Interaction - toward a precise understanding of a scientific term

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1. The interaction chaos

Quite a lot of studies in the review we did on effects of low alcohol effects on behavior (see KRÜGER, 1992, in these proceedings) not only looked at the main effects of alcohol but also investigated whether these main effects are moderated by other variables. When using repeated measurement designs, researchers are interested in how the effects change over time, when introducing personality variables (like age or sex) they try to find out whether alcohol acts differentially, when using easy and difficult tasks they try to specify the deteriorations induced by alcohol. A second kind of studies investigates the combined action of alcohol and other psychotropic drugs (see GOLD, KRÜGER & HÜPPE, 1992, in these proceedings). The third group of researches investigate system processes like "man-machine interactions". In all these contexts, variations in main effects are termed "interactions" without specifying more closely what this term means. The following paper will try to make some basic distinctions essentially needed for the correct use and understanding of this term "interaction".

2. Interaction as a descriptive term

The first and most important distinction is whether interaction is used as a

- descriptive or as an
- explanatory

term. Most of the confusion in the literature is due to this confusion. The experimental designs and the statistical evaluations to prove interactions are purely descriptive, even if they are tested by inferential statistical procedures. They explain nothing, they describe only the fact that the result of a two- (or higher-) dimensional cell entry is not the sum of the respective one-dimensional marginals. This is the understanding in most statistical textbooks, e.g., WINER (1971). In the case of a descriptive use of the term interaction it must first be distinguished whether the interaction concerns factors or observables. Both are treated under the heading "multivariate procedures" as shown in Figure 1.

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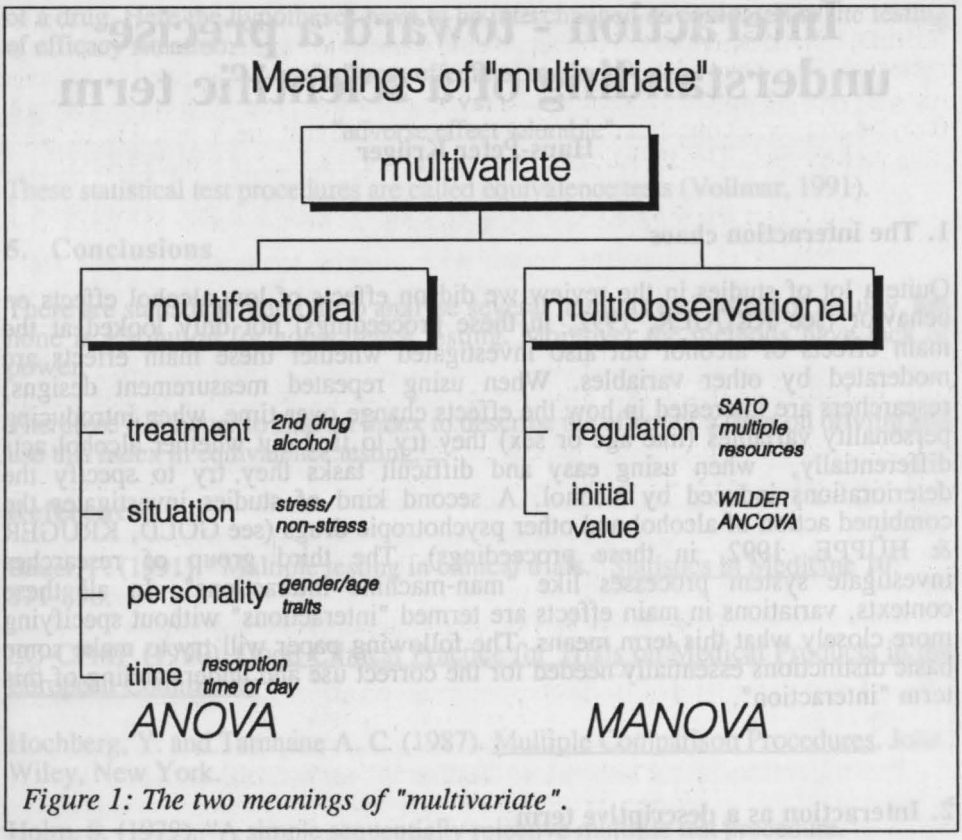


Figure 1: The two meanings of "multivariate".

The term "multivariate" is ambiguous: on the one hand it means that more than one observable is under study. Those data were regularly evaluated by a Multivariate Analysis of Variance (MANOVA). Our review on alcohol effects did not find one study which investigated "multiobservationally" in this sense. This is a great factual deficit: the organism is a regulated system. That means that the basic treatment effect is modulated by processes of compensation, dependencies on the initial values (e.g., WILDERs law of initial values), hierarchies of resources are influenced by the experimental treatment. Statistically all these processes lead to a treatment dependent change in the correlation between observables.

> Take for example the speed-accuracy trade off (SATO). It means that there is a typical (regularly positive) correlation between speed and accuracy. This correlation changes into the negative when the subject gets tired. The appropriate statistical procedure would be a multiobservational MANOVA.

While studies of this type are still missing, the scientific reality is characterized by a multifactorial approach where two or more factors are varied hierarchically or in a nested design. Here, the interaction hypothesis refers to the independent variables. The standard evaluation is done with the ANOVA. But:

approximately one half of the studies in the review on alcohol-drug interactions (GOLD, KRÜGER & HÜPPE, 1992) tries to prove interaction one-dimensionally. One of the standard designs is a one factor experiment with the three levels "placebo", "verum1" (maybe the drug) and "verum1+verum2" (maybe drug + alcohol). The aim of the study is to test the interaction between drug and alcohol. The statistical tests were done as two-group comparisons:

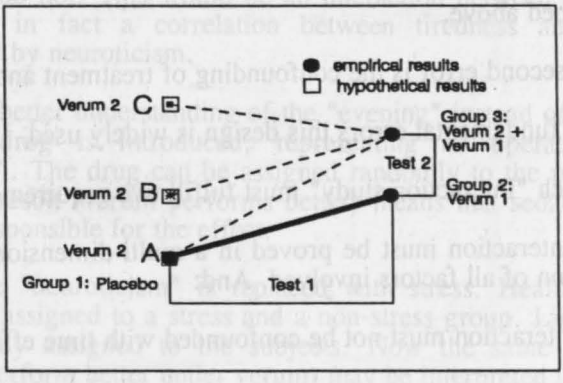
- to prove the drug effect, the difference between placebo and verum1 is tested (test 1),

- to prove the interaction effect the group "verum1" is tested against the group "verum1+verum2" (test2).

This procedure is often used also in the case when a fourth group of "verum2 alone" is introduced. It is immediately evident that this one-dimensional procedure is not appropriate to test a two-dimensional concept. Figure 2 shows that there are at least three possible ways by which a significant interaction in test 2 can occur.

1 * 3 does not equal 2 * 2

Group 1	Group 2	Group 3
Plac	Ver1	Ver1+Ver2



A ordinal interaction
B no interaction
C disordinal interaction

Figure 2: Pitfalls in the interpretation of interactions from one-dimensional designs.

The decision between the three cases in Figure 2 can only be made by

introducing a fourth group "verum2 alone". The possible results of this groups (all yielding significant interaction terms in the comparison of "verum1" vs. "verum1+verum2") are depicted in Fig. 2 as open squares:

Case A: verum2 alone has no effects as compared to placebo. In conjunction with verum1 it increases the effect of the latter. This is meant by "ordinal interaction".

CASE B: verum2 alone has an effect as compared to placebo. The effect of "verum1+verum2" is simply the sum of both single or main effects. In fact, despite a significant result there is no interaction at all.

CASE C: verum2 alone has a marked effect as compared to placebo. This effect is decreased by the introduction of verum1. This is meant by disordinal interaction.

(The fourth case of a semi-disordinal interaction is not described here. For a detailed description of the different types of statistical interactions and their nonparametric testing see KRÜGER, 1977). It is obvious that the same result of the test 2 in Figure 2 can be caused by fully different processes. These causes cannot be described adequately if an unifactorial approach has been chosen.

Even worse are designs where two independent groups get either placebo or verum, and, after the first test, are additionally treated with alcohol. If there is a difference between the alcoholized groups an interaction is assumed. This design combines two errors:

- the first is the one-dimensional test of a two-dimensional concept as described above.

- The second error is the confounding of treatment and time effects.

Despite these fundamental errors this design is widely used.

Therefore, each "interaction study" must fulfill two requirements:

- the interaction must be proved in a multi-dimensional design with full variation of all factors involved. And:

- the interaction must not be confounded with time effects.

2. Interaction as an explanatory term

2.1. Random versus organismic factors

The correct statistical description of an "interaction" is the prerequisite for its use in scientific explanation. Interaction as an explanatory term must first avoid the basic pitfall of confounding correlative and causal interpretations. This first and necessary distinction must be made on the nature of the factors involved.

For each factor must be decided: is it a random (treatment) or an organismic (block, attribute) variable?

A random factor is characterized by the fact that the treatments could be assigned to the subjects by a random procedure. Whether a subject gets placebo or verum is decided by the coin. Therefore random variables do not correlate with any other feature of the subject - the expectation value for this correlation is zero. On the other hand organismic factors cannot be assigned to the subjects but only be controlled by the experimenter. Gender or age are variations caused by nature, not by the experimenter. This is also the case with most of the sociodemographic variables used in drug research.

The distinction "random - organismic" is essential. In an experiment we found a significant ordinal interaction on perceived loudness between sex and sound pressure measured in db. Is sex the cause for different loudness? Are women more irritable? One fact perplexed us: we only found the effect when using earphones. This opened the door to the understanding it: the basic variable is not sex but the physical size of the auditory channel. Subjects with smaller heads hear the same signal louder.

That means: when using organismic variables only correlative interpretations are possible. Any other variable which correlates with the organismic factor may be the cause of the observed phenomenon, too. Therefore, if a researcher is interested in a causal interpretation he has to replace his organismic variables with random ones, if at all possible. Take for example the following procedure:

- it is observed that neurotics perform better in the evening whereas non-neurotics do not. This would be an interaction between two organismic variables, in fact a correlation between tiredness and performance moderated by neuroticism.

- to get a better understanding of the "evening" instead of the day time a sedating drug is introduced, representing an operationalization of "tiredness". The drug can be assigned randomly to the patients. Getting the same result (verum performs better) means that sedation as a causal term is responsible for the effect.

- now the "neuroticism" is replaced with stress. Healthy subjects are randomly assigned to a stress and a non-stress group. Likewise the drug is randomly assigned to the subjects. Now the same result (stressed subjects perform better under verum) may be interpreted in causal terms.

2.2. Causal interpretation - Coergisms

Thus, only in the cases where the correct statistical description of an interaction is given and the factors involved can be interpreted causally, the observed interaction can be explained. The corresponding models in pharmacology are termed "coergisms". Unfortunately, up to now no stringent and generally accepted terminology exists. Three ways of approaching coergisms are widely

confounded:

a. **evaluative**: here the distinction between (desired) main effects of a compound and (undesired) side effects is crucial. Only the latter are characterized as interactions or coergisms and are investigated further for possible agents which may have caused the undesired effects.

b. **descriptive**: in what direction is the main effect changed if an additional condition (physiological or pharmacological) is introduced?

c. **explanatory**: what are the possible causes for the coergism?

The evaluative approach is not appropriate. Before evaluating an effect, its type and its possible causes must be clear. The descriptive approach deals with the typology of coergisms. A possible classification is given in Figure 3.

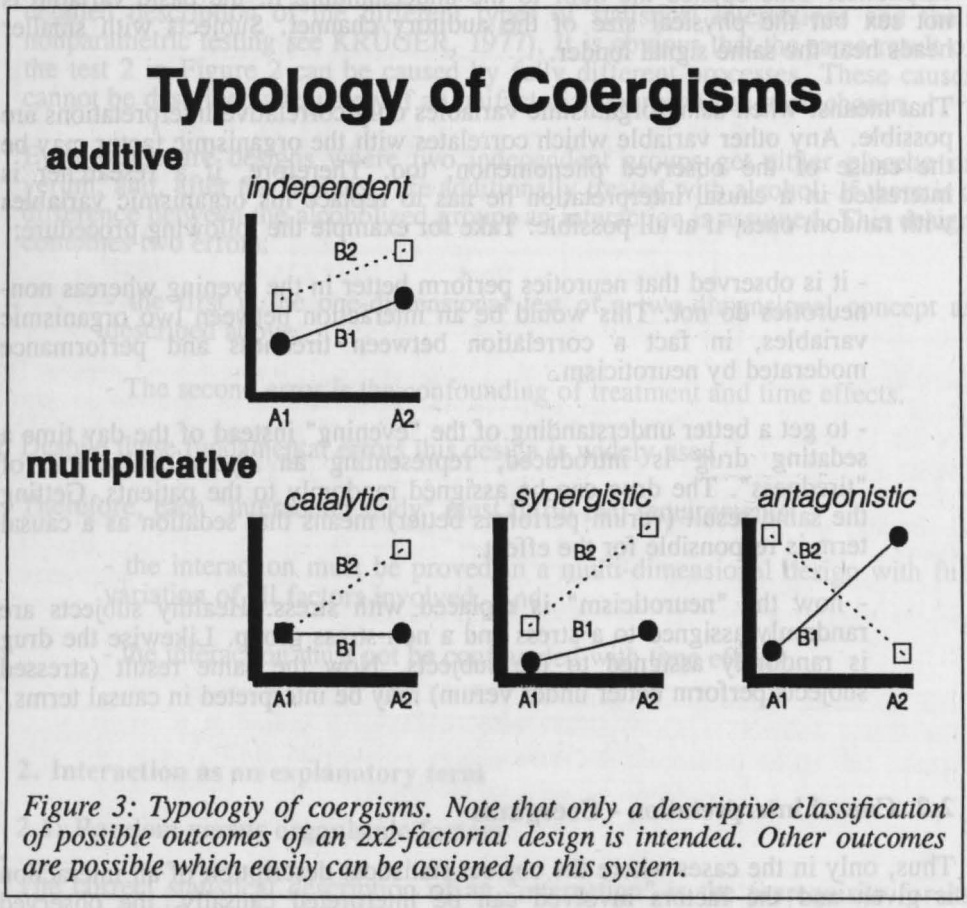


Figure 3: Typologiy of coergisms. Note that only a descriptive classification of possible outcomes of an 2x2-factorial design is intended. Other outcomes are possible which easily can be assigned to this system.

There is some confusion in the literature about the use of the term "synergistic". Sometimes the additive and catalytic coergisms of Fig.3 are also classified as synergistic. These authors contrast this broad class of synergisms with the antagonistic coergism. The reason is obvious: this class of synergisms is characterized by an increase in drug action induced by the second compound. Let B1 be the drug the researcher is interested in. Then, all so-called synergistic effects of B1+B2 act in the same direction as the effect of B1 alone. That is why this classification is mostly used in the evaluative context mentioned above.

In contrast, the system of Figure 3 is oriented toward the statistical evaluation. An additive coergism is only assumed in the case when main effects occur whereas the interaction term in the statistical evaluation is not significant. All multiplicative coergisms are characterized by a significant interaction term. Catalytic and synergistic coergisms are in the statistical terminology ordinal interactions, whereas the antagonistic coergism corresponds to a statistical disordinal interaction. Catalytic coergism is separated from synergistic coergism by the fact that only in the presence of both compounds an effect occurs. Thus, only a thorough analysis of the cell means is able to detect the correct type of interaction (see ROSNOW & ROSENTHAL, 1989).

The investigation of the mechanisms underlying the effect is carried out independently of the type of coergism. Basically, this is the true domain of explanation. At this level, the researcher tries to conceive the processes which lead to the observed phenomena. This level must be clearly separated from the descriptive level of typologies. Figure 4 gives the necessary distinctions.

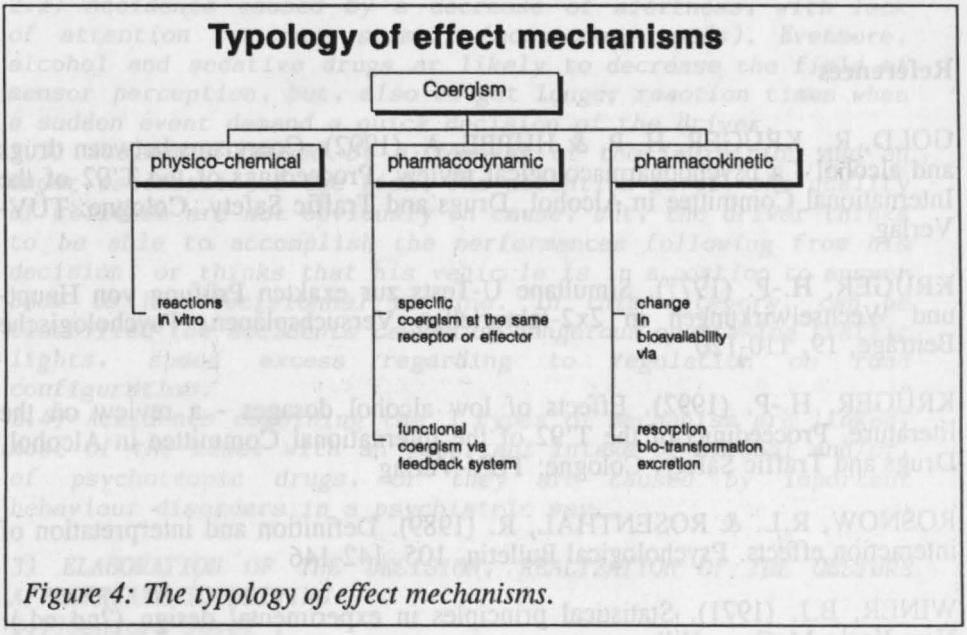


Figure 4: The typology of effect mechanisms.

First, physico-chemical mechanisms may cause an interaction. If so, these

processes should be found even when experimenting in vitro. Second, the cause of the coergism may be a special interaction of the compound(s) with the organism. This may happen at the level of receptors or effectors directly (specific) or it may be the result of a systemic response to the compound. In the latter case the interacting compounds are acting at different sites of the organism and these sites are linked by the system (functional or systemic coergism). Third, the bio-availability of one compound may be influenced by the other compound. This may happen either during the phase of resorption, or the phase of bio-transformation (metabolism) or in the phase of excretion.

3. Summary

The term "interaction" must be used carefully. First, it has to be stated whether interactions between observables or experimental factors are meant. The factorial understanding of interaction calls for at least two-dimensional factorial designs. Only on the basis of those designs an adequate explanation of the type of the interaction is possible. The first step in explanation is the correct typological classification of an interaction. Therefore, it must be distinguished between additive and multiplicative coergisms, the latter including catalytic, synergistic, and antagonistic coergisms. The typology correctly defined, the coergism is open to causal explanation. Different causes for coergisms may be found in physico-chemical, pharmacodynamic, and pharmacokinetic interactions.

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