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Conceptualizing Agonistic Interaction in a Marginal Sufficient Component Cause Model: An Alternative Interpretation for Subadditive Interaction

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ABSTRACT

The sufficient-component cause (SCC) framework, one of the most sophisticated techniques for the methodological development of causal inference, has the advantage of visualizing the interaction effect of synergism or antagonism. However, statistical interaction occurs even without synergism or antagonism, and vice versa. In this study, we propose a marginal SCC (mSCC) model and incorporate it into the counterfactual framework. The mSCC model can visualize agonism, which is a crucial subtype of interaction apart from synergism and antagonism. Causal pie weight (CPW) and population attributable fraction are also illustrated in the mSCC framework. A hypothetical example is used to demonstrate the use of the mSCC model to identify the agonist and connect mechanistic and causal interaction. Our method is applied to Taiwanese cohort data. We perform simulation studies to evaluate the performance of our proposed CPW estimator in separate scenarios of no synergistic interaction and no agonistic interaction. The small biases indicate that the estimated CPWs are close to the true values, and the coverage rates are approximately 0.95. Among all cases of

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hepatocellular carcinoma (HCC), independent effects due to hepatitis C virus (HCV), hepatitis B virus (HBV), and the lower bound of agonistic interaction account for 20.3%, 30.8%, and 12.6% cases of HCC, respectively. Under the assumption of no synergistic interaction, the proportion of agonistic interaction is exactly 12.6%. Our finding regarding agonism

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1. Introduction

Counterfactual outcome framework (Hernán 2004; Imai *et al.* 2008; Pearl 2009; Rubin 1990), causal directed acyclic graphs (DAGs) (Greenland *et al.* 1999; Pearl 1995; Pearl 2009), and sufficient-component cause (SCC) framework (Rothman 1976) are three of the most well-established techniques for the methodological development of causal inference. Counterfactual outcome framework is widely used for quantitative definition for causal effect, successfully providing unbiased estimates in several types of complicated systems, such as the causal effect of time-varying exposures (Logan *et al.* 2015; Robins 1986; Robins and Wasserman 1997) and direct and indirect effects for mediation analysis (Pearl 2001; Robins and Greenland 1992; van der Laan and Petersen 2008; VanderWeele and Vansteelandt 2009; VanderWeele 2015). As a complement to the counterfactual framework, DAGs visualize the causal relation among all variables (Greenland *et al.* 1999; Pearl 1995). Although both the counterfactual framework and DAGs contribute to the investigation of the "effect of a certain set of causes", the SCC framework mainly focuses on the "cause of effect," modeling causation as a series of various types of causal mechanisms, called "sufficient causes" (VanderWeele 2015; VanderWeele and Robins 2009). Each sufficient cause can be considered as minimal sets of actions, events, or states of nature that suffice to initiate a process resulting in the outcome. The SCC framework can successfully visualize interaction effects (Lee 2012; VanderWeele 2009b; VanderWeele and Robins 2007a; VanderWeele and Robins 2007b), which are difficult to illustrate using DAGs.

Interaction is categorized into three types-statistical, causal, and mechanistic-according to different definition systems. Statistical interaction is defined as the coefficient of the product term of two factors based on a statistical model. Causal interaction is defined as the difference between the joint effect of two factors and the sum of the effects of each factor based on a counterfactual model (VanderWeele 2015). Causal interaction is also called causal interdependence in the literature (Greenland and Poole 1988; VanderWeele and Robins 2007b). On the basis of the direction of causal interaction, it can be divided into two subtypes-superadditive and subadditive interaction. Compared with statistical and causal interaction, mechanistic interaction does not have a standard definition. Sometimes it is defined as a situation in which the outcome is induced if two exposures exist but not if only one exposure exists; some researchers refer to it as a general concept of all interactions that imply two exposures interacting in the formation of the outcome through the same mechanism (VanderWeele 2015). In this paper, we define mechanistic interaction as the existence of two factors (or its complement) on the same mechanism, which is based on the SCC model or even the new SCC model we proposed. This definition is similar to the concept of causal coaction, another type of mechanistic interaction (VanderWeele and Knol 2011). Mechanistic interaction can also be further divided into two subtypes-synergism and antagonism (VanderWeele 2015). The presence of two factors initiating the occurrence of an outcome because of a certain sufficient cause is called synergism or synergistic interaction. By contrast, the sufficient cause for which the presence of one factor and the absence of the other can initiate the outcome is antagonism (or antagonistic interaction).

Statistical interaction is equal to causal interaction under the unconfoundedness assumption. However, a gap exists between causal interaction and mechanistic interaction. Causal interaction occurs even in the absence of mechanistic interaction, and vice versa (VanderWeele 2015), and although intuitively, synergism and antagonism appear similar to superadditive and subadditive causal interactions, respectively.

In this study, we propose a marginal SCC (mSCC) model. In this version of SCC, the marginal performance of all SCCs within an individual is visualized as one causal pie. All possible combinations of background conditions for each sufficient cause are recategorized and transformed as new conditions, which are mutually exclusive and ex-

haustive (i.e., one of these conditions certainly occurs, but no two can occur together). When two exposures of interest are considered with the monotonicity assumption, the mSCC model has a unique advantage of identifying agonism (also called agonistic interaction). Agonism is a crucial subtype of mechanistic interaction apart from synergism and antagonism. The concept of agonism is widely adopted in basic science such as chemistry, pharmacology, and immunology and defined as a type of interaction between two factors (such as molecules, drugs, or ligands) that can initiate a similar effect by binding to the same location of certain receptors (Brody *et al.* 1998). We extend the concept of agonists to the field of data science (such as epidemiology and social sciences) and visualize agonism by using the mSCC model. This finding regarding agonism explains the gap between causal and mechanistic interaction, contributing to the comprehensive understanding of the causal mechanism.

2. Methods

2.1 General mSCC framework with two exposures under monotonicity assumptions

In this section, we provide a general framework for mSCC. Let $X = (X_1, X_2)$ denote two exposures of interest and Y the outcome of interest. Both Y and X are binary variables with values of {0,1}. In the traditional SCC framework, a series of events is a sufficient cause for Y if the occurrence of all events in the series implies the occurrence of Y. In total, nine types of sufficient causes are expressed as S_i, where $i = 1, 2, \ldots, 9$. The corresponding background condition for each sufficient cause is expressed as V_i, which is presented in Figure 1. The sufficient cause occurs only if all of its events, called components or component causes, occur. For example, the components of S_1 are (X_1, X_2, V_1). If $X_1 = X_2 = V_1 = 1$, then $S_1 = 1$; otherwise, $S_1 = 0$. Similarly, the components of S_4 are (X_1^c, X_2, V_4). If $X_2 = V_4 = 1$ and $X_1 = 0$, then $S_4 = 1$; otherwise, $S_4 = 0$. Similar rules apply for other S_i.

For simplicity, we assume sufficient-cause positive monotonicity for X_1 and X_2 (Suzuki *et al.* 2012; VanderWeele 2010b). Under the monotonicity assumption, all sufficient causes with X_1^c or X_2^c are excluded, and only four sufficient causes (S_1, S_3, S_7, S_9)

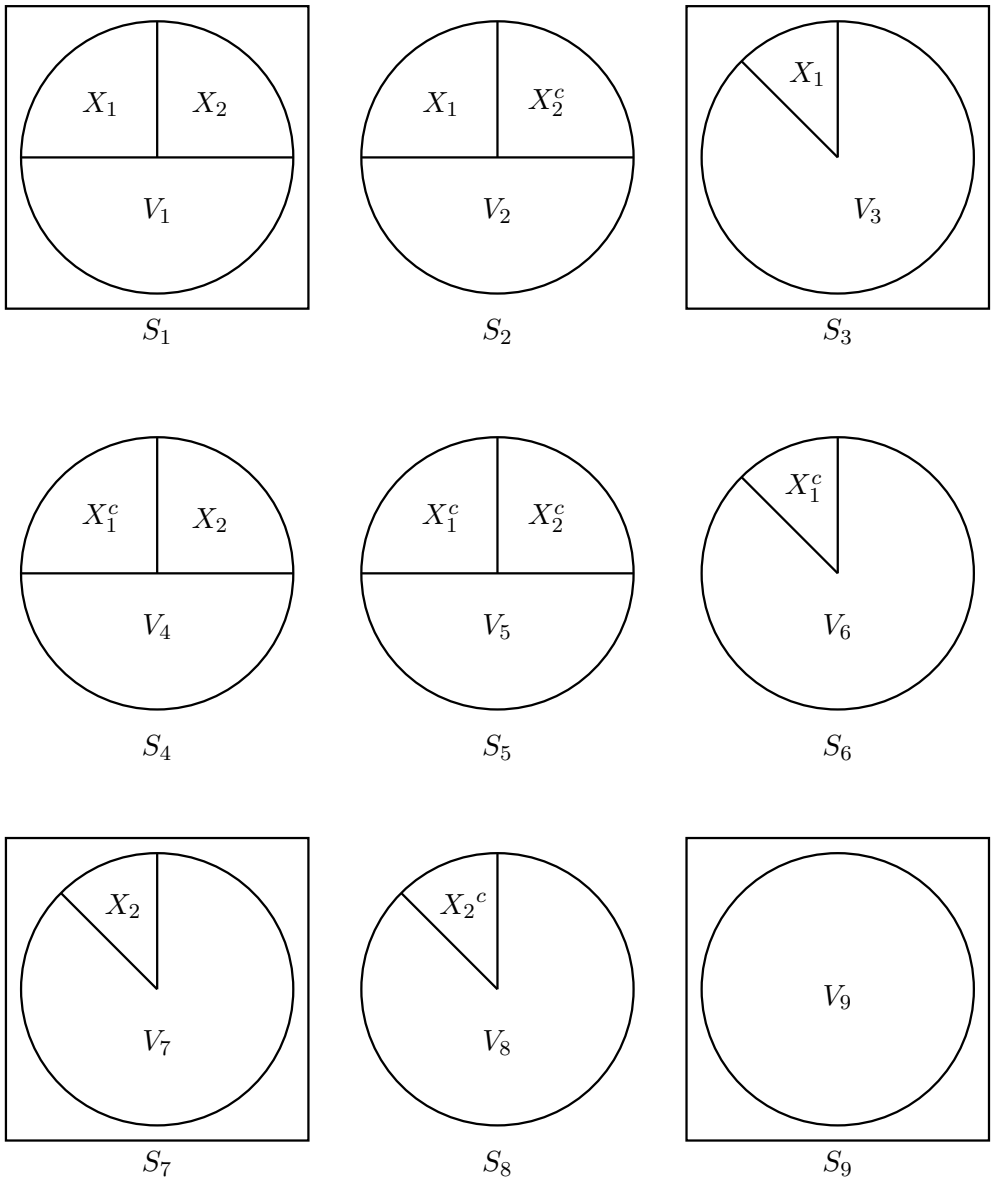


Figure 1: Nine possible sufficient-component cause models for a two-factor model. Under the monotonicity assumption, only S_1, S_3, S_7, and S_9 remain.

remain. This assumption also implies positive monotonicity, under which the effects of X_1 and X_2 on Y increase monotonically such that neither of them can ever prevent disease. Two types of monotonicity have been precisely described in the literature, and we hereafter refer to the sufficient-cause positive monotonicity assumption as the "monotonicity assumption."

Table 1: Response types with and without the monotonicity assumption.

All possible response types (Y(1,1),Y(1,0),Y(0,1),Y(0,0))	Response types under monotonicity
$(1,1,1,1)$	$(1,1,1,1)$
$(1,1,1,0)$	$(1,1,1,0)$
$(1,1,0,1)$	NA
$(1,1,0,0)$	$(1,1,0,0)$
$(1,0,1,1)$	NA
$(1,0,1,0)$	$(1,0,1,0)$
$(1,0,0,1)$	NA
$(1,0,0,0)$	$(1,0,0,0)$
$(0,1,1,1)$	NA
$(0,1,1,0)$	NA
$(0,1,0,1)$	NA
$(0,1,0,0)$	NA
$(0,0,1,1)$	NA
$(0,0,1,0)$	NA
$(0,0,0,1)$	NA
$(0,0,0,0)$	$(0,0,0,0)$

The response type (Greenland and Poole 1988 Suzuki *et al.* 2011; Suzuki *et al.* 2012) (also called response pattern (Flanders 2006)) based on the counterfactual model should be introduced before continuing to the mSCC framework. Let $Y(x_1, x_2)$ denote the hypothetical value of Y given that X is intervened as (x_1, x_2).

For example, if we intervene X_1 as 1 and X_2 as 0, then the value of Y is equal to $Y(1,0)$. The response type of Y for all possible values of exposures is defined as RT $= (Y(1,1), Y(1,0), Y(0,1), Y(0,0))$. In total, 16 outcome response types are possible, and each individual to one (Greenland and Poole 1988). Under the monotonicity assumption, only six possible response types exist, which are presented in Table 1. Two response types (RT $= (1,0,0,0)$ and $(1,1,1,0)$) are regarded as causal interaction, which is visualized in the mSCC model and defined as two types of mechanistic

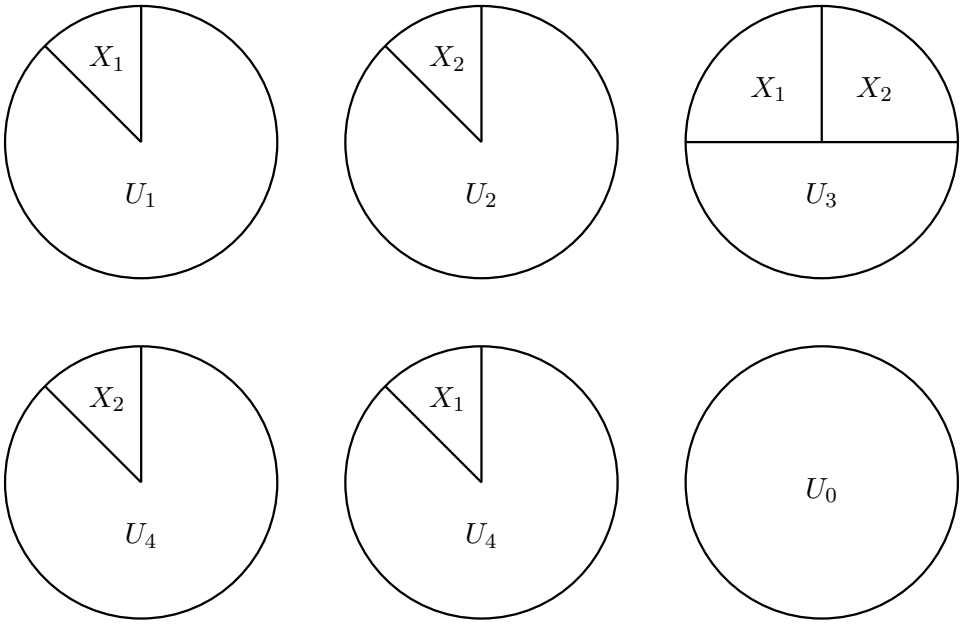


Figure 2: Two-factor marginal sufficient-component cause model.

interaction subsequently. In contrast to response type, each individual can have several background conditions of sufficient causes. Therefore, 2^4 (=16) combinations of background conditions are possible if there are four possible sufficient causes, and each individual can have only one type of these combinations. Some studies have proposed an independent competing assumption (also called the no-redundancy assumption) in which each individual can have only one background condition in a short period when each background condition is regarded as a stochastic process (Lee 2012; Robins and Greenland 1989; Weinberg 1986). However, the background condition for mSCC is defined as a condition in a relatively long period; therefore, the independent competing assumption is not necessary here. It implies that mSCC can interpret the mechanistic interactions more flexible than previous models.

We further categorize all individuals into six groups according to different response types (RT $= (1,1,0,0), (1,0,1,0), (1,0,0,0), (1,1,1,0), (1,1,1,1)$, and $(0,0,0,0)$), respectively. For the first five groups that potentially develop the outcome, we adapt the concept of SCC to visualize the formation of Y for each response type in Figure 2. V_i denotes the background condition for S_i in SCC model, and we let $U = 1, 2, 3, 4, 0$, -1

Table 2: Response types and corresponding marginal sufficient-component cause (SCC) and SCC models under the monotonicity assumption.

Group	RT[a]	Description	Interpretation	mSCC	Corresponding $V = (V_1, V_3, V_7, V_9)$
1	$(1,1,0,0)$	If $X_1 = 1$, then $Y = 1$, otherwise, $Y = 0$	Effect of X_1	U_1X_1	$(1,1,0,0), (0,1,0,0)$
2	$(1,0,1,0)$	If $X_2 = 1$, then $Y = 1$, otherwise, $Y = 0$	Effect of X_2	U_2X_2	$(1,0,1,0), (0,0,1,0)$
3	$(1,0,0,0)$	If both X_1 and X_2 are equal to 1, then $Y = 1$, otherwise, $Y = 0$	Synergistic interaction	$U_3X_1X_2$	$(1,0,0,0)$
4	$(1,1,1,0)$	If either X_1 or X_2 are equal to 1, then $Y = 1$, otherwise, $Y = 0$	Agonistic interaction	U_4X_1 U_4X_2	$(1,1,1,0), (0,1,1,0)$
5	$(1,1,1,1)$	No matter the value of X_1 and X_2, $Y = 1$	Always occurs	U_0	$(0,0,0,1), (1,0,0,1)$, $(0,1,0,1), (1,1,0,1)$
6	$(0,0,0,0)$	No matter the value of X_1 and X_2, $Y = 0$	Never occurs	No mSCC	$(0,0,0,0)$

[a] RT: response type, defined as $(Y(1,1), Y(1,0), Y(0,1), Y(0,0))$.

indicate individuals belonging to groups $1, 2, 3, 4, 5, 6$, respectively. We further define $U_0, U_1, \ldots, U_4$, as $I(U = 0)$, $I(U = 1)$, $\ldots$, $I(U = 4)$, respectively. $I(U = -1)$ can be expressed as $U_0 = U_1 = U_2 = U_3 = U_4 = 0$. The first causal pie represents individuals with U_1, which requires X_1 to induce Y. The second causal pie represents individuals with U_2, which requires X_2 to induce Y. The other causal pies follow similar rules. Because these causal pies are based on the marginal response of all SCCs, this is called a "marginal" SCC model. It can be regarded as an SCC-like expression for response types (or counterfactual models). We have summarized the interpretation and connection between mSCC and SCC in Table 2. Effects of X_1 and X_2 can be represents by U_1X_1 and U_2X_2, respectively. $U_3X_1X_2$ is referred to be synergistic interaction. U_4X_1 or U_4X_2 both indicate agonistic interaction. Lastly, U_0 means the outcome always occurs regardless of the statuses of X_1 and X_2. More details regarding the connection between the SCC model and counterfactual model (and response profile) have been widely discussed and can be referred to in relevant literature (Flanders 2006; Greenland and Poole 1988; Suzuki *et al.* 2011; Suzuki *et al.* 2012; VanderWeele and Hernán 2006).

We further express the counterfactual outcome as the following formula:

$$\begin{aligned} Y(x_1, x_2) &= U_0 + U_1x_1 + U_2x_2 + U_3x_1x_2 + U_4(x_1 + x_2 - x_1x_2) \\ &= U_0 + (U_1 + U_4)x_1 + (U_2 + U_4)x_2 + (U_3 - U_4)x_1x_2 \end{aligned} \tag{1}$$

and

$$\begin{aligned} \Pr(Y(x_1, x_2) = 1) &= P_0 + P_1x_1 + P_2x_2 + P_3x_1x_2 + P_4(x_1 + x_2 - x_1x_2) \\ &= P_0 + (P_1 + P_4)x_1 + (P_2 + P_4)x_2 + (P_3 - P_4)x_1x_2 \end{aligned} \tag{2}$$

where P_k is defined as $\Pr(U_k = 1)$ for k in $\{0, 1, 2, 3, 4\}$, and P_k satisfies $\Sigma_{j=0}^{4} p_j \leq 1$. Both x_1 and x_2 have values of $\{0, 1\}$. Notably, $\Pr(Y(x_1, x_2) = 1)$ represents the probability of an individual's counterfactual outcome equals to 1 when the X_1 and X_2 are hypothetical intervened as x_1 and x_2. The probability of the counterfactual outcome cannot be observed generally. For inference through observations, the identification procedure is required and shown in the following context. On the basis of Formula (2), the probabilities of the counterfactual outcomes given the four combinations of (x_1, x_2) are listed as follows:

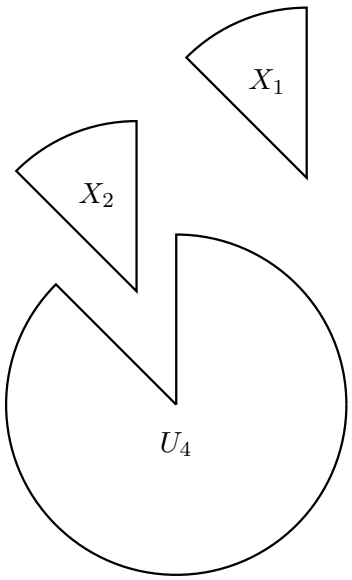
$$\Pr(Y(1, 1) = 1) = P_0 + P_1 + P_2 + P_3 + P_4 \tag{2-1}$$

$$\Pr(Y(1, 0) = 1) = P_0 + P_1 + P_4 \tag{2-2}$$

$$\Pr(Y(0, 1) = 1) = P_0 + P_2 + P_4 \tag{2-3}$$

$$\Pr(Y(0, 0) = 1) = P_0. \tag{2-4}$$

As shown in previous works (Vanderweele 2010a; VanderWeele and Robins 2008), the causal interaction is defined as $\Pr(Y(1, 1) = 1) - \Pr(Y(1, 0) = 1) - \Pr(Y(0, 1) = 1) + \Pr(Y(0, 0) = 1)$, and thus from the formulas above, $P_3 - P_4$ can be referred to as the causal interaction. Moreover, the indicator corresponding to P_3 (i.e., U_3) is the condition in which X_1 and X_2 have synergic interaction because they occur on the same sufficient cause. U_4, corresponding to P_4, is the condition in which either X_1 or X_2 can induce the outcome Y. In the relevant literature of causal inference, U_4 is rarely noted or well identified. In pharmacology and immunology, U_4 acts as a receptor,



U_4 is analogous to the receptor, whereas X_1 and X_2 are analogous to ligands with the same binding site on U_4. Each ligand can activate the receptor and consequently initiate the occurrence of the outcome.

Figure 3: Marginal sufficient-component cause model for agonists that are analogous to ligand–receptor theory.

and both sufficient causes, X_1U_4 and X_2U_4, are two active forms of U_4 that suffice to initiate downstream signal transduction, that is, the occurrence of the outcome (shown in Figure 3). In other words, both X_1 and X_2 can activate the receptor U_4. Such a relationship between X_1 and X_2 on Y is called "agonistic interaction" (Christopoulos and El-Fakahany 1999; Ross and Kenakin 2001).

Several conclusions can be made from this result: First, mechanistic interaction consists of three parts: synergistic, agonistic, and antagonistic interactions. Our setting has no antagonistic interaction because of the monotonicity assumption. The direction that the agonism contributes to the overall interaction is the same as antagonism and is negative. In the standard SCC, conceptualizing agonistic interaction from synergistic and antagonistic interactions is challenging.

2.2 Identification of mechanistic interaction

We create a linear probability model for Y on X_1 and X_2 as follows:

$$\Pr(Y = 1|X_1, X_2) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 \tag{3}$$

If the consistency assumption (VanderWeele 2009a) has been made and all potential confounders of the relationship between Y and (X_1, X_2) are collected and denoted as C, under a stratum of $C = c$, this model (3) is equal to the causal model in (2), that is, $\beta_0 = P_0$; $\beta_1 = (P_1 + P_4)$; $\beta_2 = (P_2 + P_4)$; and $\beta_3 = (P_3 - P_4)$. Because of the restriction on degrees of freedom, three subtypes of interaction cannot be identified using empirical data without making additional assumptions. Several empirical test techniques have been developed to investigate the sufficient conditions for the existence of synergistic and even antagonistic interaction. A method has been proposed to empirically test the existence of synergism (VanderWeele and Robins 2007b). This method has been further extended to test the existence of agonism by treating it as a special type of synergism with a reversed sign for both exposure and outcome (VanderWeele and Knol 2011). On the basis of the monotonicity and independent competing assumptions, a series of methods, such as the PRISM test, have been developed to test for synergism and demonstrate better statistical power than empirical tests (Lee 2013a; Lee 2013b; Lin and Lee 2015). All the aforementioned approaches are based on relatively strong assumptions, and thus methodological improvement is required.

In the mSCC setting, if the effects of X_1 and X_2 on the outcome are monotonic, there is no antagonistic interaction. As a result, the interaction term β_3 reduces to $P_3 - P_4$. The condition of $\beta_3 < 0$ indicates the existence of agonistic interaction. If we can assume no synergistic interaction based on background knowledge, agonistic interaction can be identified as $-\beta_3$. Otherwise, we can merely interpret $-\beta_3$ as the lower bound of agonism. Similarly, if we can assume no agonistic interaction based on background knowledge, synergistic interaction can be identified as β_3, which is the traditional assumption and interpretation for interaction.

2.3 Identification of population attributable fraction and causal pie weighting in the mSCC model

Population attributable fraction (PAF) is a crucial measurement widely used in epidemiology. It can be conceptually defined as the reduction in incidence of a certain population if they had been entirely unexposed compared with its current exposure status (Suzuki *et al.* 2012; VanderWeele 2010b). Hoffmann (Hoffmann *et al.* 2005) proposed a measurement called "the proportion of disease due to a class of sufficient cause (PDC)" to link PAF to the SCC model. Suzuki *et al.* proposed a comprehensive framework for the connection of PAF, SCC, and counterfactual models under one exposure (Suzuki *et al.* 2011; Suzuki *et al.* 2012). VanderWeele (VanderWeele 2010b) further clarified the definition and connected the PAF to sufficient cause interaction. Lee extended the idea of PDC and explicitly defined causal pie weight (CPW). The connection between PAF and CPW has also been described (Liao and Lee 2010). In this section, we mainly use the CPW and extend Lee's method to mechanistic interaction based on the mSCC model.

CPW is conceptually defined as the proportion of cases that can be attributed to the completion of a particular causal pie. In our mSCC model, five causal pies of interest and the corresponding CPWs are mathematically defined as

$$\begin{aligned}
\mathrm{CPW}_0 &= \Pr(U_0 = 1|Y = 1) = \frac{\Pr(U_0 = 1)}{\Pr(Y = 1)} \\
\mathrm{CPW}_1 &= \Pr(U_1X_1 = 1|Y = 1) = \frac{\Pr(U_1X_1 = 1)}{\Pr(Y = 1)} \\
\mathrm{CPW}_2 &= \Pr(U_2X_2 = 1|Y = 1) = \frac{\Pr(U_2X_2 = 1)}{\Pr(Y = 1)} \\
\mathrm{CPW}_3 &= \Pr(U_3X_1X_2 = 1|Y = 1) = \frac{\Pr(U_3X_1X_2 = 1)}{\Pr(Y = 1)} \\
\mathrm{CPW}_4 &= \Pr(U_4(X_1 + X_2 - X_1X_2) = 1|Y = 1) = \frac{\Pr(U_4(X_1 + X_2 - X_1X_2) = 1)}{\Pr(Y = 1)}
\end{aligned} \tag{4}$$

Based on (1) and (2), we derive

$$\begin{aligned}\Pr(Y=1) &= P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2]) \\ &= P_0 + (P_1+P_4)\mathrm{E}[X_1] + (P_2+P_4)\mathrm{E}[X_2] + (P_3-P_4)\mathrm{E}[X_1X_2] \end{aligned} \tag{5}$$

From (4) and (5), we obtain

$$\begin{aligned}
\mathrm{CPW}_0 &= \frac{P_0}{(P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2]))} \\
\mathrm{CPW}_1 &= \frac{P_1\mathrm{E}[X_1]}{P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2])} \\
\mathrm{CPW}_2 &= \frac{P_2\mathrm{E}[X_2]}{P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2])} \\
\mathrm{CPW}_3 &= \frac{P_3\mathrm{E}[X_1X_2]}{P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2])} \\
\mathrm{CPW}_4 &= \frac{P_4(\mathrm{E}[X_1 + X_2 - X_1X_2]}{P_0 + P_1\mathrm{E}[X_1] + P_2\mathrm{E}[X_2] + P_3\mathrm{E}[X_1X_2] + P_4(\mathrm{E}[X_1 + X_2 - X_1X_2])}
\end{aligned} \tag{6}$$

We can estimate the expectation by using the empirical mean (i.e., to estimate $\mathrm{E}[X_1]$ by using $\bar{X}_1$; $\mathrm{E}[X_2]$ by using $\bar{X}_2$; $\mathrm{E}[X_1X_2]$ by using $\overline{X_1X_2}$; and $\mathrm{E}[X_1+X_2-X_1X_2]$ by using $\overline{X_1 + X_2 - X_1X_2}$. We can use the maximal likelihood estimates of all β in (3), that is, $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3)$, to estimate P_0 to P_4 by assuming no synergistic interaction or no agonistic interaction. If we assume no agonism ($P_4 = \mathrm{CPW}_4 = 0$), then

$$\begin{aligned}
\widehat{\mathrm{CPW}}_0^a &= \frac{\hat{\beta}_0}{\hat{\beta}_0 + \hat{\beta}_1\bar{X}_1 + \hat{\beta}_2\bar{X}_2 + \hat{\beta}_3\overline{X_1X_2}} \\
\widehat{\mathrm{CPW}}_1^a &= \frac{\hat{\beta}_1\bar{X}_1}{\hat{\beta}_0 + \hat{\beta}_1\bar{X}_1 + \hat{\beta}_2\bar{X}_2 + \hat{\beta}_3\overline{X_1X_2}} \\
\widehat{\mathrm{CPW}}_2^a &= \frac{\hat{\beta}_2\bar{X}_2}{\hat{\beta}_0 + \hat{\beta}_1\bar{X}_1 + \hat{\beta}_2\bar{X}_2 + \hat{\beta}_3\overline{X_1X_2}} \\
\widehat{\mathrm{CPW}}_3^a &= \frac{\hat{\beta}_3\overline{X_1X_2}}{\hat{\beta}_0 + \hat{\beta}_1\bar{X}_1 + \hat{\beta}_2\bar{X}_2 + \hat{\beta}_3\overline{X_1X_2}}
\end{aligned} \tag{7}$$

When we assume no synergistic assumption ($P_3 = \mathrm{CPW}_3 = 0$),

$$
\begin{aligned}
\widehat{\mathrm{CPW}}_0 &= \frac{\hat{\beta}_0}{\hat{\beta}_0 + (\hat{\beta}_1 + \hat{\beta}_3)\bar{X}_1 + (\hat{\beta}_2 + \hat{\beta}_3)\bar{X}_2 + (-\hat{\beta}_3)\overline{X_1 + X_2 - X_1X_2}} \\
\widehat{\mathrm{CPW}}_1 &= \frac{(\hat{\beta}_1 + \hat{\beta}_3)\bar{X}_1}{\hat{\beta}_0 + (\hat{\beta}_1 + \hat{\beta}_3)\bar{X}_1 + (\hat{\beta}_2 + \hat{\beta}_3)\bar{X}_2 + (-\hat{\beta}_3)\overline{X_1 + X_2 - X_1X_2}} \\
\widehat{\mathrm{CPW}}_2 &= \frac{(\hat{\beta}_2 + \hat{\beta}_3)\bar{X}_2}{\hat{\beta}_0 + (\hat{\beta}_1 + \hat{\beta}_3)\bar{X}_1 + (\hat{\beta}_2 + \hat{\beta}_3)\bar{X}_2 + (-\hat{\beta}_3)\overline{X_1 + X_2 - X_1X_2}} \\
\widehat{\mathrm{CPW}}_4 &= \frac{(-\hat{\beta}_3)\overline{X_1 + X_2 - X_1X_2}}{\hat{\beta}_0 + (\hat{\beta}_1 + \hat{\beta}_3)\bar{X}_1 + (\hat{\beta}_2 + \hat{\beta}_3)\bar{X}_2 + (-\hat{\beta}_3)\overline{X_1 + X_2 - X_1X_2}}
\end{aligned}
\tag{8}
$$

Moreover, the connection between PAF and CPW are discussed in the mSCC framework. PAF is conceptually defined as the proportion of cases that can be attributed to a certain factor or a set of factors. The mathematical definitions of PAFs and the relationship between PAF and CPW for two risk factors are detailed in Appendix. If we assume no agonistic interaction, the CPW and PAF are identical to the result of a previous study (Liao and Lee 2010). If interaction is negative, and synergism is assumed to be excluded, we can still estimate all CPWs based on PAFs. We apply the aforementioned method to Taiwanese hepatocellular carcinoma (HCC) cohort data in the subsequent section.

3. Results

3.1 Hypothetical example

In this section, we use a hypothetical example illustrating a negative additive interaction without mechanistic interaction, which is adopted from VanderWeele's book (VanderWeele 2015). As illustrated in Figure 4, a particular disease Y can arise only through one of three mechanisms, one involving a genetic factor X_1, one involving an environmental factor X_2, and one involving neither the genetic nor the environmental factor. The genetic factor X_1 is only sufficient for developing disease Y with some other factors V_1. The environmental factor X_2 is only sufficient for developing disease Y with some other factors V_2. These factors that are sufficient to lead to disease Y are

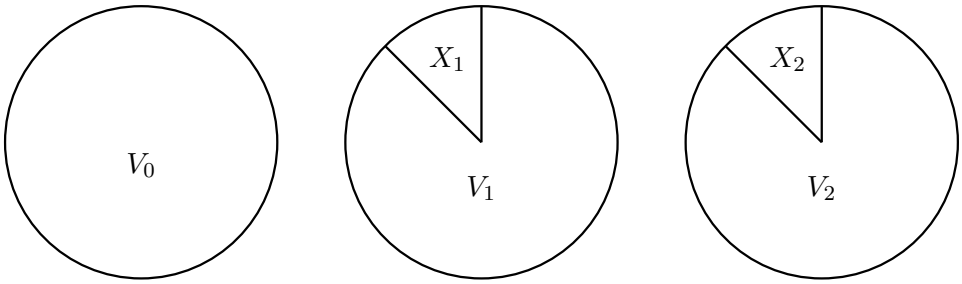


Figure 4: Three sufficient causes for the hypothetical example depicted in VanderWeele's book.

denoted as V_0 regardless of the presence of X_1 or X_2. No mechanism requires both X_1 and X_2 to operate in this case; therefore, no synergism between X_1 and X_2 exists. The monotonicity assumption also holds because no mechanism requires the absence of X_1 or X_2. For simplicity, we assume that the distributions of X_1, X_2, V_0, V_1, and V_2 are all statistically independent and V_0, V_1, and V_2 do not affect X_1 and X_2. Suppose the probabilities of X_1 and X_2 are 0.2 and 0.5, respectively, and the probability of V_0, V_1, and V_2 are all 0.1.

The additive interaction is -0.009; which indicates negative causal interaction in the additive scale. However, this case has no synergism between X_1 and X_2 and no mechanism that requires both X_1 and X_2 to operate, despite the causal interaction. This is a standard example illustrating that interaction does not necessarily allow us to draw conclusions regarding synergism. Similar conclusions for antagonism can be drawn (VanderWeele 2015).

We now reconsider this case in terms of the novel mSCC model. Eight combinations are possible for (V_0, V_1, V_2) — $(1,1,1)$, $(1,1,0)$, $(1,0,1)$, $(1,0,0)$, $(0,1,1)$, $(0,1,0)$, $(0,0,1)$, and $(0,0,0)$. These combinations can be categorized into groups according to the response types, as presented in Table 3. Group 3 has no combinations, but $(0,1,1)$ is in Group 4. No synergism exists in this population, but agonism exists for those with both V_1 and V_2, with probability $P_4 = \Pr(V_0 = 0, V_1 = 1, V_2 = 1) = 0.9 \times 0.1 \times 0.1 = 0.009$, which is exactly the absolute value of causal interaction, $P_3 - P_4 = 0 - P_4$. The agonistic interaction, in terms of mSCC, contributes to the subadditive interaction, whereas the synergistic interaction contributes to the superadditive interaction.

Table 3: Response types and corresponding marginal sufficient-component causes for the example.

Group	All possible response types (Y(1,1), Y(1,0), Y(0,1), Y(0,0))	Response types under monotonicity
1	$(1,1,0,0)$	$(0,1,0)$
2	$(1,0,1,0)$	$(0,0,1)$
3	$(1,0,0,0)$	N/A
4	$(1,1,1,0)$	$(0,1,1)$
5	$(1,1,1,1)$	$(1,0,0),(1,0,1),(1,1,0),(1,1,1)$
6	$(0,0,0,0)$	$(0,0,0)$

This gap between mechanistic interaction and causal interaction is interpreted as the presence of agonistic interaction, which is elusive in the conventional SCC model.

3.2 Simulation study

We performed simulation studies to evaluate the performance of our proposed CPW estimator in separate scenarios of no synergistic interaction and no agonistic interaction. The parameter setting uses the estimates derived from the analysis of the Taiwanese HCC cohort dataset. We generated the two exposures X_1 and X_2 by using the Bernoulli distribution with $P_1 = 0.147$ and $P_2 = 0.082$, respectively. Subsequently, the vector of indicator variables representing the groups individuals belong to, $(U_{-1}, U_0, U_1, U_2, U_3, U_4)$ was generated using the multinomial distribution: Multinomial $(N = 1, P = (p_{-1}, p_0, p_1, p_2, p_3, p_4))$. In the case of assuming no synergistic interaction, P is set as $(p_{-1}, p_0, p_1, p_2, p_3, p_4) = (0.161, 0.123, 0.237, 0.102, 0.377, 0)$, and in the case of no agonism, P is $(0.285, 0.215, 0.299, 0.084, 0, 0.117)$. Finally, the outcome Y was determined using $Y = U_0 + U_1X_1 + U_2X_2 + U_3X_1X_2 + U_4(X_1 + X_2 - X_1X_2)$.

For each simulation study, we simulated 999 replicates to estimate bias, standard deviation, mean square error, and coverage rate of the 95% confidence interval for CPW. Standard deviation was calculated using the standard bootstrap approach. The CPW results are presented in Table 4 and 5. The small biases indicate that the estimated CPWs are close to the true values, and the coverage rates are approximately 0.95.

Table 4: Simulation results of causal pie weight estimation when assuming no agonistic interaction.

	True	Estimate	Bias	SD	MSE	CR
CPW_0	0.7210	0.7190	−0.0020	0.0236	0.0006	0.9548
CPW_1	0.2017	0.2059	0.0042	0.0206	0.0004	0.9296
CPW_2	0.0491	0.0478	−0.0013	0.0134	0.0002	0.9497
CPW_3	0.0283	0.0273	−0.0009	0.0064	0.0001	0.9598

Notes Abbreviations: SD, standard deviation; MSE, mean square error; CR, coverage rate.

Table 5: Simulation results of causal pie weight estimation when assuming no synergistic interaction.

	True	Estimate	Bias	SD	MSE	CR
CPW_0	0.7404	0.7396	−0.0008	0.0164	0.0003	0.9397
CPW_1	0.1495	0.1463	−0.0032	0.0399	0.0016	0.9497
CPW_2	0.0237	0.0224	−0.0013	0.0211	0.0004	0.9447
CPW_4	0.0864	0.0917	0.0053	0.0608	0.0037	0.9598

Notes Abbreviations: SD, standard deviation; MSE, mean square error; CR, coverage rate.

In conclusion, the proposed estimators perform efficiently for the inferred CPWs with proper coverage rates.

3.3 Application on Taiwanese HCC cohort

In total, 23,820 residents from seven townships in Taiwan aged 30–65 years were recruited from 1991 to 1992. We linked data available from the national cancer registry in June 2008 and 477 incident cases of HCC developed during this period. Participants provided written informed consent for the questionnaire interview, health examinations, biospecimen collection, and data linkage of health status with death certification profiles and national cancer registry. Blood samples collected at enrollment were tested for seromarkers and viral load of hepatitis B virus (HBV) and hepatitis C virus (HCV).

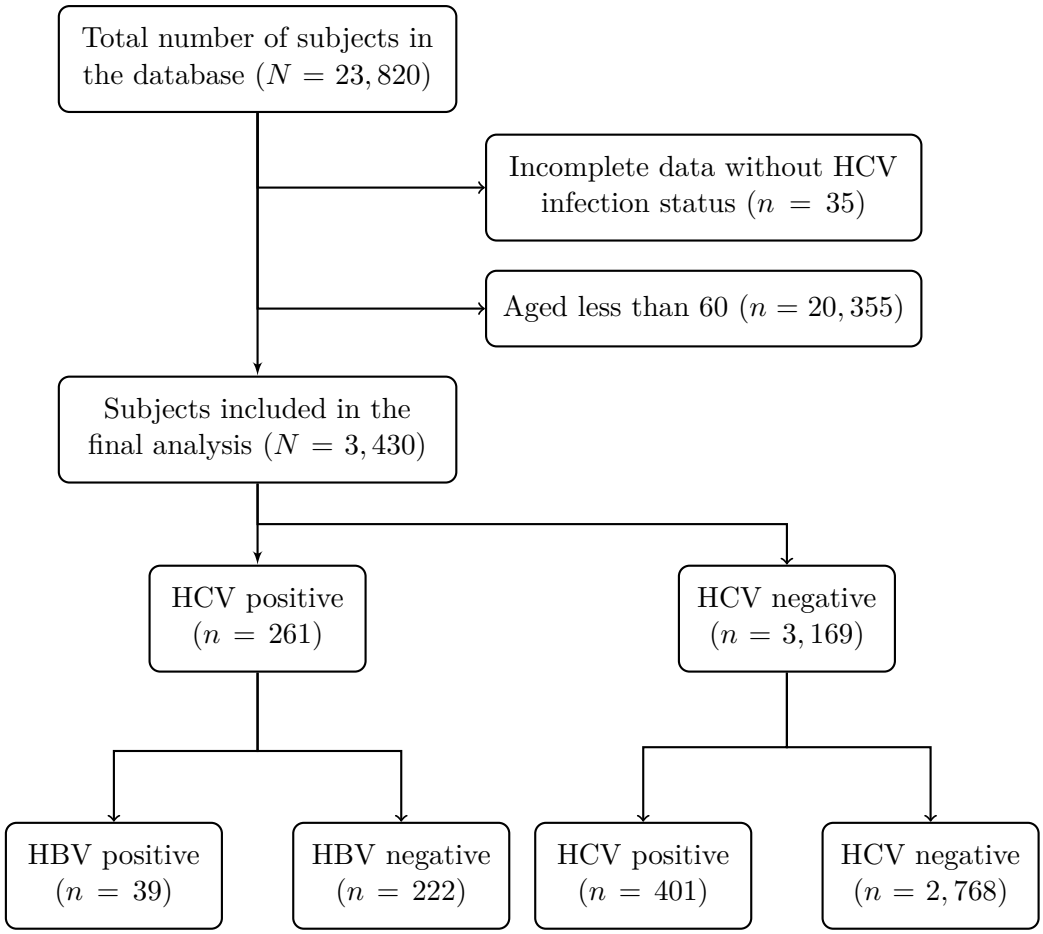


Figure 5: Selection procedure flowchart for the population included from Taiwanese cohort data.

Newly developed HCC was confirmed through computerized data linkage with national cancer registry and death certification systems. The details of the study design and participant enrollment has been described previously (Chen *et al.* 2008; Iloeje *et al.* 2007; Lee *et al.* 2010).

We focus on the elderly population aged more than 60 years with sample size = 3430. Among all elderly participants, 3.79% developed HCC; 7.61% had HCV; 12.83% had HBV; 1.14% had dual viruses; and 19.30% had either HCV or HBV. A flowchart of the selection procedure is illustrated in Figure 5.

Estimation of regression coefficients by using the generalized linear model with identity link for the binomial outcome are listed in Table 6 based on (3), and the CPWs

Table 6: Estimation of regression coefficients.

	Estimate	**SE**	**p-value**
Intercept	0.0137	0.0022	<0.001
HCV	0.1259	0.0234	<0.001
HBV	0.1159	0.0169	<0.001
HCV×HBV	−0.0248	0.0733	0.735

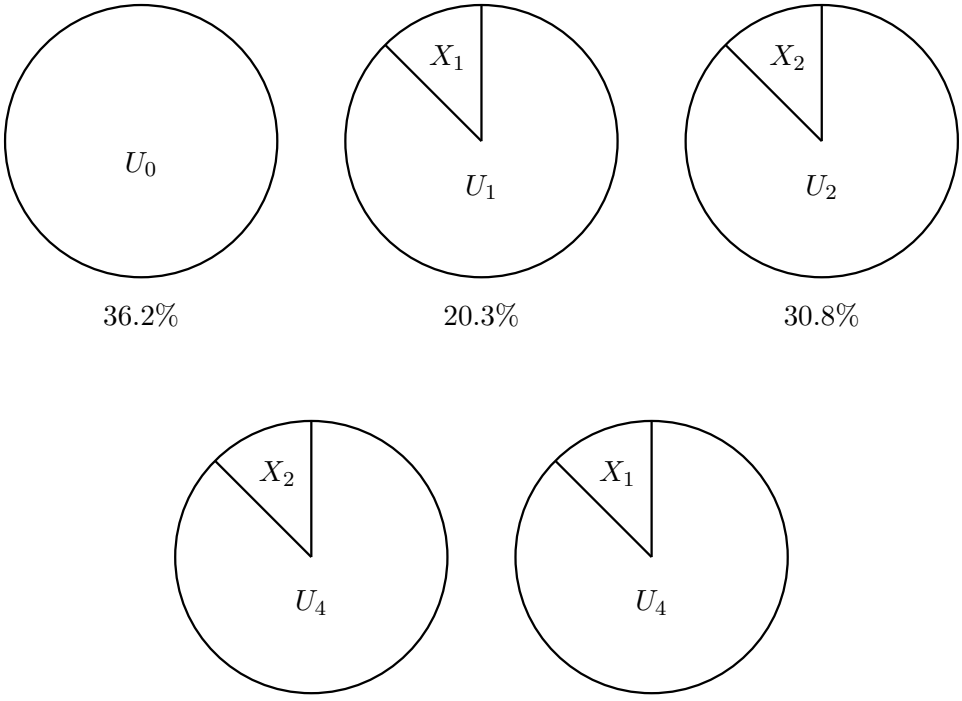


Figure 6: Causal pie weights for Taiwanese cohort data under the no-synergism assumption.

based on (8) are displayed in Figure 6. The interaction term is negative but nonsignificant (−0.0248) and has the same direction as that in previous literature (Chien-An *et al.* 2003; Huang *et al.* 2011; Kuper *et al.* 2000). Approximately 36.2% of HCC cases developed through pathways involving neither HBV nor HCV; independent effect due to HCV accounted for 20.3%; independent effect due to HBV accounted for 30.8%; and

Table 7: Causal pie weight estimation when assuming no synergistic interaction.

	CPW	**S.E.**	**LCI**	**UCI**	**P value**
None of HBV or HCV	36.22%	0.0492	0.2658	0.4586	<0.001
Due to HCV	20.30%	0.1417	0	0.4807	0.1521
Due to HBV	30.84%	0.2449	0	0.7884	0.2078
Agnostic interaction	12.64%	0.3788	0	0.8688	0.7386

the lower bound of agonistic interaction accounted for 12.6%. Under the assumption of no synergistic interaction, the proportion of agnostic interaction would be exactly 12.6%. The detailed result of CPW estimation is presented in Table 7.

4. Discussion

The mSCC model has two advantages. First, although the counterfactual outcome and causal effect can be expressed in terms of the joint distribution probability of the stochastic part in a certain combination of sufficient causes in standard SCC, it is complicated (Flanders 2006; VanderWeele 2015). Because the background conditions in mSCC of each sufficient cause are mutually exclusive, their joint probability is additive, that is, the causal effect simply equals the total probability of the complementary cause (U_i) of a certain sufficient cause. An independent competing assumption has been proposed in which the background condition is viewed as a stochastic process (Lee 2012; Robins and Greenland 1989; Weinberg 1986). Different conditions are assumed not to occur simultaneously; thus, the joint distribution of all stochastic components is also additive. In the mSCC model, such an assumption is unnecessary. Therefore, this method can be widely applied to all types of cases.

The other advantage of the mSCC model is the identification of the agonistic interaction with intuitive visualization. The existence of agonistic interaction partly contributes to the reason that statistical or mechanistic interaction cannot be fully explained by the SCC model, even if the interaction effect is not confounded by other covariates. Agonism can be established according to the response types defined on

the basis of counterfactual outcome models and can sometimes be categorized as a special type of antagonism, called competitive antagonism, because it has the same direction as antagonism (VanderWeele 2015). A study proposed a similar concept called parallelism (Darroch 1997). However, it is difficult to conceptualize in the standard SCC framework. In the mSCC framework, a complementary set of causes can be identified and fits the definition of agonism, which is a well-established concept in biomedical sciences such as pharmacology and immunology (Brody *et al.* 1998). In this study, we extend the concept of agonists to the field of data science in terms of background conditions. U_s is analogous to receptors, whereas X_1 and X_2 are analogous to ligands. The completion of a sufficient cause is analogous to an activated receptor that can initiate the occurrence of Y. The condition corresponding to agonistic interaction can be activated by X_1 or X_2, illustrated in Figure 3.

Mechanistic interaction can generally be referred to as all interactions that imply two exposures interacting in the formation of an outcome through the same mechanism, including biological interaction, singular interaction, sufficient cause interaction, causal coaction, synergism, and antagonism. Biological interaction, sometimes called physical interaction or functional interaction, is conceptually defined as "the two exposure interact in any biological or physical way" (VanderWeele 2015). Causal coaction is defined as the presence of two factors (or its complement) acting on the formation or inhibition of the outcome (VanderWeele 2015), including synergism and antagonism. The mechanism is defined in the SCC model. Sufficient cause interaction and singular interaction (researchers sometimes specifically include mechanistic interaction in this class) are defined on the basis of response type. Sufficient cause interaction refers to individuals with $(Y(1,1), Y(1,0), Y(0,1)) = (1,0,0)$, which includes RT $= (1,0,0,0)$ and $(1,0,0,1)$, whereas the others refer to those with RT $= (1,0,0,0)$ only. These interactions defined on the basis of response type can be visualized by mSCC and can be regarded as synergism at the individual level given that monotonicity is assumed, whereas causal coaction is conventionally defined at the SCC level.

Although agonism is considered at the individual level, this finding can also be considered at the SCC level because all Vs are a union of several mechanisms (or SCCs) with some factor requirements. For example, suppose $V_3 = (V_{31}, V_{32}, V_{33})$, $V_7 =$

(V_{71}, V_{72}), and $V_{31} = V_{71} = V_{\text{Agonism}}$, both $X_1 V_{\text{Agonism}}$ and $X_2 V_{\text{Agonism}}$ can induce the outcome through the same mechanism (i.e., completion of a similar causal pie). Agonism at the mSCC level, although insufficient, implies the existence of agonism at the SCC level. This agonism can exist even under the no-redundancy assumption and indicates that two factors share the same mechanism if they interact agonistically. For example, our study and previous literature demonstrated that HBV and HCV have subadditive interaction on the incidence of HCC (Chien-An *et al.* 2003; Huang et al. 2011; Kuper *et al.* 2000). To understand the mechanism, distinguishing the subtype of interaction is critical. An agonistic interaction can be interpreted as HBV and HCV working on the same pathological pathway to induce HCC. Consequently, the two factors with agonistic interaction can be prevented using the same strategy. If the negative interaction is treated as antagonistic, the factors do not only induce HCC through the same pathway, but the existence of one factor interferes with the risk of HCC caused by the other factor.

Our method has several limitations. First, we consider only two exposures. Settings with more than two exposures warrant further research for a generalized formula of multiple interactions. In addition, the conventional SCC framework only allows for dichotomous variables. Although the models are restricted to binary variables, this restriction makes interpretation in biomedical applications easier. Binary-variable models are also less vulnerable to model misspecification relative to models of the liner outcome. Moreover, the methodology for binary variables is the foundation for extensions to a dose–response or linear model. However, we acknowledge that extending the current SCC model to nonbinary settings will increase its utility and should be pursued in further research. Although the methods developed in this article must be refined for wide application in data analysis, the main contribution is the connection of current SCC theory to the counterfactual framework and DAGs and the conceptualization of the novel type of interaction. Finally, a monotonicity assumption is required to simplify the proposed model. However, this assumption may not hold in the presence of antagonistic interaction, which represents the effect of two factors is actually less than the sum of the effect of the two factors taken independently of each other. Although releasing the monotonicity assumption can further study antagonistic interaction, the

estimation procedure suffers the problem of unidentifiability when the monotonicity assumption fails. Developing a new technique for addressing unidentifiability is required in the future.

5. Conclusions

The mSCC framework has strong potential to incorporate SCC to the counterfactual framework and DAGs for interaction analyses. It can also visualize the existence of agonism, a crucial subtype of mechanistic interaction, to explain the gap between superadditive and synergistic interaction. Our finding contributes to the comprehensive understanding of causal mechanisms.

Appendix

Here, we demonstrate the connection between PAF and CPW in the mSCC framework. PAF is conceptually defined as the proportion of cases that can be attributed to a certain factor or a set of factors. When two risk factors (X_1 and X_2) are of interest, three PAFs can be defined mathematically as follows:

$$\begin{aligned}\mathrm{PAF}(x_1, x_2) &= \frac{\Pr(Y=1) - \Pr(Y(x_1=0, x_2=0)=1)}{\Pr(Y=1)} \\ &= 1 - \frac{\Pr(Y(x_1=0, x_2=0)=1)}{\Pr(Y=1)}\end{aligned}$$

$$\mathrm{PAF}(x_1) = \frac{\Pr(Y=1) - \Pr(Y(x_1=0)=1)}{\Pr(Y=1)} = 1 - \frac{\Pr(Y(x_1=0)=1)}{\Pr(Y=1)}$$

$$\mathrm{PAF}(x_2) = \frac{\Pr(Y=1) - \Pr(Y(x_2=0)=1)}{\Pr(Y=1)} = 1 - \frac{\Pr(Y(x_2=0)=1)}{\Pr(Y=1)}$$

Based on (5), we can obtain

$$\mathrm{PAF}(x_1, x_2) = \frac{(P_1+P_4)\mathrm{E}[X_1] + (P_2+P_4)\mathrm{E}[X_2] + (P_3-P_4)\mathrm{E}[X_1X_2]}{P_0 + (P_1+P_4)\mathrm{E}[X_1] + (P_2+P_4)\mathrm{E}[X_2] + (P_3-P4)\mathrm{E}[X_1X_2]}$$

$$\mathrm{PAF}(x_1) = \frac{(P_1+P_4)\mathrm{E}[X_1] + (P_3-P_4)\mathrm{E}[X_1X_2]}{P_0 + (P_1+P_4)\mathrm{E}[X_1] + (P_2+P_4)\mathrm{E}[X_2] + (P_3-P4)\mathrm{E}[X_1X_2]}$$

$$\mathrm{PAF}(x_2) = \frac{(P_2 + P_4)\mathrm{E}[X_2] + (P_3 - P_4)\mathrm{E}[X_1X_2]}{P_0 + (P_1 + P_4)\mathrm{E}[X_1] + (P_2 + P_4)\mathrm{E}[X_2] + (P_3 - P4)\mathrm{E}[X_1X_2]}$$

The relationship between PAF and CPW can be expressed as follows:

$$\mathrm{PAF}(x_1, x_2) = \mathrm{CPW}_1 + \mathrm{CPW}_2 + \mathrm{CPW}_3 + \mathrm{CPW}_4$$

$$\mathrm{PAF}(x_1) = \mathrm{CPW}_1 + \mathrm{CPW}_3 + \mathrm{CPW}_4 \times \frac{\mathrm{E}[X_1] - \mathrm{E}[X_1X_2]}{\mathrm{E}[X_1 + X_2 - X_1X_2]}$$

$$\mathrm{PAF}(x_2) = \mathrm{CPW}_2 + \mathrm{CPW}_3 + \mathrm{CPW}_4 \times \frac{\mathrm{E}[X_2] - \mathrm{E}[X_1X_2]}{\mathrm{E}[X_1 + X_2 - X_1X_2]}.$$

Abbreviations

SCC, sufficient-component cause; mSCC, marginal sufficient-component cause; CPW, causal pie weight; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; DAGs, directed acyclic graphs; PDC, the proportion of disease due to a class of sufficient cause; PAF, population attributable fraction.

Ethics statement

Our study involves comparison and analysis of variables at the population level rather than at the individual level. No personal data were handled.

Data accessibility

Data is from a published study that has been approved by the Research Ethics Committee, Taiwan. Identifier: DOI:10.1001/jama.295.1.65. All datasets that are relevant to this study are accessed from Taiwan Liver Cancer Network located at http://tlcn.nhri.edu.tw/etlcn/.

Competing interests

The authors report no conflicts of interest in this work.

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視覺化同效型交互作用之充分組成病因模型: 對次加成作用的另類詮釋

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摘 要

充分組成病因模型架構爲目前因果推論中極重要的模型之一, 特別是能夠定義以及視覺化機制型交互作用(包含協同型交互作用與拮抗型交互作用)。然而, 機制型交互作用與統計上的交互作用往往並不一致。因此, 本篇研究在反事實模型的框架下, 提出邊際充分組成病因模型; 並使用該模型識別出一個不同於「協同」與「拮抗」的機制型交互作用 — 同效型交互作用, 以及重新詮釋因果圓派權重與族群可歸因比率。除此之外, 邊際充分組成病因模型能使統計上的交互作用都能有特定的機制型交互作用的解釋。在數值分析的部分, 本研究採用模擬分析以評估該模型之效能。模擬結果顯示該模型估計式具有不偏的性質且其覆蓋率能有效地被控制在 95%。同時, 此方法被套用至台灣肝癌資料庫以探討 C 型肝炎病毒與 B 型肝炎病毒對於肝癌的致病機制。分析結果顯示 C 肝病毒獨立作用、B 肝病毒獨立作用以及兩病毒的同效作用在全體肝癌患者中分別佔有 20.3%、30.8% 以及 12.6%。我們對同效作用的發現成功地解釋了統計上的交互作用與機制型交互作用之間的不一致, 這將有助於更深入地瞭解因果機制。

關鍵詞: 交互作用、同效作用、協同作用、充分組成病因模型、因果推論、機制型交互作用。

JEL classification: C49.

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