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COMBO: A new approach to the design and analysis of experiments on antiviral drug combinations.

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Prompted by the need to analyze data from our own experiments on combinations of dipyridamole with dideoxynucleosides (see, e.g., PNAS 86:3842, 1989), we have taken a fresh look at the problem of identifying potentiation, synergy, antagonism, enhancement of therapeutic index, and other types of drug interactions. This investigation has revealed a need for the following capabilities: (i) flexible choice of interaction models; (ii) parametric and non-parametric (Monte Carlo) statistical methods to estimate p-values and confidence limits (a sound statistical basis is critical in this field); (iii) flexibility with respect to experimental design (e.g., checkerboard, constant-ratio, etc.); and (iv) statistical techniques to reduce the size of experiments by reducing the number of replicates required. These requirements motivated the development of a computer program package, COMBO, that operates in the MLAB computing environment on personal computers. It provides a variety of models, e.g. "robust potentiation," "robust antagonism," "pure potentiation," and "eff-tox" (the latter for instances in which both efficacy and toxicity are observed simultaneously). COMBO can also be used for experiments on single drugs. Graphical displays, multiple statistical diagnostics, and identifiers of aberrant data are included. We have used the COMBO paradigm and program package to analyze data on combinations that include AZT, ddC, ddI, ddA, dipyridamole, interferons, tumor necrosis factor, suramin, and CD4-pseudomonas exotoxin, *inter alia*. Preliminary descriptions can be found in PNAS 87: 8889, 1990 and in Annals N.Y. Acad. Sci. v. 616, 1990, in press (Bunow and Weinstein; Weinstein, et al.). Supported in part by the NIH Intramural Targeted AIDS Antiviral Program.

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A Three-Dimensional Model to Analyze Drug-Drug Interactions. M. N. PRICHARD and C. SHIPMAN, JR. The University of Michigan, Ann Arbor, Michigan, U.S.A.

The interactions between two drugs are defined inherently by three-dimensional (3-D) dose-response surfaces, but until recently technical limitations have forced investigators to utilize two-dimensional approximations to analyze experimental data. Recently, we have developed a method which exploits powerful new microcomputer graphics programs to analyze drug-drug interactions in the appropriate 3-D context. Experimental data are plotted as a 3-D dose-response surface which incorporates the individual dose-response curves on the X and Y axes, respectively. These dose-response curves subsequently are used to calculate theoretical additive effects, which then are subtracted from the experimental dose-response surface to reveal aberrant interactions. This approach facilitates (1) the visualization of the complete 3-D dose-response surface, (2) the location and quantitation of synergistic or antagonistic interactions, and (3) the statistical evaluation of the synergy or antagonism. Three-dimensional dose-response surface analysis reveals relationships that are difficult to understand using two-dimensional methods and offers investigators a practical and desirable alternative for the rigorous examination of interactions between drugs.