Interacting environmental influences: Concepts of synergism, antagonism, and superposition

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Since an enormous number of different pollutants is usually simultaneously present in a certain environmental area, it must be expected that interactions between these pollutants may occur frequently. Nevertheless, not very much is known about the combined impact of several pollutants and the environmental policy ignores these effects in defining pollution standards and limits just for single pollutants. Moreover, it is not at all clear how these effects should precisely be described. Starting from definitions of interactions between different environmental influences introduced by Ott [7] and one of the present authors [8], new concepts of synergism (and antagonism and superposition) in a deterministic context will be presented. It is analyzed which properties an environmental quality index has to have in order to describe such interactions.

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1. Introduction

Typically, the real situation of all environmental areas, such as water, air, and soil, is characterized by the fact that there are in general several substances simultaneously present influencing the environmental quality or the welfare of the organisms living in this area. Therefore, combined effects or interactions of some of these substances must be expected – at least under certain conditions. Indeed, several examples of interactions between different environmental influences have been observed. Such examples are the interactions between SO_2 and particulate matter (Ott [7, p. 18]), between SO_2 and NO_x (Last [6, p. 112]), and very likely between SO_2 and other gases like ozone (Commission of the European Community [5, p. 63]). More examples can be found in the pharmacological literature; pharmacology can be defined as the science of the interactions between chemical substances and organisms (see Ariëns et al. [3, p. 1 and pp. 147–156]).

With regard to several aspects, the occurrence of combined effects is important: Since in these cases adverse effects on the environment have multiple causes which cannot be separated,

- it is not appropriate to define *pollution standards* for single pollutants independently as is usually done;

- it is not appropriate to introduce *effluent charges* or *taxes* for single types of emissions separately and independently;
- it is not appropriate to auction *pollution permits* separately for single emissions;
- the introduction of a liability insurance and the calculation of an appropriate *insurance premium* for the emittents of single pollutants is problematic.

This shows that, in the case of interactive environmental influences, several classical instruments of environmental policy at least must be reformulated.

Although the terms "synergism" and "synergistic effects" are often used with different meanings in the literature to describe combined and, in a certain sense, strengthened effects of two or more substances, there is a remarkable lack of precise definitions of these terms; exceptions can be found in Ott [7] and in Stehling [8] for the case of deterministic concepts of interaction. Therefore, the objective of this paper is to give precise definitions of the notions synergism, antagonism, and superposition, even in the case of three and more interacting variables, which has not been done till now, and to investigate their consequences to the functional form of a dose–response function or damage function describing such interactions. The paper is organized as follows. After some notations in section 2, we analyze the case of just two interacting variables in section 3. It turns out that there are different plausible and new possibilities to generalize these definitions to the case of three and more variables, which is done in section 4. There, the first precise and general definition of a multiple synergism is given. Moreover, the main and new results are two theorems providing necessary conditions for dose–response functions or damage functions describing multiple synergisms or antagonisms. As an application of the newly introduced concepts, in section 5 we analyze some empirical results reported in the literature.

2. Notations

In the following, it is assumed that there are n variables influencing the environment and that these variables can be measured in non-negative, real-valued quantities $x_1,\dots,x_n$ which, for example, may be interpreted as concentrations of n pollutants. It is further assumed that the (combined) effect of these variables can be described by a real-valued deterministic function

$$D : \mathbb{R}_+^n \to \mathbb{R}, \tag{2.1}$$

where $\mathbb{R}$ ($\mathbb{R}_+$) is the set of all (non-negative) real numbers; by $\mathbb{R}_{++}$ we will denote the set of all positive real numbers.

D may be interpreted, for example, as a damage function, as a (multiple) dose–response function, or as an index measuring the environmental quality. For the sake of simplification, in what follows we choose the first interpretation of D. Let us denote by ΔD_i the increment of the adverse environmental effect if x_i is increased by a (sufficiently small) increment $\Delta x_i > 0$, all other variables being at a constant level, i.e.

$$\Delta D_i := D(x_1, \ldots, x_i + \Delta x_i, \ldots, x_n) - D(x_1, \ldots, x_i, \ldots, x_n). \tag{2.2}$$

Analogously, let us denote by ΔD_{ij} the increment of the environmental effect if x_i and x_j are increased, respectively, by (sufficiently small) increments $\Delta x_i > 0$ and $\Delta x_j > 0$, all other variables being at a constant level, i.e.

$$\begin{aligned}\Delta D_{ij} := {} & D(x_1, \ldots, x_i + \Delta x_i, \ldots, x_j + \Delta x_j, \ldots, x_n) \\ & - D(x_1, \ldots, x_i, \ldots, x_j, \ldots, x_n);\end{aligned} \tag{2.3}$$

similarly, ΔD_{ijk} is defined by

$$\begin{aligned}\Delta D_{ijk} := {} & D(x_1, \ldots, x_i + \Delta x_i, \ldots, x_j + \Delta x_j, \ldots, x_k + \Delta x_k, \ldots, x_n) \\ & - D(x_1, \ldots, x_i, \ldots, x_j, \ldots, x_k, \ldots, x_n).\end{aligned} \tag{2.4}$$

3. Concepts of bi-synergism, bi-antagonism, and bi-superposition

If the damage function D depends only on two possibly interactive variables, three types of interactions are, in principle, possible, which may be called, respectively, (bi-)synergism, (bi-)antagonsim and (bi-)superposition and which are usually defined in the following way (see Ott [7, pp. 330–332]):

DEFINITION 3.1 (SYN A)

Synergism (antagonism, superposition) between variable 1 and variable 2 prevails at $x = (x_1, x_2)$ if the overall damage caused by the simultaneous influence of x_1 and x_2 is greater than (smaller than, equal to) the sum of the damages caused by the single effects of x_1 and x_2, i.e. if

$$D(x_1, x_2) \begin{pmatrix} > \\ < \\ = \end{pmatrix} D(x_1, 0) + D(0, x_2), \tag{3.1}$$

where, in the case of an antagonism, (3.1) holds with the "<"-sign and, in the case of superposition, (3.1) holds with the "="-sign.

Implicitly, this definition is used by Beckmann [4] in defining the synergistic effect of combined inputs in a production theoretical context.

As an example, consider

$$D(x_1, x_2) = ax_1 + bx_2 + cx_1x_2, \qquad a, b \in \mathbb{R}_+, \quad c \in \mathbb{R}.$$

Synergism (antagonism, superposition) prevails if $c > (<, =)\ 0$.

A similar concept of synergism and antagonism is used by Ariëns et al. [3, p. 156]):

DEFINITION 3.2 (SYN B)

For $x_1 > 0$, let $x_2 > 0$ be chosen in such a way that $D(x_1, 0) = D(0, x_2)$, i.e. x_1 and x_2 are iso-effective doses. Then, synergism (antagonism, superposition) between variable 1 and variable 2 prevails at x_1 and x_2 if for all λ with $0 < \lambda < 1$,

$$D(x_1, 0) = D(0, x_2) \begin{pmatrix} < \\ > \\ = \end{pmatrix} D(\lambda x_1, (1 - \lambda) x_2). \tag{3.2}$$

The geometric meaning of this definition of synergism (antagonism) is that, given two iso-effective pure doses x_1 and x_2 of two substances, the corresponding isobole, i.e. the line of all combinations yielding exactly the same damage as x_1 or x_2, lies under (above) the straight line connecting the points $(x_1, 0)$ and $(0, x_2)$ on the axes; this is indicated in figure 1.

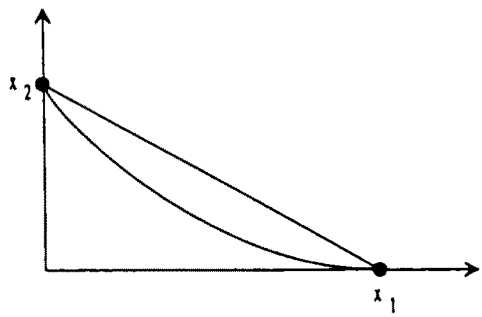

Figure 1.

As an example for this kind of interpretation of synergism, consider

$$D(x_1, x_2) = (x_1 + a)^{\alpha} (x_2 + b)^{\beta}, \qquad a, b, \alpha, \beta \in \mathbb{R}_{++}.$$

In principle, the isoboles may have an arbitrary shape; they are not necessarily convex. Therefore, requiring this, we obtain a more restrictive definition of synergism:

DEFINITION 3.2′ (SYN B′)

Synergism (antagonism, superposition) between variable 1 and variable 2 prevails at $x = (x_1, x_2)$ if the isobole through x is convex (concave, a straight line).

As an example, consider

$$D(x_1, x_2) = x_1^{\alpha} x_2^{\beta}, \qquad \alpha, \beta \in \mathbf{R}_{++},$$

which describes synergistic effects in the sense of definition 3.2′.

The problem with the first two definitions is

- that they apply only to the case of two variables (but they can easily be generalized to the case of interaction between more than two variables);
- that in order to identify one of the three effects, the situations (x_1, x_2) or $(\lambda x_1, (1-\lambda)x_2)$ have to be compared with situations where one of the variables is held on the zero level which, even in experiments, is sometimes impossible. Moreover, the application of definition 3.2 needs the determination of an iso-effective dose x_2 for a given dose x_1 of the first pollutant. In some case, this may be impossible, for example if one pollutant has a positive environmental effect in the absence of the other pollutant, which by itself has an adverse environmental effect in the absence of the first pollutant; this is in a certain sense true for NO_x and SO_2, see Last [6, p. 112]).

Therefore, it is more useful, more natural, and at least reasonable to define interaction phenomena in terms of increments of the variables and the impacts (damages) they cause. One possibility is (see, e.g. Stehling [8, pp. 358–359]):

DEFINITION 3.3 (SYN C)

Synergism (antagonism, superposition) prevails between variable 1 and variable 2 at $x = (x_1, x_2)$ if the additional damage caused by any sufficiently small simultaneous increments $\Delta x_1 > 0$ of x_1 and $\Delta x_2 > 0$ of x_2 is greater than (less than, equal to) the sum of the additional damages caused by the increments Δx_1 and Δx_2 separately. Hence, using the notations (2.2) and (2.3), a damage function D describes these effects if and only if

$$\Delta D_{12} \begin{pmatrix} > \\ < \\ = \end{pmatrix} \Delta D_1 + \Delta D_2 \tag{3.3}$$

for all (sufficiently small) $\Delta x_1 > 0$ and $\Delta x_2 > 0$. It is said that D describes synergism (antagonism, superposition) between variable 1 and variable 2 *everywhere* if (3.3) holds for all $x = (x_1, \ldots, x_n) \in \mathbf{R}_+^n$.

As an example for this definition, consider

$$D(x_1, x_2) = ax_1 + bx_2 + cx_1x_2 + d, \qquad a, b, d \in \mathbf{R}_+, \; c \in \mathbf{R}.$$

Synergism, antagonism, superposition prevails if $c > 0$, $c < 0$, and $c = 0$, respectively. This example is similar to the example belonging to (3.1), but allows for a pollutant-independent basic damage d. For $d = 0$, the examples are identical.

With respect to the concepts of definitions 3.2′ and 3.3, we can derive some properties which a damage function D has to have in order to describe interactions in the sense of these definitions. For this, let

$$D_{x_1} := \frac{\partial D}{\partial x_1}, \quad D_{x_2} := \frac{\partial D}{\partial x_2}, \quad D_{x_1x_1} := \frac{\partial D_{x_1}}{\partial x_1}, \quad D_{x_1x_2} := \frac{\partial D_{x_1}}{\partial x_2},$$

and analogously for other and higher derivatives.

THEOREM 3.4

Let D be a damage function depending on the non-negative variables $x_1,\ldots,x_n$; let D be twice continuously differentiable with respect to the first two variables with $\partial D/\partial x_1 > 0$ and $\partial D/\partial x_2 > 0$. If D describes bi-synergism (bi-antagonism) between the first two variables everywhere in the sense of definition 3.2′, then

$$\frac{D_{x_2}}{D_{x_1}} D_{x_1x_1} + \frac{D_{x_1}}{D_{x_2}} D_{x_2x_2} \underset{(>)}{<} 2D_{x_1x_2}. \tag{3.4′}$$

Proof

Let $x^* = (x_1^*, x_2^*,\ldots,x_n^*) \in \mathrm{R}_+^n$ be an arbitrary point and let

$$x_2 = h(x_1)$$

be the equation of the isobole through x^*, i.e.

$$D(x_1, h(x_1), x_3^*,\ldots, x_n^*) \equiv c = \text{const.}$$

for all x_1 in a (small) neighbourhood of x_1^*. From this, it follows that

$$D_{x_1} + D_{x_2} h' = 0$$

with $h' = dh/dx_1$. Differentiating the last equation once more yields, with $D_{x_1x_2} = D_{x_2x_1}$

$$D_{x_1x_1} + 2h'D_{x_1x_2} + D_{x_2x_2}(h')^2 + D_{x_2} h'' = 0.$$

By assumption, the isoboles are convex (concave), which means that $h'' >(<) 0$. Therefore, the above equation implies

$$0 \underset{(>)}{<} h'' = -\frac{1}{D_{x_2}}[D_{x_1x_1} + 2h'D_{x_1x_2} + (h')^2 D_{x_2x_2}].$$

In view of $D_{x_2} > 0$, the term in the parentheses must be negative (positive); from this, the inequality (3.4′) follows by using $h' = -D_{x_1}/D_{x_2}$ and rearranging the terms. □

The properties of a damage function D describing synergism (antagonism, superposition) in the sense of definition 3.3 were investigated in Stehling [8, pp. 359–361].

4. Concepts of triple and multiple synergism, antagonism, and superposition

To describe the effects of interaction between more than two variables, we can generalize the definitions of the last section. However, we will see that the definition of SYN C allows for different generalizations. First, it is easy to generalize the definitions of SYN A, SYN B, and SYN B′ in a straightforward manner to the case of three and more interacting variables, which is omitted. The simplest way of generalizing definition 3.3 of SYN C to the case of three (or more) interacting variables is (see Stehling [8, pp. 361–363]):[1)]

DEFINITION 4.1 (SYN C1)

Synergism (antagonism, superposition) prevails between the first three variables of the damage function D at $(x, y, z, \ldots,)$ if the additional damage caused by any (sufficiently small) simultaneous increments $\Delta x, \Delta y, \Delta z > 0$ is greater than (less than, equal to) the sum of the additional damages caused by the increments Δx, Δy, Δz separately, i.e. if

$$\Delta D_{xyz} \begin{pmatrix} > \\ < \\ = \end{pmatrix} \Delta D_x + \Delta D_y + \Delta D_z \tag{4.1}$$

for all (sufficiently small) $\Delta x, \Delta y, \Delta z > 0$.

It is obvious how this type of triple synergism can be generalized to the case of more than three interacting variables, which we call a multi-synergism. Damage functions describing synergism of that type must have a special functional form:

THEOREM 4.2

Let the damage function $D : \mathbb{R}_+^n \to \mathbb{R}_+$ be three times continuously partially differentiable with respect to the first three variables. If D describes synergism (antagonism) between the first three variables everywhere in the sense of (4.1) then, necessarily, for all arguments

$$D_{xy} + D_{yz} + D_{xz} \overset{\geq}{(\leq)} 0 . \tag{4.2}$$

For a proof, see Stehling [8].

[1)] For convenience, in the following let us denote the first three variables of the damage function D by x, y, and z.

A shortcoming of the definition of SYN C1 is that the inequality (4.1) can already hold if only two of the first three variables interact and the impact of the third variable can be separated. This means that a triple synergism can prevail which is caused already by a bi-synergism; hence, by this definition it cannot be distinguished between bi-synergisms and a *proper* triple synergism. This can be avoided by the following new definition.

DEFINITION 4.3 (SYN C2)

Synergism (antagonism, superposition) prevails between the first three variables of the damage function D at $(x, y, z, \ldots)$ if the additional damage caused by any (sufficiently small) simultaneous increments $\Delta x, \Delta y, \Delta z > 0$ is greater than (less than, equal to) *all* sums of additional damages caused by the simultaneous increments of any two variables and the remaining third; formally, if (with the notations of section 2) the following three inequalities hold simultaneously:

$$\left.\begin{aligned} \Delta D_{123} &\begin{pmatrix} > \\ < \\ = \end{pmatrix} \Delta D_{12} + \Delta D_3, \\ \Delta D_{123} &\begin{pmatrix} > \\ < \\ = \end{pmatrix} \Delta D_{23} + \Delta D_1, \\ \Delta D_{123} &\begin{pmatrix} > \\ < \\ = \end{pmatrix} \Delta D_{31} + \Delta D_2. \end{aligned}\right\} \tag{4.3}$$

Again, it is possible to derive conditions in terms of second derivatives of the damage function D which must be satisfied if D describes synergism (antagonism) in the sense of (4.3):

THEOREM 4.4

Let the damage function $D : \mathbb{R}_+^n \to \mathbb{R}_+$ be three times continuously partially differentiable with respect to the first three variables. If D describes synergism (antagonism) between the first three variables everywhere in the sense of (4.3) then, necessarily, for all arguments

$$\left.\begin{aligned} D_{xz} + D_{yz} &\underset{(\leq)}{\geq} 0, \\ D_{yx} + D_{zx} &\underset{(\leq)}{\geq} 0, \\ D_{xy} + D_{zy} &\underset{(\leq)}{\geq} 0. \end{aligned}\right\} \tag{4.4}$$

Proof

Using the Taylor expansion for D, we have for $\Delta x, \Delta y, \Delta z > 0$

$$\begin{aligned}\Delta D_{123} &= \Delta x D_x(x, y, z, \dots) + \Delta y D_y(x, y, z, \dots) + \Delta z D_z(x, y, z, \dots) \\ &\quad + \tfrac{1}{2}(\Delta x)^2 D_{xx}(\dots) + \tfrac{1}{2}(\Delta y)^2 D_{yy}(\dots) + \tfrac{1}{2}(\Delta z)^2 D_{zz}(\dots) \\ &\quad + \Delta x\, \Delta y D_{xy}(\dots) + \Delta y\, \Delta z D_{yz}(\dots) + \Delta z\, \Delta x D_{zx}(\dots) + R_{xyz},\end{aligned}$$

where

$$R_{xyz} := \frac{1}{3!}\left(\Delta x \frac{\partial}{\partial x} + \Delta y \frac{\partial}{\partial y} + \Delta z \frac{\partial}{\partial z}\right)^3 D(x + \kappa_1 \Delta x, y + \kappa_2 \Delta y, z + \kappa_3 \Delta z, \dots),$$

with constants κ_1, κ_2, κ_3 satisfying $0 \le \kappa_1, \kappa_2, \kappa_3 \le 1$ and where the arguments of all second-order derivatives are the same as those of the first-order derivatives. Correspondingly, one has

$$\begin{aligned}\Delta D_{12} &= \Delta x D_x(\dots) + \Delta y D_y(\dots) + \tfrac{1}{2}(\Delta x)^2 D_{xx}(\dots) + \tfrac{1}{2}(\Delta y)^2 D_{yy}(\dots) \\ &\quad + \Delta x \Delta y D_{xy}(\dots) + R_{xy},\end{aligned}$$

$$\Delta D_3 = \Delta z D_z(\dots) + \tfrac{1}{2}(\Delta z)^2 D_{zz}(\dots) + R_z,$$

where

$$R_{xy} := \frac{1}{3!}\left(\Delta x \frac{\partial}{\partial x} + \Delta y \frac{\partial}{\partial y}\right)^3 D(x + \mu_1 \Delta x, y + \mu_2 \Delta y, z, \dots),$$

$$R_z := \frac{1}{3!}(\Delta z)^3 D_{zzz}(x, y, z + \mu_3 \Delta z, \dots),$$

with $0 \le \mu_1, \mu_2, \mu_3 \le 1$.

Inserting these three Taylor expansions into the first defining inequality of (4.3) leads for the special case of sufficiently small $\Delta x = \Delta y = \Delta z > 0$ to the inequality

$$0 < (\Delta x)^2 (D_{xz}(\dots) + D_{yz}(\dots)) + \tilde{R}_{xyz} - \tilde{R}_{xy} - \tilde{R}_z,$$

where $\tilde{R}_{xyz}, \tilde{R}_{xy}, \tilde{R}_z$ are the expressions for R_{xyz}, R_{xy}, R_z defined above but evaluated at $\Delta x = \Delta y = \Delta z$. Since

$$0 = \lim_{\Delta x \to 0} \frac{\tilde{R}_{xyz}}{(\Delta x)^2} = \lim_{\Delta x \to 0} \frac{\tilde{R}_{xy}}{(\Delta x)^2} = \lim_{\Delta x \to 0} \frac{\tilde{R}_z}{(\Delta x)^2},$$

the last inequality implies that

$$0 \le D_{xz}(\dots) + D_{yz}(\dots).$$

This proves the first inequality of (4.4). The second and third inequality of (4.4) can be proved in the same way. □

The difference in the above two definitions of a triple synergism is the following: In the first definition, the combined additional effect ΔD_{123} of the whole set $\{1, 2, 3\}$ of all three variables is compared with the sum of the additional effects of the special partition $P_1 = \{\{1\}, \{2\}, \{3\}\}$; in the second definition, ΔD_{123} is compared with the sum of the additonal effects of the partitions $P_2 = \{\{1, 2\}, \{3\}\}$, $P_3 = \{\{2, 3\}, \{1\}\}$, $P_4 = \{\{1, 3\}, \{2\}\}$. But, of course, it is rather arbitrary to pick out for such definitions only special partitions for these comparisons. This becomes much clearer if we try to further generalize the definitions for the interaction of four and more variables: for example, if there are four interacting variables, we can compare ΔD_{1234} with the sums

- $\Delta D_1 + \Delta D_2 + \Delta D_3 + \Delta D_4$,
- $\Delta D_1 + \Delta D_2 + \Delta D_{34}, \Delta D_1 + \Delta D_3 + \Delta D_{24}, \Delta D_1 + \Delta D_4 + \Delta D_{23}$,
- $\Delta D_2 + \Delta D_3 + \Delta D_{14}, \Delta D_2 + \Delta D_4 + \Delta D_{13}, \Delta D_3 + \Delta D_4 + \Delta D_{12}$,
- $\Delta D_{12} + \Delta D_{34},\ \Delta D_{13} + \Delta D_{24}, \Delta D_{14} + \Delta D_{23}$,
- $\Delta D_{123} + \Delta D_4, \Delta D_{124} + \Delta D_3,\ \Delta D_{134} + \Delta D_2, \Delta D_{234} + \Delta D_1$.

Similarly to the two definitions of triple synergism, this would give rise to – at least – four different definitions of a quadruple synergism. Since this is rather unsatisfactory, we suggest a general definition of a proper m-synergism in which the sums of the effects of *all* partitions of n variables are simultaneously taken into consideration:

DEFINITION 4.5 (m-SYN)

Let $P = \{S_1, \ldots, S_{l(P)}\}$ be an arbitrary partition of the set $\{x_1, \ldots, x_m\}$ of $m \leq n$ variables. Denote by ΔD_{S_t} the additional damage caused by the simultaneous (sufficiently small) increments of the variables in S_t. A proper m-synergism (m-antagonism, m-superposition) prevails at $x = (x_1, \ldots, x_m, \ldots)$ if for all partitions $P \neq \{\{x_1, \ldots, x_m\}\}$ of the set $\{x_1, \ldots, x_m\}$

$$\Delta D_{\{x_1, \ldots, x_m\}} \begin{pmatrix} > \\ < \\ = \end{pmatrix} \sum_{S_t \in P} \Delta D_{S_t} \,. \tag{4.5}$$

The advantage of this definition is that a proper m-synergism (m-antagonism) cannot be generated already by a synergism of a proper subgroup of variables. Its disadvantage is that the number of comparisons, which have to be made in order to decide whether an m-synergism actually prevails, increases enormously with m because the number $B(m)$ of partitions of a set of m elements increases rapidly with m. So we have $B(3) = 5$, $B(4) = 15$, $B(5) = 52, \ldots$. In general, $B(m)$ are the Bell numbers (see e.g. Aigner [2, p. 92]).

In complete analogy to theorems 4.2 and 4.4, we can prove as a generalization:

THEOREM 4.6

Let D be three times continuously partially differentiable with respect to $x_1,\dots,x_m$. If D describes a proper m-synergism (m-antagonism) then, for all partitions $P \neq \{\{x_1,\dots,x_m\}\}$ of $\{x_1,\dots,x_m\}$,

$$\sum_{\substack{x_j \in S_t \in P \\ x_k \in S_{t'} \in P \\ S_t \neq S_{t'} \\ t < t'}} D_{x_j x_k} \underset{(\leq)}{\geq} 0. \tag{4.6}$$

Proof

Because of the symmetry in the definitions of synergism and antagonism, it is sufficient to prove only the assertion for m-synergism.

Using the Taylor expansion for D, we have for $\Delta x_1,\dots,\Delta x_m > 0$

$$\Delta D_{\{x_1,\dots,x_m\}} = \sum_{i=1}^{2} \sum_{j=1}^{m} \frac{1}{i!}(\Delta x_j)^i \frac{\partial^i D}{(\partial x_j)^i}(x_1,\dots,x_m,\dots)$$
$$+ \sum_{j<k}^{m} \Delta x_j \Delta x_k \frac{\partial^2 D}{\partial x_j \partial x_k}(x_1,\dots,x_m,\dots) + R_{\{x_1,\dots,x_m\}},$$

where

$$R_{\{x_1,\dots,x_m\}} := \frac{1}{3!}\left(\Delta x_1 \frac{\partial}{\partial x_1} + \dots + \Delta x_m \frac{\partial}{\partial x_m}\right)^3 D(x_1 + \kappa_1 \Delta x_1,\dots,x_m + \kappa_m \Delta x_m,\dots),$$

with constants $\kappa_1,\dots,\kappa_m$ satisfying $0 \leq \kappa_1,\dots,\kappa_m \leq 1$. Correspondingly, we obtain

$$\Delta D_{S_t} = \sum_{i=1}^{2} \sum_{x_j \in S_t} \frac{1}{i!}(\Delta x_i)^i \frac{\partial^i D}{(\partial x_j)^i}(x_1,\dots,x_m,\dots)$$
$$+ \sum_{\substack{x_j, x_k \in S_t \\ j<k}} \Delta x_j \Delta x_k \frac{\partial^2 D}{\partial x_j \partial x_k}(x_1,\dots x_m,\dots) + R_{S_t},$$

where

$$R_{S_t} := \frac{1}{3!}\left(\sum_{i \in S_t} \Delta x_i \frac{\partial}{\partial x_i}\right)^3 D(x_{t_1} + \mu_{t_1}\Delta x_{t_1},\dots,x_{t_{|S_t|}} + \mu_{t_{|S_t|}}\Delta x_{t_{|S_t|}}, x_{u_1},\dots,x_{u_{(n-|S_t|)}}),$$

with $S_t = \{x_{t_1},\dots,x_{t_{|S_t|}}\}$ and $0 \leq \mu_{t_1},\dots,\mu_{t_{|S_t|}} \leq 1$.

Inserting these Taylor expansions into inequality (4.5) leads, for the special case of sufficiently small $\Delta x_1 = \dots = \Delta x_m > 0$, to

$$\sum_{i=1}^{2}\sum_{j=1}^{m}\frac{1}{i!}(\Delta x)^i\frac{\partial^i D}{(\partial x_j)^i}(x_1,\ldots,x_m,\ldots)+\sum_{j<k}^{m}(\Delta x)^2\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)+\tilde{R}_{\{x_1,\ldots,x_m\}}$$

$$\begin{pmatrix}>\\<\\=\end{pmatrix}$$

$$\sum_{S_t\in P}\left(\sum_{i=1}^{2}\sum_{x_j\in S_t}\frac{1}{i!}(\Delta x)^i\frac{\partial^i D}{(\partial x_j)^i}(x_1,\ldots,x_m,\ldots)+\sum_{\substack{x_j,x_k\in S_t\\ j<k}}(\Delta x)^2\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)+\tilde{R}_{S_t}\right),$$

where $\tilde{R}_{\{x_1,\ldots,x_m\}}$ and $\tilde{R}_{S_t}$ are the expressions for $R_{\{x_1,\ldots,x_m\}}$ and R_{S_t} defined above but evaluated at $x_1=x_2=\ldots=x_m$.

Since P is a partition, $S_t\cap S_{t'}=\varnothing$ (for $S_t\neq S_{t'}$) and $\bigcup_{t=1}^{l(P)}S_t = P$, and therefore

$$\sum_{i=1}^{2}\sum_{j=1}^{m}\frac{1}{i!}(\Delta x)^i\frac{\partial^i D}{(\partial x_j)^i}(x_1,\ldots,x_m,\ldots)=\sum_{S_t\in P}\left(\sum_{i=1}^{2}\sum_{x_j\in S_t}\frac{1}{i!}(\Delta x)^i\frac{\partial^i D}{(\partial x_j)^i}(x_1,\ldots,x_m,\ldots)\right)$$

holds. For this, we can simplify the above inequality to

$$0<\sum_{j<k}^{m}(\Delta x)^2\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)-\sum_{S_t\in P}\left(\sum_{\substack{x_j,x_k\in S_t\\ j<k}}(\Delta x)^2\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)\right)$$

$$+\ \tilde{R}_{\{x_1,\ldots,x_m\}}-\sum_{S_t\in P}(\tilde{R}_{S_t}).$$

Since

$$0=\lim_{\Delta x\to 0}\frac{\tilde{R}_{\{x_1,\ldots,x_m\}}}{(\Delta x)^2}=\lim_{\Delta x\to 0}\frac{\tilde{R}_{S_t}}{(\Delta x)^2},$$

one has

$$0\le\sum_{j<k}^{m}\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)-\sum_{S_t\in P}\left(\sum_{\substack{x_j,x_k\in S_t\\ j<k}}\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots x_m,\ldots)\right)$$

$$\Leftrightarrow\quad 0\le\sum_{\substack{x_j\in S_t\in P\\ x_k\in S_{t'}\in P\\ S_t\neq S_{t'}\\ t<t'}}\frac{\partial^2 D}{\partial x_j\partial x_k}(x_1,\ldots,x_m,\ldots)\Leftrightarrow 0\le\sum_{\substack{x_j\in S_t\in P\\ x_k\in S_{t'}\in P\\ S_t\neq S_{t'}\\ t<t'}}D_{x_jx_k}.$$

□

5. An application

As an application of the concepts developed above, we analyze some results of experiments of Adaros et al. [1]. During 1988 and 1989, some species of wheat ("Turbo" and "Star") and barley ("Arena" and "Alexis") were exposed during the whole growing season to either charcoal-filtered air (control) or charcoal-filtered air supplemented with discrete single or simultaneous concentrations of the pollutants SO_2, NO_2, and O_3. In table 1, the variables x, y, z denote concentrations of the pollutants O_3, SO_2, and NO_2, respectively. Analogously, Δx, Δy, Δz denote additional concentrations of the particular pollutants. Their effect on the plants is basically measured by the grain dry weight per pot of the potted plants, $W(x, y, z)$, which are exposed to the concentrations x, y, z of SO_2, NO_2, and O_3, respectively. For the sake of simplicity, we use the notation

$$D(x + \Delta x, y, z + \Delta z) = - \frac{W(x + \Delta x, y, z + \Delta z) - W(x, y, z)}{W(x, y, z)} \cdot 100.$$

This, for example, is the additional impact of the pollutants O_3 and NO_2 caused by additional discrete concentrations Δx and Δz expressed in percent of the basic effect $W(x, y, z)$. Analogously, the terms $D(x + \Delta x, y + \Delta y, z + \Delta z)$, $D(x, y + \Delta y, z)$,... are defined.

Table 1

Examination of a potential triple-interaction of SO_2, NO_2, and O_3 to the grain (dry weight per pot) of some species of wheat and barley.

		Turbo '88	Star '88	Arena '89	Alexis '89
O_3	$D(x + \Delta x, y, z)$	26	20	6	−4
SO_2	$D(x, y + \Delta y, z)$	7	−2	8	1
NO_2	$D(x, y, z + \Delta z)$	1	2	−3	4
$O_3 \cup SO_2$	$D(x + \Delta x, y + \Delta y, z)$	38	27	8	−3
$O_3 + SO_2$	$D(x + \Delta x, y, z) + D(x, y + \Delta y, z)$	33	18	14	−3
$O_3 \cup NO_2$	$D(x + \Delta x, y, z + \Delta z)$	31	18	14	3
$O_2 + NO_2$	$D(x + \Delta x, y, z) + D(x, y, z + \Delta z)$	27	22	3	0
$SO_2 \cup NO_2$	$D(x, y + \Delta y, z + \Delta z)$	4	−7	8	14
$SO_2 + NO_2$	$D(x, y + \Delta y, z) + D(x, y, z + \Delta z)$	8	0	5	5
$O_3 \cup SO_2 \cup NO_2$	$D(x + \Delta x, y + \Delta y, z + \Delta z)$	44	36	17	11
$O_3 + SO_2 + NO_2$	$D(x + \Delta x, y, z)$ $+ D(x, y + \Delta y, z)$ $+ D(x, y, z + \Delta z)$	34	20	11	1
$O_3 + (SO_2 \cup NO_2)$	$D(x + \Delta x, y, z) + D(x, y + \Delta y, z + \Delta z)$	30	13	14	10
$SO_2 + (O_3 \cup NO_2)$	$D(x, y + \Delta y, z) + D(x + \Delta x, y, z + \Delta z)$	38	16	22	4
$NO_2 + (O_3 \cup SO_2)$	$D(x, y, z + \Delta z) + D(x + \Delta x, y + \Delta y, z)$	39	29	5	1

Let us now explain the signs "$\cup$" and "+" in table 1: For this explanation, we stay in the "Turbo '88" column. The first figure, "26", is the result of an additional donation of a discrete concentration of O_3. Similarly, "7" arises from an additional donation of SO_2. In the next block, we find "$O_3 \cup SO_2$" and the figure "38". This is the result of the simultaneous ($\cup$) donation of the pollutants O_3 and SO_2; it is an empirical result. The next row contains "$O_3 + SO_2$" and the figure "33". This is the sum of the two isolated effects (+) "26" (additional donation of O_3) and "7" (additional donation of SO_2); this is an artificial result arising from summing up two empirical results. "$\cup$" is used to denote the effect of the additional simultaneous donation of the $\cup$-connected pollutants; "+" is used to denote the summed up effects of the additional isolated donations of the +-connected pollutants. The single and interactive effects of the exposure to the yield parameter "grain dry weight per pot" of the potted plants are shown in table 1.

- The table shows a bi-synergism for Turbo '88 and Star '88, a bi-antagonism for Arena '89, and for Alexis '89 a bi-superposition between O_3 and SO_2 in the sense of definition 3.3;
- for Turbo '88, Arena '89, and Alexis '89 a bi-synergism and for Star '88 a bi-antagonism between O_3 and NO_2;
- for Arena '89 and Alexis '89 a bi-synergism and for Turbo '88 and Star '88 a bi-antagonism between SO_2 and NO_2;
- for Turbo '88, Star '88, and Alexis '89 a triple synergism between O_3, NO_2 and SO_2 in the sense of the general definition 4.5 and hence in the sense of definitions 4.1 and 4.3, too; for Arena '89, a triple synergism prevails only in the sense of definition 4.1, but not in the sense of definitions 4.3 and 4.5.

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