Journal of Discrete Mathematical Sciences and Cryptography

ISSN: 0972-0529 (Print) 2169-0065 (Online) Journal homepage: https://www.tandfonline.com/loi/tdmc20

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To cite this article: Vladimir G. Panov & Julia V. Nagrebetskaya (2018) Classification of combined action of binary factors and Coxeter groups, Journal of Discrete Mathematical Sciences and Cryptography, 21:3, 661-677, DOI: 10.1080/09720529.2016.1222733

To link to this article: https://doi.org/10.1080/09720529.2016.1222733

Journal of Discrete Mathematical Sciences & Cryptography
ISSN 0972-0529 (Print), ISSN 2169-0065 (Online)
Vol. 21 (2018), No. 3, pp. 661–677
DOI : 10.1080/09720529.2016.1222733

Classification of combined action of binary factors and Coxeter groups

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Abstract

A general model of an experiment with a finite number of two-level factors and a two-level outcome is considered. Joint action types are identified within the formalism developed. It is shown that the experiment can be represented by a free Boolean algebra and the identification of joint action types in this experiment reduces to the study of action orbits of an automorphism group over the Boolean algebra. Two types of symmetries are considered, and related classifications are provided.

Keywords*: Sufficient cause component theory, causality in epidemiology, Neyman-Holland-Rubin causality theory, Boolean algebras, automorphism group over Boolean algebra, group action orbit over a set, Dihedral groups, Coxeter groups.*

1. Introduction

In the 20 century, mathematical methods started to be actively used in such sciences as biology and medicine [6, 7, 11], with the prevalence of mathematical statistics applications in these areas, especially in medicine. Less common and more specialized are applications of algebraic methods to biological and medical problems [3, 22]. In what follows we consider an application of the theory of free Boolean algebras and the theory of groups to epidemiology (the sufficient cause component theory) [6, 19, 23].

The main goal pursued by the theory of sufficient causes is to describe the mechanisms of causality underlying a disease. Building a model of

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causality in medicine is complicated by a variety of factors that influence the onset of disease [23, 24]: *constitutional cause, direct cause, endogenous cause, exogenous cause, indirect cause, necessary cause, precipitating cause, predisposing cause, primary cause, secondary cause, specific cause, sufficient cause.* This list can be continued, if desired.

Of the above causal relationships "factor (cause)-disease", the concept of sufficient cause has so far been best formalized. The basic principles of the sufficient cause formalism were considered in [13] for an experiment with two two-level factors X_1 and X_2 and two-level outcome Y (binary experiment). In the same paper, Miettinen showed for this case how to reduce the sufficient-cause framework to a counterfactual. Let us denote the reference categories of the factors X_1 and X_2 with 0 and 1, Y_{x_1, x_2} is denoted as the value of the outcome Y under the condition $X_1 = x_1, X_2 = x_2, x_i = 0,1, i = 1,2.$ Y_{x_2, x_2} determines a real or potential response of an individual to exposure to the factors at the given combination of their levels. The response type for the given individual is a set of values $(Y_{00}, Y_{10}, Y_{01}, Y_{11})$ (below it is referred to as 'full response'). This allowed sufficient causes to be presented within the Neyman-Holland-Rubin causality theory [12]. Finally, Miettinen [13] argued for a classification of two-factor interactions by type of full response, and suggested a term for every such type reflecting the character of interaction or lack of it. Unfortunately, there were logical gaps in Miettinen's classification, which were noticed by Greenland and Poole [9].

In a medical or biological experiment, factors X_1 and X_2 typically mean an exposure of subjects to two toxins (or drugs), with the levels of these factors specifying concentrations of these substances. The sought-for indicator variable Y means, for example, the presence ($Y = a$) or absence $(Y = b, a \neq b)$ of a specified effect, such as an expected change in a physiological index.

Of particular interest in this context is the question of joint (combined) action produced by these factors. The most important (but not the only) types of combined effect from the two factors are described by the following terms: *additivity*, i.e. the combined effect is approximately equal to the sum of their isolated effects; *superadditivity* (or *synergism*), i.e. the combined effect is significantly greater than the sum of the isolated effects; and *subadditivity* (or *antagonism*), i.e. the combined effect is significantly less than the sum of the isolated effects.

It should be noted that the factors are often nominal and their levels are equivalent states of the system being studied, differing only in the values assigned to the factors' levels. In this case, the properties of the system under study, such as the type of combined action should not depend on the numeric coding of a factor's level. In particular, without loss of generality, a factor's level can be coded by values 0 and 1. An exposure to the factors with a given combination of their levels results in an outcome Y taking on values 0 or 1. In the sufficient cause theory, the relationship between the outcome Y and the factors X_1 and X_2 is expressed by the equality [9, 13, 21]:

$$Y = a_1X_1 \vee a_2X_2 \vee a_3 \vee \overline{X}_1 \vee a_4\overline{X}_2 \vee a_5X_1X_2 \vee a_6\overline{X}_1X_2 \vee a_7X_1\overline{X}_2 \vee a_8\overline{X}_1\overline{X}_2 \qquad (1)$$

The conjunction sign is omitted and the disjunction sign $\vee$ is used in the common logical sense. The binary constants a_i take on values 0 and 1 and determine the presence (if $a_i = 1$) or absence (if $a_i = 0$) of the corresponding conjunction in (1). The expression (1) is convenient for understanding the dependence of the response Y on the variables X_1 and X_2, but generally, it is redundant and inconvenient for further analysis [16, 17].

In what follows we consider a formal model of the binary experiment and a classification of combined effect types within the formalism developed. We do not try to define the notion of the *type* (or *character*) of joint action produced by the factors. Instead, we will examine the combined effects in terms of those properties of the joint action, which the experimenter finds believable in his/her experiment. Verification of these properties may be more easy and even obvious in some cases, that facilitates the adoption of the conclusions that follow from these properties.

2. Formalisation of the binary experiment

Although we mainly consider the most frequently discussed case of two variables, formal constructions can be easily introduced for n variables (binary factors). For illustration, however, we will refer to the case of two variables.

2.1 *State space*

Assuming that the levels of the factors and the response have been chosen to be equal to 0 and 1, we can represent the response Y as a Boolean function of the factors $X_1,\ldots,X_n$. For example, X_1 means the effect (its presence in the experiment) of the factors X_1 at level $X_1 = 1$; accordingly, $\overline{X}_1$ means the effect of the factor at level $X_1 = 0$. To avoid confusion between the original factors and the Boolean variable in the model, let the Boolean variables be denoted as $x_1,\dots,x_n$. Then the response Y is a Boolean function of these variables. Let the set of all Boolean functions of n variables be designated by $\mathbb{B}(x_1,\dots,x_n)$. With respect to conjunction, disjunction and complement, the set $\mathbb{B}(x_1,\dots,x_n)$ forms a free Boolean algebra. We can also introduce into the algebra $\mathbb{B}(x_1,\dots,x_n)$ an operation of addition mod 2, which will be designated by +. Each Boolean function in $\mathbb{B}(x_1,\dots,x_n)$ can be written in a form similar to (1). However, it would be handier to choose some of the standard representations for the Boolean function, for example, in the form of a full disjunctive normal form [5]. For example, any Boolean function $f(x_1, x_2)$ in $\mathbb{B}(x_1, x_2)$ may be uniquely represented as

$$f(x_1,x_2) = f_{00}\overline{x}_1\overline{x}_2 \vee f_{01}\overline{x}_1 x_2 \vee f_{10}x_1\overline{x}_2 \vee f_{11}x_1x_2 = \bigvee_{\alpha,\beta\in\mathbb{B}} f_{\alpha\beta}x_1^{\alpha}x_2^{\beta}, \qquad (2)$$

where $f_{\alpha\beta} = f(\alpha,\beta),\ \alpha,\beta \in \mathbb{B},\ x_i^{\gamma} = \begin{cases} x_i, \text{ if } \gamma = 1, \\ \overline{x}_i, \text{ if } \gamma = 0. \end{cases}$

Since the conjunction of any two different elementary conjunctions in (2) is equal to zero, any Boolean function in $\mathbb{B}(x_1, x_2)$ can be represented as

$$f(x_1,x_2) = f_{00}\overline{x}_1\overline{x}_2 + f_{01}\overline{x}_1 x_2 + f_{10}x_1\overline{x}_2 + f_{11}x_1x_2,$$

and, like representation (2), this representation is unique.

2.2 *Symmetries of joint action*

An essential element in the formalization of the binary experiment is identification of its symmetries, which in this case are the invariance conditions mentioned in the Introduction. It is those symmetries of combined effect that determine the various types of joint action produced by the factors.

The initial classification of the types of joint action produced by the binary factors in the theory of sufficient causes was considered by Miettinen [13, 14]. Greenland and Poole [9] criticized his solution, primarily for the noninvariance of the responses in relation to a recoding of factor levels: "…without the adoption of a deeper theory about how effects result, no reference category can be regarded as correct'' and "…it would seem worthwhile to discover what, if any, properties of joint action are invariant under recoding or changes in reference levels'' [9]. In the same paper, they proposed a more precise classification allowing for the invariance conditions. In [9], however, this invariance was not used fully, which was noted in [21].

2.2.1 Symmetries in the theory of sufficient causes

In [20, 21], the invariance mentioned in [9] was used more consistently. In the formal model of binary experiment under consideration, this leads to the fact that a breakdown of responses into classes with similar joint-action characteristics should be invariant with respect to a recoding of the factor levels [16, 17]. For the case $n = 2$, these properties could be written in the form of the following two axioms:

A1) The character of the joint action produced by the factors X_1 and X_2 is the same as for the factors X_2 and X_1.

A2) The character of the joint action produced by the factors X_1 and X_2 is the same as for the factors $\overline{X}_1$ and X_2.

More precisely, the axiom A1 suggests that the character of the joint action produced by the factor X_1 at level $X_1 = 1$ and the factor X_2 at level $X_2 = 1$ will be the same as that of the factor X_2 at level $X_2 = 1$ and the factor X_1 at level $X_1 = 1$ (symmetry of joint action). This requirement is, presumably, met always. The axiom A2 means that the type of the joint action produced by the factors X_1 and X_2 at given levels will be the same as at any other levels of these factors.

For the Boolean variables x_1, x_2, the properties of A1, A2 result in mappings T_1, T_2 of the set of free generators $\{x_1, x_2, \overline{x}_1, \overline{x}_2\}$ of the algebra $\mathbb{B}(x_1, x_2)$ into itself and, hence, into the set $\mathbb{B}(x_1, x_2)$ under the rules

$$\begin{aligned} T_1(x_1) &= x_2 & T_2(x_1) &= \overline{x}_1 \\ T_1(x_2) &= x_1 & T_2(x_2) &= x_2 \\ T_1(\overline{x}_1) &= \overline{x}_2 & T_2(\overline{x}_1) &= x_1 \\ T_1(\overline{x}_2) &= \overline{x}_1 & T_2(\overline{x}_2) &= \overline{x}_2 \end{aligned}$$

or

$$\begin{aligned} T_1(x_1, x_2, \overline{x}_1, \overline{x}_2) &= (x_2, x_1, \overline{x}_2, \overline{x}_1) \\ T_2(x_1, x_2, \overline{x}_1, \overline{x}_2) &= (\overline{x}_1, x_2, x_1, \overline{x}_2) \end{aligned}$$

These transformations could be continued to the automorphisms of the Boolean algebra $\mathbb{B}(x_1, x_2)$ by the equality:

$$T_i(f(x_1, x_2)) = f_{00}T_i(\overline{x}_1\overline{x}_2) + f_{01}T_i(\overline{x}_1x_2) + f_{10}T_i(x_1\overline{x}_2) + f_{11}T_i(x_1x_2),$$

where

$$T_1\left(x_1^\alpha x_2^\beta\right) = x_1^\beta x_2^\alpha,\ T_2\left(x_1^\alpha x_2^\beta\right) = x_1^{\overline{\alpha}} x_2^\beta,\ \overline{\alpha} = 1 - \alpha,\ \alpha, \beta \in \mathbb{B}$$

Let G denote a group of transformations of the Boolean algebra $\mathbb{B}(x_1, x_2)$ generated by transformations T_1 and T_2. Then any transformation $T \in G$ acts on the Boolean function $f(x_1, x_2)$ as per the following rule:

$$T(f(x_1, x_2)) = f_{00}T(\overline{x}_1\overline{x}_2) + f_{01}T(\overline{x}_1x_2) + f_{10}T(x_1\overline{x}_2) + f_{11}T(x_1x_2).$$

In the "coordinates", this action is given by:

$$T\left(f_{00}, f_{01}, f_{10}, f_{11}\right) = \left(f_{T^{-1}(0,0)}, f_{T^{-1}(0,1)}, f_{T^{-1}(1,0)}, f_{T^{-1}(1,1)}\right).$$

Remark 2.1: The group G is not a group of all automorphisms of the algebra $\mathbb{B}(x_1, x_2)$. For example, it is easy to show that the mapping φ of the Boolean algebra $\mathbb{B}(x_1, x_2)$ into itself determined by the equalities $\varphi(x_1) = x_1x_2 + \overline{x}_1\overline{x}_2$, is continued to the automorphism of the Boolean algebra $\mathbb{B}(x_1, x_2)$, but it does not belong to the group G.

Remark 2.2: Geometrically, the group of transformations G generated by the transformations T_1 and T_2 is nothing but a symmetry group of unit square, i.e. a dihedral group D_8 (notation D_4 is also used), or a Coxeter group B_2 [10].

In the general case of binary experiment with n factors, the corresponding axioms A1 and A2 take on the form:

B1) The character of the joint action produced by the factors $X_1,\dots,X_n$ does not depend on the numbering order of these factors.

B2) The character of the joint action produced by the factor $X_1, X_2,\dots,X_n$, is the same as for the factors $\overline{X}_1, X_2,\dots,X_n$.

Let us introduce multi-index notations

$$\begin{aligned} \boldsymbol{\alpha} &= (\alpha_1, \alpha_2, \ldots, \alpha_n), \quad \alpha_i \in \mathbb{B} \\ \overline{\boldsymbol{\alpha}} &= (\overline{\alpha}_1, \overline{\alpha}_2, \ldots, \overline{\alpha}_n) = \mathbf{1} - \boldsymbol{\alpha} = (1-\alpha_1, 1-\alpha_2, \ldots, 1-\alpha_n) \\ \boldsymbol{x} &= (x_1, \ldots, x_n), \quad \overline{\boldsymbol{x}} = \left(\overline{x}_1, \ldots, \overline{x}_n\right) \quad \boldsymbol{x}^{\boldsymbol{\alpha}} = (x_1^{\alpha_1}, \ldots, x_n^{\alpha_n}) \end{aligned}$$

Then the properties of B1 and B2 yield the following transformations on the set of variables $\left\{x_1, \ldots, x_n, \overline{x}_1, \ldots, \overline{x}_n\right\}$

$$T_P\left(\boldsymbol{x}, \overline{\boldsymbol{x}}\right) = \left(P\boldsymbol{x}, P\overline{\boldsymbol{x}}\right), \quad T_0\left(\boldsymbol{x}, \overline{\boldsymbol{x}}\right) = \left(\overline{x}_1, x_2, \ldots, x_n, x_1, \overline{x}_2, \ldots, \overline{x}_n\right)$$

where P is an arbitrary permutation of a set of n elements ($P \in S_n$).

The symmetry group G_n in the theory of sufficient causes with n binary factors is generated by transformations $\{T_P\}_{P \in S_n}$, and T_0, which are naturally continued to the automorphisms of the free Boolean algebra $\mathbb{B}(x_1,\ldots,x_n)$. This group has been well studied in another context (see, e.g., [15, 18]).

Theorem 2.3: *The symmetry group in an n-dimensional binary theory of sufficient causes is isomorphic to the symmetry group of an n-dimensional cube, or to the hyperoctahedral group Oct_n.*

Remark 2.4: The hyperoctahedral group Oct_n is a Coxeter group of reflections of the n-dimensional cube and is isomorphic to the group B_n, defined as follows

$$\begin{aligned} B_n = \Big\langle b_1, \ldots, b_n \quad | \, b_i^2 = e, \left(b_1 b_2\right)^4 = e, \left(b_i b_{i+1}\right)^3 = e, \\ i \in \{2, \ldots, n-1\}, \left(b_l b_k\right)^2 = e, \, l, k \in \{1, \ldots, n\}, |\, l-k \,| \neq 1 \Big\rangle \end{aligned}$$

where b_i is a reflection with respect to the hyperplane $x_{i-1} = x_i$ (transformation $T_{i-1,\, i}$), $i \in \{2, \ldots, n\}$, b_1 is a reflection with respect to the hyperplane $x_i = 0$ (transformation T_0). The hyperoctahedral group Oct_n is also isomorphic to the wreath product $\mathbb{Z}_2 \wr S_n$ [1, 2] and, hence, to the semidirect product $\mathbb{Z}_2^n \rtimes S_n$. In particular, $|G_n| = 2^n \cdot n!$ In the wreath product $\mathbb{Z}_2 \wr S_n$, the subgroup $\langle T_0 \rangle$ of the group G_n corresponds to the group $\mathbb{Z}_2$ and a subgroup $\left\{T_p \,|\, p \in S_n\right\} = \langle T_{ij} \,|\, i \neq j \rangle$ corresponds to the group S_n. Consequently, we have

Theorem 2.5: *The symmetry group G_n of an n-dimensional binary theory of sufficient causes is isomorphic to the group* $Oct_n \cong \mathrm{Aut}(\mathbb{B}^n) \cong \mathbb{Z}_2 \wr S_n \cong \mathbb{Z}_2^n \rtimes S_n \cong B_n$.

2.2.2 Symmetries of an experiment with isoeffective levels

Another experiment is possible in which the character of joint action at levels $X_1 = 0$, $X_2 = 0$ and $X_1 = 1$, $X_2 = 1$, should be regarded to be the same for certain reasons. The type of joint action could differ in, for example, some characteristic of strength, i.e. quantitatively, but would not differ qualitatively. For example, if $X_1 = 0$ and $X_2 = 0$ represent the actions of some toxic substances in their isoeffective doses (expressed, for example, as the isoeffective dose ED_{95}), while $X_1 = 1$ and $X_2 = 1$ represent the action of the same substances in the isoeffective doses ED_{10}, it is to be expected that the joint action of these factors at levels $X_1 = 1$ and $X_2 = 1$ would be of the same type as at levels $X_1 = 1$ and $X_2 = 1$ although these cases may differ in the strength of interaction. At the same time, the character of interaction between the levels $X_0 = 0$ and $X_2 = 1$ could be substantially different, for example, the impact of the level $X_2 = 1$ could swallow the presence of the level $X_1 = 0$. From the viewpoint of maintaining the type of joint action in this case, the only possible option is to recode simultaneously the levels $X_1 = 0$ and $X_2 = 0$ into $X_1 = 1$ and $X_2 = 1$, respectively. For brevity, below the experiment which allows such recodings only will be called *experiment with isoeffective levels.*

In this experiment, the symmetry conditions are given by:

A1) The character of joint action produced by the factors X_1 and X_2 is the same as for the factors X_2 and X_1.

C2) The character of joint action produced by the factors X_1 and X_2 is the same as for the factors $\overline{X}_1$ and $\overline{X}_2$.

For these symmetries, the corresponding group of transformations G_1 is defined by the following generators:

$$T_1\left(x_1, x_2, \overline{x}_1, \overline{x}_2\right) = \left(x_2, x_1, \overline{x}_2, \overline{x}_1\right)$$
$$T_2\left(x_1, x_2, \overline{x}_1, \overline{x}_2\right) = \left(\overline{x}_1, \overline{x}_2, x_1, x_2\right)$$

As before, the group G_1 is formed by a natural spreading of these relations to the automorphisms of the Boolean algebra $\mathbb{B}(x_1, x_2)$. Its explicit representation is given by:

$$G_1 = \{e, T_1, T_2, T_1T_2 = T_2T_1\}$$

Hence, the group G_1 is nothing but a dihedral group D_4, or a Klein's four-group, i.e. a direct product of two cyclic groups of order 2, $G_1 = \mathbb{Z}_2 \times \mathbb{Z}_2$. Being a dihedral group, it is also a Coxeter group.

Generalization of this situation to the case of n binary variables is ambiguous since condition C2 could be fulfilled either for all factors together or for some proper subset of these factors. Instead of condition C2, let us introduce the condition

C2k) The character of joint action produced by the factors $X_1,\dots,X_n$, is the same as for the factors $\overline{X}_1, \overline{X}_2, \dots, \overline{X}_k, X_{k+1}, \dots, X_n$.

The experiment in which the axioms B1 and C2k are fulfilled will be said to be described by an n-dimensional theory of sufficient causes with k isoeffective factors.

As before, the conditions B1 and C2k determine the transformations T_P, T_{0k} on the set $\left\{x_1, \dots, x_n, \overline{x}_1, \dots, \overline{x}_n\right\}$ of the variables of algebra $\mathbb{B}(x_1,\dots,x_n)$

$$\begin{aligned} T_P\left(\boldsymbol{x}, \overline{\boldsymbol{x}}\right) &= \left(P\boldsymbol{x}, P\overline{\boldsymbol{x}}\right), \\ T_{0k}\left(\boldsymbol{x}, \overline{\boldsymbol{x}}\right) &= \left(\overline{x}_1, \overline{x}_2, \dots, \overline{x}_k, x_{k+1}, \dots, x_n, x_1, \dots, x_k, \overline{x}_{k+1} \dots, \overline{x}_n\right) \end{aligned}$$

where P is an arbitrary permutation of the set of n elements ($P \in S_n$).

Before formulating the basic theorem of this part, let us introduce some notations.

Let t_i be a transformation of the set $(x, \overline{x})$, defined by the equality $t_i(x, \overline{x}) = (x_1, \dots, x_{i-1}, \overline{x}_i, x_{i+1}, \dots, x_n, \overline{x}_1, \dots, \overline{x}_{i-1}, x_i, \overline{x}_{i+1}, \dots, \overline{x}_n, \dots, \overline{x}_n)$, $1 \leqslant i \leqslant n$. The set A is a certain subset of the set $\{1, 2, \dots, n\}$, $|A|$ being the cardinality of the set A. Let the transformation t_A be defined as a product of all t_i, $i \in A$ and considered as continued to the automorphism on $\mathbb{B}(x_1,\dots,x_n)$. Then $T_{0k} = t_1 t_2 \cdots t_k$. The transformation t_A may be represented by a row from $\mathbb{Z}_2^n$, in which the positions with indices $i \in A$ are occupied by zeros and the rest of the positions by unities. In this representation, the composition of the transformations t_A and t_B is equivalent to the modulo-2 summation of the corresponding rows, i.e. $t_A t_B = t_A + t_B$.

Let us define the subgroup H_A in G_n as a subgroup generated by the automorphism t_A and the group S_n. If $A = \{1, 2, \dots, k\}$ then we will denote the group H_A simply as H_k i.e. $H_k = H_{\{1,2,\dots,k\}}$. From Theorem 2.5 follows

Lemma 2.6: *If A and B are equinumerous subsets of {1, 2, ..., n}, then* $H_A = H_B = H_k$*, where* $k = |A| = |B|$.

The next statement also follows from Theorem 2.5 and describes the structure of the subgroups H_k for $k < n$.

Lemma 2.7: *For any* $1 \leqslant k < n$*, there is the equality* $H_k = H_1$ *if k is odd, and* $H_k = H_2$ *if k is even.*

Remark 2.8: Since $G_n \cong \mathbb{Z}_2^n \rtimes S_n$, the group H_2 can be identified with the group $Z \rtimes S_n$, where Z is a subgroup of $\mathbb{Z}_2^n$ consisting solely of such collections which contain an even number of unities. As a subgroup of Oct_n, the group H_2 is a normal divisor of index 2. In [2] have shown that the group $Z \rtimes S_n$ is isomorphic with the semidirect product $\mathbb{Z}_2^{n-1} \rtimes S_n$ and is a Coxeter group D_n. In particular, $|H_2| = 2^{n-1} \cdot n!$

Like the group B_n, the group D_n may be represented as follows [2]

$$D_n = \Big\langle d_1, \ldots, d_n \quad | \, d_i^2 = e, 1 \leqslant i \leqslant n; \left(d_i d_{i+1}\right)^3 = e, 2 \leqslant i \leqslant n-1; \\ \left(d_l d_k\right)^2 = e, |l-k| \neq 1, (l,k) \neq (1,3); (d_1 d_2)^2 = (d_1 d_3)^3 = e \Big\rangle$$

where d_1 corresponds to a reflection with respect to the hyperplane $x_1 = -x_2$, and $d_i, 2 \leqslant i \leqslant n$ corresponds to a reflection with respect to the hyperplane $x_{i-1} = x_i$. Geometrically, the group D_n is a symmetry group of an n-dimensional half-cube, while B_n is a symmetry group of a complete n-dimensional cube.

For the remaining case of $k = n$, there holds the following

Lemma 2.9: *The group* H_n *is isomorphic to the direct product* $\mathbb{Z}_2 \times S_n$.

Proof: The statement follows from the fact that $H_n = \langle t_{\{1,2,\ldots,n\}}, S_n \rangle$ and any transformation $t \in H_n$ is unambiguously representable in the form of the product $t = t_{\{1,\ldots,n\}}\sigma$, and this product being commutative. Hence, $H_n = \langle t_{\{1,2,\ldots,n\}} \rangle \times S_n \cong \mathbb{Z}_2 \times S_n$.

Since the symmetry group S_n is also a Coxeter group A_{n-1} [4], we obtain

Corollary 2.10. $H_n \cong \mathbb{Z}_2 \times A_{n-1}$, *where* A_{n-1} *is a Coxeter group and* $|H_n| = 2n!$

The group A_{n-1} is represented by [4]

$$A_{n-1} = \left\langle a_1, \ldots, a_{n-1} \mid a_i^2 = e, 1 \leqslant i \leqslant n-1; \left(a_i a_{i+1}\right)^3 = e, 1 \leqslant i \leqslant n-2; \left(a_l a_k\right)^2 = e, 1 \leqslant l < k-1 \leqslant n-2 \right\rangle$$

Consequently, the group H_n is represented by

$$H_n = \left\langle a_1, \ldots, a_{n-1}, a_n \mid a_i^2 = e, 1 \leqslant i \leqslant n-1; \left(a_i a_{i+1}\right)^3 = e, 1 \leqslant i \leqslant n-2; \left(a_l a_k\right)^2 = e, 1 \leqslant l < k-1 \leqslant n-2; a_n a_i = a_i a_n, 1 \leqslant i \leqslant n-1; a_n^2 = e \right\rangle$$

where the transformation a_i corresponds to a reflection with respect to the plane $x_i = x_{i+1}$, and a_n is a symmetry with respect to zero. Since S_n is the symmetry group of an n-dimensional simplex, then $H_n \cong \mathbb{Z}_2 \times S_n$ is the symmetry group of this simplex and of its copy, which is symmetrical to it with respect to zero.

Thus, we have

Theorem 2.11: *The symmetry group of an n-dimensional theory of sufficient causes with k isoeffective factors is isomorphic to*

a) *the group* $Oct_n \cong \mathbb{Z}_2^n \rtimes S_n \cong \mathbb{Z}_2 \wr S_n$ *if k is odd and* $1 \leqslant k \leqslant n-1$;
b) *the Coxeter group* $D_n \cong \mathbb{Z}_2^{n-1} \rtimes S_n$ *if k is even and* $1 \leqslant k \leqslant n-1$;
c) *the group* $\mathbb{Z}_2 \times S_n \cong \mathbb{Z}_2 \times A_{n-1}$ *if* $k = n$.

3. Classification of joint actions produced by factors in a binary experiment

It follows from the above formal binary experiment model that the natural classification of responses from $\mathbb{B}(x_1,\ldots,x_n)$ into classes characterized by like properties of combined action of the factors $X_1,\ldots,X_n$ arises from the partitioning of the algebra $\mathbb{B}(x_1,\ldots,x_n)$ into the action orbits of a corresponding group of symmetries of this experiment.

3.1 *Types of joint action in the theory of sufficient causes*

Let us recall the concept of orbit of an action group. The Boolean functions f and g lie in the same orbit with respect to an action of the group G if and only if there is such a transformation $T \in G$ that $g = T(f)$.

Consider the case of $n = 2$ and the sufficient causes theory with symmetry group B_2 (see Section 2.2.1). Let $\langle f \rangle$ denote the orbit of an element f in $\mathbb{B}(x_1, x_2)$. By means of straightforward computations we can prove the following statement.

Theorem 3.1: *The orbits of action of the group $G = B_2$ on the Boolean algebra $\mathbb{B}(x_1, x_2)$ are the following sets of Boolean functions*

$$\begin{aligned}\langle 0\rangle &= \{0\},\quad \langle 1\rangle = \{1\},\quad \langle x_1\rangle = \{x_1, \overline{x}_1, x_2, \overline{x}_2\},\\ \langle x_1 \vee x_2\rangle &= \{x_1 \vee x_2, \overline{x}_1 \vee x_2, x_1 \vee \overline{x}_2, \overline{x}_1 \vee \overline{x}_2\},\\ \langle x_1x_2\rangle &= \{x_1x_2, \overline{x}_1x_2, x_1\overline{x}_2, \overline{x}_1\overline{x}_2\},\\ \langle x_1x_2 \vee \overline{x}_1\overline{x}_2\rangle &= \{x_1x_2 \vee \overline{x}_1\overline{x}_2, \overline{x}_1x_2 \vee x_1\overline{x}_2\}\end{aligned}$$

Comparing the classification of the types of response into orbits of action of the group G with the classification presented in works on the theory of sufficient causes (see, e.g.[9, 21]), we should note the following. In [9], the responses

$$\begin{aligned}\langle x_1 \vee x_2\rangle &= \{x_1 \vee x_2, \overline{x}_1 \vee x_2, x_1 \vee \overline{x}_2, \overline{x}_1 \vee \overline{x}_2\},\\ \langle x_1x_2\rangle &= \{x_1x_2, \overline{x}_1x_2, x_1\overline{x}_2, \overline{x}_1\overline{x}_2\},\\ \langle x_1x_2 \vee \overline{x}_1\overline{x}_2\rangle &= \{x_1x_2 \vee \overline{x}_1\overline{x}_2, \overline{x}_1x_2 \vee x_1\overline{x}_2\}\end{aligned}$$

were combined in one and the same class as responses describing *causal interdependence*. However, it follows from Theorem 3.1 that such class is not homogeneous in relation to classification of joint actions. A more precise classification was proposed in [21], whose authors divided the responses representing causal interdependence into two classes

$$\{x_1 \vee x_2, \overline{x}_1 \vee x_2, x_1 \vee \overline{x}_2, \overline{x}_1 \vee \overline{x}_2\}$$

and

$$\{x_1x_2, \overline{x}_1x_2, x_1\overline{x}_2, \overline{x}_1\overline{x}_2, x_1x_2 \vee \overline{x}_1\overline{x}_2, \overline{x}_1x_2 \vee x_1\overline{x}_2\}$$

The disjunctions are considered as of two kinds type of joint action, which can exhibit both synergism and additivity. The authors [21] proposed to resolve this ambiguity depending on a specific mechanism of action of the factors. At the same time, the types of response occurring in the second class, by the definition from [21], are called responses representing *definite* *interdependence* of sufficient causes, i.e. such joint action that necessarily exhibits synergism or antagonism. However, here as well, the inclusion of the latter two Boolean functions leads to the inhomogeneity of the class.

It is obvious that classification of joint actions produced by n binary factors for the symmetries of the sufficient cause theory, i.e. for Oct_n as a group of automorphisms acting in the state space $\mathbb{B}(x_1,...,x_n)$ is computationally much more complicated, though quite algorithmizable. For any concrete values of n, computations may be performed using some computer algebra system over the time $K \cdot 2^{2^n}$, K being some *const*. Note that considerable difficulties arise in a meaningful interpretation of the resulting classes; in particular, in contrast to the two-dimensional case (see, e.g. [9, 21]) it is difficult to substantiate which responses should be regarded as representing synergism (antagonism) and which should not.

As an example, we present without proof a classification for $n = 3$ (representatives of the classes are written in the form of minimal DNF)

Theorem 3.2: *An action of the group Oct_3 on the Boolean algebra $\mathbb{B}(x_1, x_2, x_3)$ partitions the latter into 22 orbits represented by the following Boolean functions*

$$\langle 0\rangle,\ \langle 1\rangle,\ \langle x_1\rangle,\ \langle x_1 \vee x_2\rangle,\ \langle x_1 \vee x_2 \vee x_3\rangle,\ \langle x_1x_2\rangle,\ \langle x_1x_2 \vee \overline{x}_1\overline{x}_2\rangle,$$
$$\langle x_1 \vee x_2x_3\rangle,\ \langle x_1 \vee x_2x_3 \vee \overline{x}_2\overline{x}_3\rangle,\ \langle x_1x_2 \vee x_1x_3\rangle,\ \langle x_1x_2 \vee \overline{x}_1x_3\rangle$$
$$\langle x_1x_2 \vee x_1x_3 \vee x_2x_3\rangle,\ \langle x_1x_2 \vee \overline{x}_1x_3 \vee x_2x_3\rangle,\ \langle x_1x_2 \vee \overline{x}_1\overline{x}_2 \vee x_2x_3\rangle$$
$$\langle x_1x_2x_3\rangle,\ \langle x_1x_2x_3 \vee \overline{x}_1\overline{x}_2\overline{x}_3\rangle,\ \langle x_1x_2x_3 \vee x_1x_2\overline{x}_3\rangle,\ \langle x_1x_2x_3 \vee x_1\overline{x}_2\overline{x}_3 \vee \overline{x}_1x_2\overline{x}_3\rangle,$$
$$\langle x_1x_2x_3 \vee x_1\overline{x}_2\overline{x}_3 \vee \overline{x}_1x_2\overline{x}_3 \vee \overline{x}_1\overline{x}_2x_3\rangle,\ \langle x_1x_2x_3 \vee \overline{x}_1\overline{x}_2\rangle,$$
$$\langle x_1x_2x_3 \vee \overline{x}_1\overline{x}_2 \vee \overline{x}_2\overline{x}_3\rangle,\ \langle x_1x_2x_3 \vee \overline{x}_1\overline{x}_2 \vee \overline{x}_2\overline{x}_3 \vee \overline{x}_1\overline{x}_3\rangle$$

As can be seen, many of the classes are represented by rather complex combinations which are difficult to interpret in the usual epidemiological paradigm “synergism, antagonism, additivity, single-factor action”.

3.2 *Types of joint action in an experiment with isoeffective levels*

Analogous consideration of an $n = 2$-experiment (see Section 2.2.2) with isoeffective levels yields the following theorem.

Theorem 3.3: *The orbits of action of the group $G_1 = D_4$ on the Boolean algebra $\mathbb{B}(x_1, x_2)$ are the following sets of Boolean functions*

$$\langle 0 \rangle = \{0\}, \quad \langle 1 \rangle = \{1\}, \qquad \langle x_1 \rangle = \{x_1, \overline{x}_1, x_2, \overline{x}_2\},$$
$$\langle x_1 \vee x_2 \rangle = \{x_1 \vee x_2, \overline{x}_1 \vee \overline{x}_2\}, \quad \langle \overline{x}_1 \vee x_2 \rangle = \{\overline{x}_1 \vee x_2, x_1 \vee \overline{x}_2\},$$
$$\langle x_1 x_2 \rangle = \{x_1 x_2, \overline{x}_1 \overline{x}_2\}, \quad \langle \overline{x}_1 x_2 \rangle = \{\overline{x}_1 x_2, x_1 \overline{x}_2\},$$
$$\langle x_1 x_2 \vee \overline{x}_1 \overline{x}_2 \rangle = \{x_1 x_2 \vee \overline{x}_1 \overline{x}_2\}, \quad \langle \overline{x}_1 x_2 \vee x_1 \overline{x}_2 \rangle = \{\overline{x}_1 x_2 \vee x_1 \overline{x}_2\}.$$

As can be seen in this case, all orbits in Theorem 3.1 containing two factors in disjunction or conjunction partitioned into subsets which are invariant with respect to the group D_4. The interpretation of these orbits is analogous to the previous case; however, we now should bear in mind that the responses

$$x_1 \vee x_2 \qquad \overline{x}_1 \vee x_2$$

represent different types of joint action. The same applies to the rest of the corresponding pairs of responses. Given what was said above about the specifics of the experiment with isoeffective levels, this is sufficiently clear.

Note that in contrast to the case of the theory of sufficient causes considered above, in this case the description of responses representing a non-trivial joint action is more complex. Thus, in the theory of sufficient causes, synergism/antagonism represent responses in which the conjunction of factors is present [19, 20, 21]. For the binary experiment with isoeffective levels, the situation is less certain because the conjunctions x_1x_2 and $\overline{x}_1x_2$ are found in different orbits, i.e. they represent *different types* of joint action.

4. Discussion

As a rule, experimental designs do not consider the features of symmetry associated with the choice of factor level coding and analysis of related experimental symmetries. At the same time, some symmetry conditions are clear to the researcher even before the beginning of the experiment. For example, any experiment provides for factor permutability when assessing the character of joint action produced by the factors (see above the axioms A1 and B1). An explicit statement of conditions which help keep the property under study (the type of joint action in the examples considered above) enables us to construct a formal model of the experiment. Given this, the character of combined action is determined not only by the setting of factors and response but also by the symmetries present in the experiment.

The proposed formalism also enables us to investigate the issue of all possible classifications of joint action types in a given binary experiment. Obviously, this task is reduced to defining those subgroups in the full group of automorphisms of the free Boolean algebra $\mathbb{B}(x_1,\ldots,x_n)$ which contain the automorphisms T_P (see the axiom B1). Then the orbits of action of such a group in the state space $\mathbb{B}(x_1,\ldots,x_n)$ determine a relevant classification.

For the case of two binary factors with an accuracy up to conjugacy and trivial groups of order 2, the admissible groups are the above considered groups D_8, D_4, the symmetric group S_3 and the full group of automorphisms S_4. It is straightforward to show that the orbits of action of the group S_4 on the Boolean algebra $\mathbb{B}(x_1, x_2)$ are represented by the following sets

$$\langle 0\rangle = \{0\}, \quad \langle 1\rangle = \{1\},$$
$$\langle x_1\rangle = \{x_1, \bar{x}_1, x_2, \bar{x}_2, x_1x_2 \vee \bar{x}_1\bar{x}_2, \bar{x}_1x_2 \vee x_1\bar{x}_2\},$$
$$\langle x_1x_2\rangle = \{x_1x_2, \bar{x}_1x_2, x_1\bar{x}_2, \bar{x}_1\bar{x}_2\},$$
$$\langle x_1 \vee x_2\rangle = \{x_1 \vee x_2, \bar{x}_1 \vee x_2, x_1 \vee \bar{x}_2, \bar{x}_1 \vee \bar{x}_2\}.$$

It is noteworthy that the responses described by the formulae $x_1x_2 \vee \bar{x}_1\bar{x}_2$ and $\bar{x}_1x_2 \vee x_1\bar{x}_2$ are found in the same class with the single-factor responses $x_1, \bar{x}_1, x_2, \bar{x}_2$. Thus, for the symmetries of the group S_4, these responses are essentially single-factor impacts. This demonstrates that it is essentially important to precisely describe a corresponding symmetry group of the experiment when analyzing combined action types.

For the group S_3 in S_4, the orbits of action form the sets

$$\langle 0\rangle = \{0\}, \quad \langle 1\rangle = \{1\},$$
$$\langle x_1\rangle = \{x_1, x_2, x_1\bar{x}_2 \vee \bar{x}_1x_2\}, \quad \langle \bar{x}_1\rangle = \{\bar{x}_1, \bar{x}_2, x_1x_2 \vee \bar{x}_1\bar{x}_2\},$$
$$\langle x_1x_2\rangle = \{x_1x_2, \bar{x}_1x_2, x_1\bar{x}_2\}, \quad \langle \bar{x}_1\bar{x}_2\rangle = \{\bar{x}_1\bar{x}_2\},$$
$$\langle x_1 \vee x_2\rangle = \{x_1 \vee x_2\}, \quad \langle \bar{x}_1 \vee x_2\rangle = \{\bar{x}_1 \vee x_2, x_1 \vee \bar{x}_2, \bar{x}_1 \vee \bar{x}_2\}$$

Consequently, in this case as well the purely single-factor functions x_1, x_2 are combined with the more complex $x_1\bar{x}_2 \vee \bar{x}_1x_2$. Moreover, the single-factor functions $\overline{x}_1, \overline{x}_2$ are also found in another class together with the function $x_1 x_2 \vee \overline{x}_1 \overline{x}_2$. Thus, the functions $x_1 \overline{x}_2 \vee \overline{x}_1 x_2$ and $x_1 x_2 \vee \overline{x}_1 \overline{x}_2$ are not only essentially single-factor ones (if S_3 is assumed to be the symmetry group of the experiment) but they also represent different types of joint action, as well as the functions x_1 and $\overline{x}_1$. A similar situation holds for the conjunctions (disjunctions) as well. Here, the function $\overline{x}_1 \overline{x}_2 (x_1 \vee x_2)$ represents a special type of joint action which is not equivalent to the rest of the conjunctions (disjunctions).

These examples show that even in such a well-studied case as a fully binary experiment, classification of joint (combined) action of factors is essentially dependent not only on the design of the experiment (i.e. the state space) but also on which symmetries of combined action takes place in a given experiment.

Acknowledgement

We thank Prof. A. S. Kondratyev, DSc., for consultations and helpful comments.

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Received December, 2015