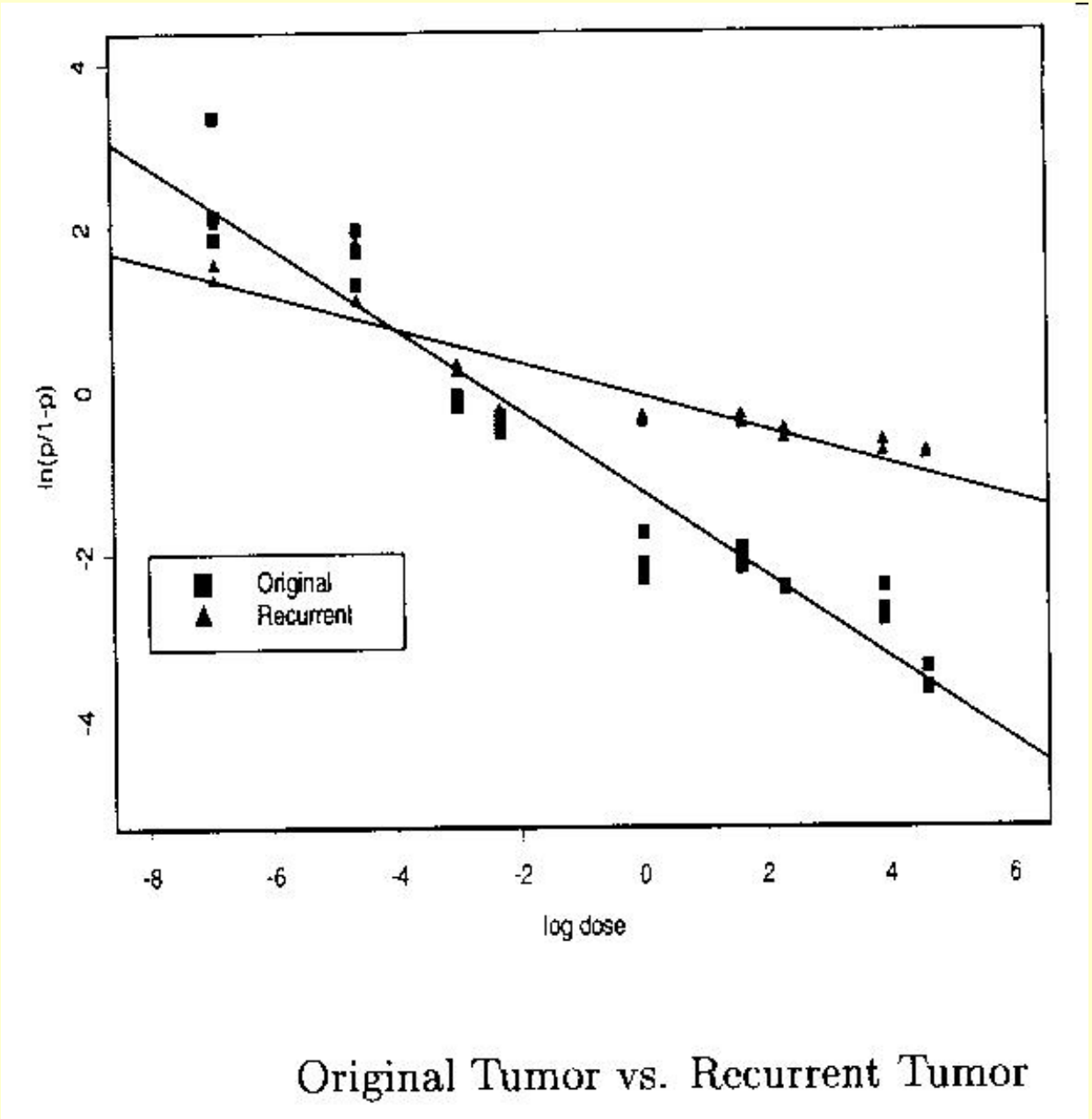
Original Tumor		Recurrent Tumor	
Dose ($\mu g/ml$)	Cell count (x 10^4)	Dose ($\mu g/ml$)	Cell Count (x 10^4)
0	233.8	0	70.8
	212.6		69.3
	221.5		66.6
.001	202.0	.001	58.2
	205.3		54.9
	197.9		58.9
.010	183.3	.010	52.9
	186.1		54.5
	187.2		57.0
.050	104.4	.050	39.1
	100.9		38.4
	106.6		38.2
.100	86.8	.100	30.2
	88.5		26.7
	91.3		29.0
1.000	21.1	1.000	28.1
	31.0		28.3
	23.2		27.8
5.000	24.9	5.000	27.5
	26.8		27.0
	22.4		27.9
10.000	18.9	10.000	24.7
	17.0		26.1
	17.5		25.1
50.000	14.5	50.000	22.2
	17.5		23.8
	12.4		22.7
100.000	5.9	100.000	21.4
	6.9		21.1
	7.2		21.41

Two straight lines:

similar intercepts;

Recurrent tumor:

smaller slope



Original Tumor vs. Recurrent Tumor

Readings & Exercises

- Readings: A thorough reading of the text's sections 14.1-14.5 (pp.555-581) is highly recommended.
- Exercises: The following exercises are good for practice, all from chapter 14 of text: 14.4, 14.5, and 14.12.

Due As Homework

#20.1 Refer to dataset "Prostate Cancer", let Y = Node and five independent variables, X_1 = X-Ray, X_2 = Grade, X_3 = Stage, X_4 = Age, and X_5 = Acid.

a) Fit the model with Acid as the only covariate and interpret the results, including the meaning of the slope.

b) Add more terms to the model in question (a) to test if Stage modifies the effect of Acid

c) In model (a) is the effect of Acid linear?

d) Fit the model containing all five covariates and interpret the results

b) In model (d) does Age modifies the effect of Acid?