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A PROBABILISTIC APPROACH FOR MODELLING THE JOINT ACTION OF DRUGS

Introduction

An understanding of the joint action of drugs is becoming increasingly important in a variety of scientific disciplines, ranging from pharmacology and toxicology on the one hand to industrial hygiene and environmental protection on the other. The action of even a single drug upon a biological organism involves a complex sequence of processes and if more than one drug is present, the situation is further complicated The role of mathematical models in this context is now widely recognized (Plackett & Hewlett 1952, Hewlett and Plackett, 1959, 1979, Ashford and Cobby 1974, Ashford 7981)

A mathematical model is, only a simplification of the real situation. The true mechanism is generally rather involved when all its details are taken into account and it is very difficult to understand. However, efforts can be made to evolve a working model that is not unrealistic for practical purposes. The first attempt generally leads to a simplistic model, which can be improved later as we learn more and more about the underlying mechanism, through further experimentation, and also from these preliminary attempts of modelling.

The process of model building has three main stages. first a set of abstract concepts must be devised to represent the essential features of the way in which the drug or drugs affect the subject. Second, the form of relationship between the concepts must be expressed in mathematical terms. This will normally call for a process of simplification and if the phenomenon involves an element of uncertainty, the model must include a random component. Third, observations and the results of experiments must be utilised to test the model over the whole range of conditions under which it is to be applied.

The mathematical model may be used for several purposes. The primary and foremost is for description, to provide a summary of what may be an extensive and complex body of data. A model may also be used for prediction, to estimate the outcome under a specified set of initial conditions. A third and more sophisticated use is as a guide to further experimentation,

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the model being employed to determine the most efficient choice of conditions for any new observations,

In this paper a general frame-work is considered for the representation of the action of drugs, when applied alone, or in combination with other drugs, Hence we restrict to mixture of two drugs and this frame work can be applied to construct a system of models for the action of mixtures of drugs.

TERMINOLOGY AND NOTATION

(a) **Quantal response** : The term is currently used in two ways. Firstly, it is used in a qualitative sense to signify a criterion whereby an individual is classified as having responded or not. Secondly used in quantitative sense, quantal response signifies the number of organisms in a randomly chosen group showing a defined quantal response in a qualitative sense, this number being expressed as a proportion.

(b) **Dose** : The variable Z is used of drug expressed in grams or directly proportional units such as micrograms, Normally each organism is assumed to have been dosed in the same way with the same dose at a given time before each is classified as having responded or not Any monotonic transformation of doss is called dosage.

(c) **Tolerance** : The tolerance Z^* of an individual organism to a given drug is the dose of that drug just insufficient to produce the quantal response (qualitative sense) in that individual. The individual responds if $Z>Z^*$ but not otherwise.

(d) **System** : This term. is used in bidlogical sense to signify a biochemical, biophysical or physiological entity within the individual organism.

(e) **Amount acting, action tolerance** : The amount of drug acting is the amount of drug transmitted to the site of action as a result or administration of a dose Z, and the action tolerance $\tilde{w}$ is the amount acting just insufficient to produce the quantal response in the individual organism.

(f) **Similar joint action** : If two drugs whether administered separately or jointly elicit a certain quantal response by causing the same physiological system to react or fail then joint action is said to be similar w. r. to that response,

(g) **Interaction :** Two drugs A and B are said to interact if the presence of A influences the amount of B reaching the site of action or changes produced by B at B's site of action and/or reversely with A and B interchanged.

(h) **Disimilar joint action** : If two drugs whether administered separately or jointly elicit a certain quantal response by causing respectively different physiological systems to react or fail, then joint action is said to be dissimilar w. r. to that response.

(i) **Synergism and antagonism** : Synergism signities that the due to simple summation and antagonism that it produces a lesser effect.

THE ACTION OF A SINGLE DRUG

The study of joint action requires a general biological picture of the way in which one drug applied singly produces a response in a individual organism. According to Veidstra's concept of drug action, when a dose of a drug is introduced into the complex systems forming an organism only a part of the dose reaches the sits of action. This part produces the biochemical and physiological changes which, if great enough, lead to the particular quantal response under consideration. The remainder goes to what Veldstra terms "site of loss". Thus of the part of dose not acting. some may be metabolized enzymically to a less active or inactive substance and some may be excreted unchanged.

We shall assume that for the individual organism the expression

$$W = aZ^{b} \qquad a,b>O \qquad (1)$$

relates with sufficient accuracy the amount of drug acting (w) to the dose (Z) over adequate ranges. w cannot exceed Z and in

(1) $W < Z$ when $Z > Zo = a^{1/(1-c)}$ if $o < b < I$, and $Z < Zo$ if $b > I$

For any individual organism, let w be the minimum amount acting so that response occurs if and only if $w > \tilde{w}$. The distribution of $\tilde{w}$ among the population can be specified by introducing a probability density function $f(\tilde{w})$ such that the proportion of organisms responding is $P = J_o^h f(\tilde{w})\, d\tilde{w}$ (2)

Mapping the interval $o < h < \infty$ on to $-\infty < x < \infty$ where x=x(h)

If theresulting distribution is M (x) then $p = M(x)$ (3)

In particular if M(x) has zero mean and unit variance, x can be

termed an equivalent deiration a common transformation is

$$X = I_1 + I_2 \log w \qquad (4)$$

using (1) this implies

$$X = c + d \log z$$

where $c = I_1 + I_2 \log a$ and $d = I_2 b$

If $M(x) = \int_{-\infty}^{x} (\pi)^{-\frac{1}{2}} \exp(-y^{2/2})\, dy$

then x is a normal equivalent deviation and x + 5 is a probit.

JOINT ACTION OF TWO DRUGS

The problem of constructing a mathematical model for the joint action of two drugs A_1 and A_2 is equivalent to finding a function $P(Z_1, Z_2)$ of the corresponding doses Z_1 and Z_2 which has the following properties $P(Z_1 Z_2)$ is intended to represent the probability of response and so $O \leq P \leq I$. $p(Z_1, O)$ is the probability of response when the joint-drug is applied alone it will be an increasing function of Z_1 and if A_1. is an agonist, and uniformly O if A_1 is an antagonist in active by itself. Plackett and Hewlett (1967) put forward a biological classification for types of joint action of drugs The type of joint action of a given pair of drugs must be defined with respect to the particular quantal response under consideration. A joint action was defined as similar or dissimilar according as the sites of primary action of the two drugs were the same or different and as interactive or non-interactive as one drug did or did not influence the biological action of the other. The table below shows the terms of the four biological categories of joint action so distinguished.

	SIMILAR	DISSIMILAR
NON-INTERACTIVE	SIMPLE SIMILAR	INDEPENDENT
INTERACTIVE	COMPLEX SIMILAR	DEPENDENT

NON-INTERACTIVE ACTION

Simple similar action and independent action are regarded as the extreme forms of non-interactive action. Basic equations for these extremes expressing the conditions of nonresponse in the individual organism are given by Hewlett and Plackett (1959). These place no restriction on the correlation of tolerances nor on the relative slopes of the N. E. D - log-dose lines for the separate drugs. Introduction of a parameter measuring the degree of similarity between the modes of action of the two drugs enables basic general equat-

ions for non-interactive joint action to be derived. When a basic general equation for non-interactive action is combined with an assumption of a bivariate-normal distribution of log tolerances, the response to a mixture of drugs can be calculated. In general the calculaticn requires integration of the bivariate-normal function over a particular non-rectangular region which is feasible with an electronic computer.

Using suffixes 1 and 2 to refer to the two drugs, the proportion of organism q1 and q2 failing to respond to separate applications of the drugs are respectively the probabilities that

$$W1 \leq \overset{S}{W}_1 \quad \text{and} \quad W_2 \leq \overset{S}{W}_2$$

Thus $q_1 = \Pr\left(W_1 \leq \overset{S}{W}_1\right) \quad q_2 = \Pr\left(W_2 \leq \overset{S}{W}_2\right)$

Obviously any equation for the joint action of two drugs must reduce to above equation if W_2 or W_1 is equal to zero.

If the action of two drugs jointly applied is independent an organism will fail to respond only when neither quantity acting exceeds the corresponding action tolerance and hence q the proportion not responding to a joint application is given by

$$q = \Pr\left(W_1 \leq \overset{S}{W}_1,\ W_2 \leq \overset{S}{W}_2\right)$$

Equivalently the proportion responding is

$$P = \Pr\left(W_1 > \overset{S}{W}_1,\ W_2 \leq \overset{S}{W}_2\right) + \Pr\left(W_1 \leq \overset{S}{W}_1 \right.$$
$$\left. W_2 > \overset{S}{W}_2\right) + \Pr\left(W_1 > \overset{S}{W}_1,\ W_2 > \overset{S}{W}_2\right.$$

Since q can be more succinctly expressed than p, we use q in formulating models for non-interactive action.

In deriving equations for similar actions if at the common site of action, the first drug is k times as the second W_1 of the first drug acting will have the same physiological effect as kw_1 of the second. Thus if both acting similarly W_1 of the first acting together with W_2 of the second can be expected to have physiological effect equal $kw_1 + w_2$ of the second. An equation for similar joint action is obtained as shown on the side.

The alternative form is

$$q = \Pr\left(KW_1 + W_2 \leq \overset{S}{W}_1\right)$$

$$q = \Pr\left(W_1 + W_2 / K \leq \overset{S}{W}_1\right)$$

Now the ratio $W/\overline{W} = \zeta$ plays an important role in the to be put forward. It varies from zero to one. If W is arbitraily divided into two parts so that

$$W = W' + W''$$

then $\zeta = \zeta' + \zeta''$

Where $\zeta' = W'/\overline{W} \qquad \zeta'' = W''/\overline{W}$

Equations above can be written as

$$q_1 = \Pr\ (\zeta_1 \leq 1)$$
$$q_2 = \Pr\ (\zeta_1 \leq 1)$$

The general equation for similar joint action $q = \Pr\ (\zeta_1 + \zeta_2 \leq 1)$ arrived at

COMPETITIVE ACTION :

Models for quantal responses to drugs acting competitively are considered by Hewlett and Plackett. The models are derived from the model for graded responses developed by Gaddum. Dynamic equilibria between the drugs and receptors in the tissues of the units of biological material are assumed. Three cases occur.

Case 1. A_1 is an agonist and A_2 is an antagonist. The probability of *response* P must be the receptors occupied by A_1 the simplest possibility is the logistid distribution for log $(m_1 w_1 / [1 + m_2 w_2])$. If w_1 is lognormaly distributed the N. E. D.. of response to A_1 alone is

$$X_1 = I_1 + I' \log w_1$$

On simplication the N E D for the jointly applied drugs will be

$$x = I_1 + I^1 \log (w_1 / c_1 + m_2 w^2)$$

provided that m_2 is fixed.

Case 2. Both A_1 and A_2 are agonists. Here p must be steadily increasing function of p_1 for fixed p_2 and of p_2 for fixed p_1.

For example $p = p_1 + p_2$ is a quantity which always lies between 0 and 1 and corresponds to a logistic distribution for log $(m_1 w_1 + m_2 w_2)$.

In this case the proportion of non-response is $q = Pr (¿_1 + ¿_2 \leq 1)$

Case 3. Two agonists separately induce different maximum response. The problem of fitting the resulting model makes it unlikely to be useful whatever the values of w_1 and w_2 quantal response occurs if

$(n_1 w_1 + n_2 w_2) (1 + m_1 w_1 + m_2 w_2) > n_1 w_1 / (1 + m_1 w_1)$

DISCUSSION :

There comments has been made by Plackett and Hewlett (1967) on the above classification. Firstly, interaction may each take different forms. Secondly, the status of independent action needs to be made clear. Thirdly, an objection to the above classification is that the action of two drugs, whether interactive or not may in some sense be partially similar, hence similar and dissimilar actions should perhaps be regarded as at opposite ends of a continuum of biological possibilities.

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