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ELEMENTARY MODELS FOR BIOLOGICAL INTERACTION

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Summary

This paper provides a brief review of two theories of biological interaction of hazardous exposures, the Hewlett—Plackett theory and the sufficient-component cause theory. Although the former has its origin in bioassay and the latter in epidemiology, it is possible to show that the two theories are isomorphic in that they imply identical relationships between biological interaction and disease rates. The relationship of biological interaction to statistical and public health interaction is also reviewed. In particular, the presence or absence of biological interaction under the two theories does not correspond in a one-to-one fashion with the presence or absence of any proposed form of statistical or public health interaction. This observation confirms the importance of clearly distinguishing different concepts of interaction.

Introduction

Much of the biological hazard associated with an individual's occupation or environment arises from joint exposure to several substances. Terms such as "interaction", "synergy", "coaction", and "interdependence of effects" naturally arise in studies of such hazards, and a series of epidemiologic commentaries have attempted to clarify the meaning of such terms [1—3]. Interestingly, these commentaries have overlooked a large segment of the bioassay literature dealing with the characterization of independent action of two factors in bringing about a response, and the detection of departures from independent action. This bioassay literature goes back very far [4]; extensive theories of interaction have been worked out [5,6], and these theories continue to be developed and applied [7]. Although the bioassay theories are presented in terms of drug actions, they can be applied to any situation involving several sources of risk. I would like to bring this literature to the attention of researchers in risk assessment, and point out some interesting parallel results regarding independent action between the Hewlett—Plackett theory [5,7] and the sufficient-component causal theory introduced by Rothman [8]. For the sake of brevity, the following discussion omits mathematical derivations and detailed illustration of the principles discussed, as both can be

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found in the cited references; the article by Rothman introducing the sufficient-component theory [8] is particularly lucid.

Independent action under two biological theories

The Hewlett—Plackett theory arises naturally out of a conception of drug action as essentially deterministic in the individual, but probabilistic when considered in the context of sampling individuals from a population. A given individual's response to single or multiple drug exposures is, in theory, fixed as a function of the underlying biology of drug action and particular aspects of individual tolerance to the drugs involved. Individuals are expected to vary in their susceptibility to drug effects, giving rise to a sampling distribution for responses to drug action. Factors affecting an individual's all-or-none response can thus be modeled rigorously, yielding not precise estimates of population probabilities of response, but rather ranges of possible population probabilities. Where, within the range, a probability actually lies depends on the population correlation of drug tolerances. Independent action in the Hewlett—Plackett theory (called by them "non-interactive joint action") is a characteristic of drug effects on the individual level: drug A does not affect the minimum dose of drug B required to elicit a response and vice versa [5,7].

In order to describe the general quantitative implications of the Hewlett—Plackett theory, let R_{00} be the sampling probability of disease in the absence of both factors and let R_{10}, R_{01}, and R_{11} be the respective probabilities in the presence of the first factor alone, the second factor alone, and both factors (if a factor is continuous, "presence" means presence at a particular dose level). Finally, define a "background cause" to be any sufficient cause of disease that does not involve the study factors. Then, assuming background causes are distributed independently of the study factors, independent action under the Hewlett—Plackett theory implies [7] that

$$\max(R_{10}, R_{01}) \leqslant R_{11} \leqslant \min(1, R_{10}+R_{01}-R_{00})$$

The preceding results correspond in a precise fashion with the results given by Koopman [9] regarding the joint action of two discrete factors. In the sufficient-component-cause theory [8] employed by Koopman, independence between two factors is defined as lack of participation in the same sufficient cause; the latter implies that if each factor alone is insufficient to produce a response in an individual, no response will result from the presence of both factors. In this theory, synergism is defined as co-participation in a sufficient cause, and an instance of synergy is the occurrence of disease in an individual for whom both factors were necessary to produce disease. Let R now be defined as the cumulative incidence of disease, i.e., the expected proportion of new cases of disease occurring in a specified population during a specified period. Koopman shows that

$R_{11} \leqslant \min(1, R_{10}+R_{01}-R_{00})$ if there are no instances of synergy present [9], which parallels the second inequality deduced from the Hewlett—Plackett theory. A parallel to the first inequality can also be derived: consider again an individual instance, and define a sufficient factor as one that completes a sufficient cause. If an instance of antagonism is defined as prevention of disease by one factor in the presence of an otherwise sufficient factor, it can be shown that $R_{11} \geqslant \max(R_{10}, R_{01})$ if no instances of antagonism are present [10]. Thus, if independent action is defined as the absence of instances of synergy or antagonism, the mathematical implications of independent action in the sufficient-component-cause theory are isomorphic to those of the Hewlett—Plackett theory. Only the interpretation of R differs: in the Hewlett—Plackett theory, R is a parameter of a tolerance distribution, while in the sufficient-component-cause theory, R is an incidence parameter.

The parallel between the above theories may be extended further. Consider first the sufficient-component-cause theory. If an individual is defined to be susceptible to a factor (or change in dose) if the factor (or change) is sufficient (i.e., completes a sufficient cause of disease), the following relationships hold under independent action [10]: R_{11} achieves its upper bound, i.e., $R_{11} = \min(1, R_{10}+R_{01}-R_{00})$, if the subpopulation of those susceptible to the first factor is disjoint from the subpopulation of those susceptible to the second factor; R_{11} achieves its lower bound, i.e., $R_{11} = \max(R_{10}, R_{01})$, if the subpopulation susceptible to the first factor contains or is a subset of the subpopulation susceptible to the second factor; and

$$R_{11}-R_{00}=(R_{10}-R_{00})+(R_{01}-R_{00})-(R_{10}-R_{00})(R_{01}-R_{00})/(1-R_{00})$$

if the susceptibilities are unassociated. The latter is precisely the condition that Rothman [11] once postulated as representing independent action; given that some association of susceptibilities may be present, however, the condition is too restrictive as a definition of independent action. The three equalities follow from the Hewlett—Plackett theory under analogous conditions: denoting the correlation of response thresholds (for the two factors) by ρ, under independent action $R_{11} = \min(1, R_{10}+R_{01}-R_{00})$ if $\rho = -1$ and $R_{11} = \max(R_{10}, R_{01})$ if $\rho = 1$; assuming $\rho = 0$ and bivariate normality of the log response thresholds, we can also obtain the same equality as found for unassociated susceptibilities. If the degree of association of susceptibilities or thresholds can be specified to lie within a certain range, correspondingly more narrow limits for R_{11} under independent action can be derived [7].

Causal interpendence in relation to statistical and public health interaction

Koopman derives some important statistical implications of the upper bound for R_{11} under the above biological models: good fit of a multiplica-

tive model (such as a first-order logistic model) is consistent with interdependent biologic action, while good fit of an additive statistical model (such as a first-order linear rate model) is consistent with independent biological action. For both statistical models, the presence of significant positive (statistical) interaction terms implies the presence of biological interaction, while the presence of significant negative interaction terms can be consistent with biologically independent action [9]. (In this context, it should be noted that the common practice of calculating a "common odds ratio" estimate from epidemiologic data assumes an underlying multiplicative statistical model [12].) Because of the low power of tests for statistical interaction [13], good fit of a statistical model (e.g., failure to reject the "no-interaction" model) should not be used as a basis for inferring the presence or absence of interdependent action. Wahrendorf and Brown [7] offer a non-parametric test of the hypothesis H_0: $\max(R_{10}, R_{01}) \leqslant R_{11} \leqslant \min(1, R_{10}+R_{01}-R_{00})$, and although failure to reject H_0 does not imply independent action, rejection of H_0 does imply the existence of biological interaction under the above biological models.

The upper bound for R_{11} also has important public health implications: exceedance by R_{11} of the upper bound is equivalent to transadditivity (exceedance of additivity) of the cumulative incidence differences, i.e.,

$$R_{11} - R_{00} > (R_{10}-R_{00}) + (R_{01}-R_{00})$$

Under the above biological theories, such transadditivity implies the existence of a subpopulation of individuals for whom only joint presence of the two factors will increase risk of disease; this is the subpopulation of individuals in whom the two factors would act synergistically. In this subpopulation, removal or prevention of one of the factors will entirely remove or prevent excess risk due to both factors (even if the other factor remains). One can easily test for transadditivity by employing upper one-sided versions of the ordinary tests of additivity of the cumulative incidences (such as the tests discussed in Ref. [13]).

Although exceedance by R_{11} of the upper bound $R_{10}+R_{01}-R_{00}$ bears an interesting, if one-sided, resemblance to the definition of "public health interaction" as departure from additivity of rate differences [1—3], it is important to maintain the distinction of the biological and public health concepts. For example, under the above models, additivity does not automatically imply absence of synergy or antagonism [10]: it is theoretically possible that both the latter phenomena occur in the study population (albeit in different subpopulations), but their impacts on incidence cancel in such a fashion that R_{11} falls within the limits given above (although the biological plausibility of such coexistence would probably be very low in most situations). Thus, judgements as to the absence of biological interaction must extend beyond incidence relations to consideration of the mechanisms whereby the factors produce disease in individuals. In contrast, it is possible to assess "public health interaction" in terms of costs of total

case occurrence alone [1—3], without regard to the specifics of biological mechanisms. As public health considerations often focus on preventive factors, it is also worth noting that the implications of the above biological theories change considerably when the factors are preventive [10].

Discussion

The sufficient-component-cause theory has been criticized by some researchers because it does not incorporate stochastic elements in its view of disease etiology: under the theory, uncertainty in epidemiologic observations derives solely from our inability to completely characterize individual susceptibility; probabilistic elements thus enter only because of the incompleteness of information on individuals. The criticisms of this view appear academic, however, for there is no universal algorithm for distinguishing observations arising from random mechanisms and observations arising from incompletely characterized deterministic systems (as random-number generators nicely illustrate).

Perhaps a more serious criticism of the theories discussed here is that (as presented thus far) they have not formally incorporated longitudinal aspects of exposure history and disease development. Thus applications of the theories have been limited to situations in which joint exposure patterns can be factored into simple forms, such as a steady intensity or single point exposure.

The theories discussed here are certainly too general and incomplete to explain case etiology in the kind of detail usually required for preventive intervention (other than complete removal of exposure). Nevertheless, the Hewlett—Plackett theory has found application in bioassay problems (where simple exposure patterns are the rule), and the sufficient-component-cause theory has provided an elementary framework for illustrating the connection of epidemiologic parameters to biological phenomena [8—10]. At the very least, the theories should continue to have didactic value for clarifying the meaning of terms such as "interaction" and for leading into discussions of more complete models of etiology.

The definitions of independent action employed by the theories discussed here are perhaps the simplest precise definitions available. Other definitions have been used, however, and lead to different relationships between biological interaction (interdependent action) and statistical models of incidence [14]. The issue is one of semantic preference, and investigators should be aware of variations in usage. Whatever definition is employed, it is essential to maintain the distinction (often clouded in the statistical literature) between statistical and biological interaction, for in no case is there a one-to-one correspondence between the presence and absence of the two phenomena [1—3, 14].

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