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Segmental linear regression analysis: A solution for automated data analysis of assays with non-linear dose response curves

Sam S. Yanari, PhD. Allergy and Clinical Immunology Research Laboratory.

In automated data analysis of radioimmunoassays the logit: log plot is widely used for curve-fitting. Often, however, non-linear plots are obtained by this as well as other common plots. Few have access to computers with curve-fitting programs; thus, many have devised means to "force-fit" the data into a linear form or provide corrective measures.

In our assays of antigen-specific-immunoglobulin (RAST technique) non-linear curves are unavoidable, since the dose/response curve, initially linear, becomes non-linear as the saturation limit of the immunosorbent is approached. Using a programmable calculator, a number of simple and, later, more complex equations were tested. None appeared reliable in curve-fitting our data. A satisfactory solution based on "segmental" LR (linear regression) analysis was then developed. Because of the limited memory capacity of the calculator, it was necessary to devise a number of step-saving sub-routines.

In the first phase of segmental analysis, the operator repeatedly tests 3-5 consecutive reference points in different segments of the dose/response curve with variations of the form:

\[ F(y) = a + b f(x) \]

where \( f \) is either a linear, log or reciprocal function of \( x \) or \( y \), \( a \) = intercept, and \( b \) = slope. The correlation coefficients from these trials will indicate the equation best suited for a given portion of the dose/response curve. Generally, two equations suffice for given assay. Next, segmental LR analyses of successive pairs of reference points yield sets of \( a \) and \( b \) constants. Interpolation is the basis for evaluation of an unknown, eg, stored \( a' \) and \( b' \) derived from LR analysis between the reference points which bracket \( y' \) are used to calculate \( x' \).

The authors have applied this program to several types of radioassays.
Scanning electron microscopy in patients with gastric ulcer treated with carbenoxolone.

Henry Ford Hospital and Edsel B. Ford Institute Research

Duane C. Roe, MD, and Bernard M. Schuman, MD, Section of Gastrointestinal Endoscopy, Department of Medicine; and John H.L. Watson, PhD, and Jessica Goodwin, BA, Edsel B. Ford Institute for Medical Research.

As part of a double-blind clinical study, the effect of carbenoxolone upon the surface of gastric mucosa was evaluated by scanning electron microscopy (SEM).

Two patients, who were part of a double-blind study, had gastroscopic biopsies taken from observed ulcers before beginning therapy, and post-therapy. Biopsy specimens were also taken similarly from two patients receiving placebo. SEM micrographs were taken and reviewed independently by one of us without knowledge of the specific treatment. Two "controls" from patients without known ulcer were included in the series, again without knowledge of the reviewer.

Previously described SEM abnormal characteristics including changes in surface contours at the pits, focal epithelial cell degeneration, and the dense patternless surface projections associated with gastritis were observed in all peri-ulcer pretreated specimens.

In the two patients receiving carbenoxolone, the gastric mucosa post-treatment appeared intact by endoscopy, the SEM micrographs revealing improved surfaces with some residual features of gastritis. The two patients on placebo, both of whom required surgical therapy, showed by SEM no beneficial changes in one case and only modest improvement in the other. The two controls were easily recognized by SEM without prejudice.

In conclusion, the mucosa surrounding gastric ulcers shows definite improvement with carbenoxolone therapy, according to SEM criteria of gastritis.

Histologic assessment of bone employing plastic-embedded thin section techniques.

Michael M. Crouch, MA, and Antonio R. Villanueva, MA. Bone & Mineral Research Laboratory, Department of Orthopedics

Plastic-embedded, mineralized thin sections of bone are stained with the Villanueva Bone Stain to study cells and structures unaltered by various chemical and physical reagents commonly employed by bone microscopic techniques.

Certain metabolic bone diseases, especially the osteomalacias, and vitamin-D resistant rickets are readily recognized. Some of the basic histodynamics involved in bone may be studied from these materials by means of in vivo tetracycline labelling. Simultaneous demonstration of tetracycline-positive osteoid seams and the number of bone forming cells can be examined in one setting with little difficulty.

Utilizing these techniques coupled with various histomorphometric quantitative analysis allows study of the following: 1) quantitative-qualitative interpretation and correlation of morphological data of osteoblasts relative to tetracycline-positive osteoid seams, 2) diagnosis and evaluation of certain metabolic bone disorders relative to normal standard, 3) evaluation and understanding some of the effects of drugs on bone, and 4) as a research tool for the study of aging.
Bone erosion in rheumatoid arthritis*

C.H.E. Mathews BA, D. Witzgall BA, and Howard Duncan, MD, Bone and Mineral Research Laboratory, Rheumatology Division, Department of Medicine

In this study we have identified several types of destruction which occur in the bones and joints of rheumatoid patients.

The conventional method of bone destruction is through the action of osteoclasts. These cells are an integral part of the normal cycle of bone turnover where an area of bone is resorbed before new bone is formed.

In some specimens we see very few osteoclasts, despite large areas of destruction. Serial sections of metacarpals show erosions in the presence of mononuclear cells, histologically very different from the multinucleated osteoclasts.

Sections of the tibial plateau in the knee joint show, in addition, a different type of erosion. In trabeculae away from the rheumatoid inflammation we see areas of demineralization around the osteocytes: each osteocyte appears to have its own domain where minerals have been removed and the collagen matrix exposed. Subsequently the matrix is destroyed leaving bone with many "holes" which become invaded by rheumatoid inflammatory cells.

This study has identified different types of erosion which occur in rheumatoid bones and joints. A possible mechanism for the mode of erosion at the osteocytes is proposed.

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Antibiotic synergism studies in enterococcal endocarditis

T. Madhavan MD, D. Pohlod MD, E. Fisher MD, K. Burch MD, F. Cox MD, and E. L. Quinn MD. Division of Infectious Diseases, Department of Medicine

Glew et al reported that the combination of nafcillin and gentamicin was synergistic against 10 to 14 strains of enterococci at clinically achievable concentrations. In contrast, the combinations of oxacillin plus gentamicin were synergistic against only 3 of 24 strains and methicillin plus gentamicin produced synergistic killing against only 1 of 14 strains (Antimicrob Ag Chemother 7:828-832, 1975).

In the present study, the effectiveness of methicillin, cloxacillin and dicloxacillin alone and in combination with gentamicin and tobramycin was tested against 8 enterococcal strains isolated from endocarditis patients.

A vigorous definition of synergism was used as advocated by the authors, ie, a decrease of 100 fold or more in colony forming units caused by combination as compared with the most effective of antibiotics used alone.

The mean inhibitory (MIC) and bactericidal (MBC) concentrations of all three semisynthetic penicillins were considerably higher (MIC and MBC 50 \( \mu \)g/ml) than those of penicillin and ampicillin (MIC and MBC 3.1 \( \mu \)g/ml). Methicillin, cloxacillin and dicloxacillin in combination with gentamicin and tobramycin were not synergistic against all strains tested. In contrast, combination of penicillin G or ampicillin plus gentamicin or tobramycin produced synergistic killing against all the strains tested.
Saimari sciureus as an animal model for noise research

Donald W. Nielsen, PhD. Otological Research Laboratory, Department of Otolaryngology.

While there is clear evidence that work-related noise can cause permanent hearing loss, few experiments have been conducted on the effects of long-term noise exposure in human subjects. Due to possible hazards of long-term injury to human ears by intense noise, a laboratory animal is needed having hearing changes similar to man in order to investigate the effects of such exposures.

The few studies that have been performed have used chinchillas for long-term noise exposure with nonhumans; this animal has an inner ear and hearing thresholds similar to man. A comparison of threshold shifts from long-term noise exposure in chinchillas and man, however, reveals several differences. Such differences may reflect different physiological or biochemical processes underlying the observed changes in hearing due to noise exposure.

Because of these differences, we decided to investigate the possibility of using the squirrel monkey as an animal model for noise research. The squirrel monkey was chosen because of three factors: 1) the structural similarity of their inner ear to man's; 2) the phyletic proximity to man; and 3) the similarities to humans in both threshold sensitivity and threshold shift after short exposure, high level acoustic stimulation.

The animals were exposed to two different octave band noises on different occasions. Length of noise exposures varied from as short as one hour to as long as 72 hours. The way in which the threshold shift changed with duration of noise exposure was very similar in monkey and man. Likewise, the recovery of that threshold shift was strikingly similar. We feel the similarities are sufficient to justify further comparative investigation.

Adjuvant treatment of solid and ascites tumors in the mouse.

R.H. Page, MS; R.W. Talley, MD, and J. Buhagiar. Division of Oncology, Department of Medicine.

Increasingly large number of studies, both in human patients and in animal tumor models, have involved the use of Bacillus Calmette-Guerin (BCG) for tumor growth inhibition. Because of the many contradictory results obtained thus far, we have looked at the effect of adjuvant therapy in three murine tumor models.

Groups of Swiss mice tumored with 100, 1,000, and 10,000 Ehrlich Ascites Tumor cells and treated with BCG at varying times: concomitant with tumor, 5 days post tumor transplant, or at 12 days pre-tumor. BALB/c mice tumored with 100, 1,000, or 10,000 reticulum cell sarcoma (RCS) cells were treated in the same manner. Also, BALB/c mice tumored with subcutaneous explants of S-180 sarcoma were treated similarly.

No significant tumor remissions were seen except in BALB/c mice tumored with RCS and given BCG at the time of tumor induction. In several instances, tumor enhancement was seen. A further study using sequential chemo- and adjuvant BCG therapy in RCS-tumored BALB/c mice yielded negative results.