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**Abstract:**

**Aim:** Different processes or events which are objectively given and real are equally one of the foundations of human life (necessary conditions) too. However, a generally accepted, logically consistent (bio)-mathematical description of these natural processes is still not in sight.

**Methods:** Discrete random variables are analysed.

**Results:** The mathematical formula of the necessary condition is developed. The impact of study design on the results of a study is considered.

**Conclusion:** Study data can be analysed for necessary conditions.

**Keywords:** necessary condition; conditio sine qua non; risk factor; p Value

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## 1. Introduction

Nature or objective reality as such is sometimes determined by changes, by processes or by events et cetera which occur **independently and outside of human mind and consciousness** too. In this context, there are events (i. e.  $A_t$ ) at a certain Bernoulli trial (or period or point in space-time)  $t$  which must be present, which must be given in order for another event (i. e.  $B_t$ ) to occur at the same Bernoulli trial (or period or point in space-time)  $t$ . To put it in exaggerated terms, there are objective and real necessary conditions which exist independently and outside any human mind and consciousness. In simple terms, necessary conditions have traditionally been discussed especially by philosopher's. Bluntly said, let us now consider a simple example. At most, it is appropriate to make it clear again that sufficient amounts of gaseous oxygen or air as such at these days is a necessary condition for humans being alive. In other words, human beings require air to live or having air to breathe is a necessary condition for survival. Broadly speaking, **without** air (i. e. gaseous oxygen) **no** human life. The relationship between air and human survival is *independent of human mind and*

*consciousness*, it is independent of the fact whether a single human being knows something about this relationship et cetera. Thus far, in order for human beings to stay alive, it is necessary that there is enough gaseous oxygen or air given. In this context it doesn't matter whether a single human being is healthy or sick, young or old, tiny or small, rich or poor et cetera. Every single human being require sufficient amounts of air to survive. However, even if air or gaseous oxygen given at certain amounts is a necessary condition for human life, air is by no means a sufficient condition, i.e. it does not, by itself, i.e. alone, suffice for human life. Theoretically, relating such a basic natural processes with mathematical reasoning is more than meaningful, it is necessary under different aspects. It is imperative to consider that the use of mathematics does not produce the relationship of a necessary condition, such a relationship is already given in nature. Still, how can we express mathematically the relationship of a necessary condition? In order to obtain a logically consistent and more adequate mathematical picture of a necessary condition, it is appropriate to consider several points of view. The (scientific) concept of a necessary condition appears to be as old as human mankind itself. Historically, *Aristotle* himself was one of the first forerunners of a theoretical concept of a necessary condition. *Anicius Manlius Torquatus Severinus Boetius* (ca. 477–524 AD), a Roman senator and philosopher of the early 6th century, elaborated among other authors, in his book *De consolacione philosophiae* on the necessary condition too. What, then, from the standpoint of classical logic, mathematics and probability theory or bio-statistics, is a necessary condition?

## 2. Material and methods

Scientific knowledge and objective reality are deeply interrelated. Seen by light, grey is never merely simply grey and many paths may lead to climb up a certain mountain. In the following of this paper we will reanalyse the relationship between oxygen and human survival in many ways and under different circumstances to reach the main goal.

### 2.1. Definitions

Definitions should help us to provide and assure a systematic approach to a mathematical formulation of the relationship of a necessary condition. It also goes without the need of further saying that a definition must be logically consistent and correct.

#### **Definition 2.1 (Two by two table of Bernoulli random variables).**

Karl Pearson was the first to introduce the notion of a two by two or contingency[55] table in 1904. A contingency table is an appropriate theoretical model for studying the relationships between two *Bernoulli*[19] (i. e. +0/+1) distributed random variables existing or occurring at the same *Bernoulli trial* [62] (period of time)  $t$ . In this context, let a Bernoulli distributed random variable  $A_t$  denote a risk factor, a condition or a cause et cetera and occur or exist with the probability  $p(A_t)$  at the *Bernoulli trial* [62] (period of time)  $t$ . Let  $E(A_t)$  denote the expectation value of  $A_t$ . In the case of +0/+1 distributed Bernoulli random variables it is

$$\begin{aligned}
 E(A_t) &\equiv A_t \times p(A_t) \\
 &\equiv p(a_t) + p(b_t) \\
 &\equiv (+0 + 1) \times p(A_t) \\
 &\equiv p(A_t)
 \end{aligned}
 \tag{2.1}$$

Let a Bernoulli distributed random variable  $B_t$  denote an outcome, a conditioned event or an effect and occur or exist et cetera with the probability  $p(B_t)$  at the Bernoulli trial (period of time)  $t$ . Let  $E(B_t)$  denote the expectation value of  $B_t$ . It is

$$\begin{aligned} E(B_t) &\equiv B_t \times p(B_t) \\ &\equiv p(a_t) + p(c_t) \\ &\equiv (+0 + 1) \times p(B_t) \\ &\equiv p(B_t) \end{aligned} \tag{2.2}$$

Let  $p(a_t) = p(A_t \cap B_t)$  denote the joint probability distribution of  $A_t$  and  $B_t$  at the same Bernoulli trial (period of time)  $t$ . In general it is

$$\begin{aligned} E(a_t) &\equiv E(A_t \cap B_t) \\ &\equiv (A_t \times B_t) \times p(A_t \cap B_t) \\ &\equiv p(A_t \cap B_t) \\ &\equiv p(a_t) \end{aligned} \tag{2.3}$$

Let  $p(b_t) = p(A_t \cap \neg B_t)$  denote the joint probability distribution of  $A_t$  and not  $B_t$  at the same Bernoulli trial (period of time)  $t$ . In general it is

$$\begin{aligned} E(b_t) &\equiv E(A_t \cap \neg B_t) \\ &\equiv (A_t \times \neg B_t) \times p(A_t \cap \neg B_t) \\ &\equiv p(A_t \cap \neg B_t) \\ &\equiv p(b_t) \end{aligned} \tag{2.4}$$

Let  $p(c_t) = p(\neg A_t \cap B_t)$  denote the joint probability distribution of not  $A_t$  and  $B_t$  at the same Bernoulli trial (period of time)  $t$ . In general it is

$$\begin{aligned} E(c_t) &\equiv E(\neg A_t \cap B_t) \\ &\equiv (\neg A_t \times B_t) \times p(\neg A_t \cap B_t) \\ &\equiv p(\neg A_t \cap B_t) \\ &\equiv p(c_t) \end{aligned} \tag{2.5}$$

Let  $p(d_t) = p(\neg A_t \cap \neg B_t)$  denote the joint probability distribution of not  $A_t$  and not  $B_t$  at the same Bernoulli trial (period of time)  $t$ . In general it is

$$\begin{aligned} E(d_t) &\equiv E(\neg A_t \cap \neg B_t) \\ &\equiv (\neg A_t \times \neg B_t) \times p(\neg A_t \cap \neg B_t) \\ &\equiv p(\neg A_t \cap \neg B_t) \\ &\equiv p(d_t) \end{aligned} \tag{2.6}$$

In general, it is

$$p(a_t) + p(b_t) + p(c_t) + p(d_t) \equiv +1 \tag{2.7}$$

Table 1 provides an overview of the definitions above.

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		Conditioned $B_t$		
		TRUE	FALSE	
Condition $A_t$	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

**Table 1.** The two by two table of Bernoulli random variables

**Definition 2.2 (Two by two table of Binomial random variables).**

Under conditions where *the probability of an event, an outcome, a success et cetera is constant from Bernoulli trial to Bernoulli trial  $t$* , it is

$$\begin{aligned}
 A &= N \times E(A_t) \\
 &\equiv N \times (A_t \times p(A_t)) \\
 &\equiv N \times (p(a_t) + p(b_t)) \\
 &\equiv N \times p(A_t)
 \end{aligned} \tag{2.8}$$

and

$$\begin{aligned}
 B &= N \times E(B_t) \\
 &\equiv N \times (B_t \times p(B_t)) \\
 &\equiv N \times (p(a_t) + p(c_t)) \\
 &\equiv N \times p(B_t)
 \end{aligned} \tag{2.9}$$

where  $N$  denotes the population size. Furthermore, it is

$$a \equiv N \times (E(a_t)) \equiv N \times (p(a_t)) \tag{2.10}$$

and

$$b \equiv N \times (E(b_t)) \equiv N \times (p(b_t)) \tag{2.11}$$

and

$$c \equiv N \times (E(c_t)) \equiv N \times (p(c_t)) \tag{2.12}$$

and

$$d \equiv N \times (E(d_t)) \equiv N \times (p(d_t)) \tag{2.13}$$

and

$$a + b + c + d \equiv A + \underline{A} \equiv B + \underline{B} \equiv N \tag{2.14}$$

Table 2 provides an overview of a two by two table of Binomial random variables.

**Definition 2.3 (Independence).**

		Conditioned $B_t$		
		TRUE	FALSE	
Condition	TRUE	a	b	A
	$A_t$	FALSE	c	d
		B	<u>B</u>	N

**Table 2.** The two by two table of Binomial random variables

The concept of independence is of fundamental[45] importance in (natural) sciences as such. In fact, it is insightful to recall again before the mind's eye Einstein's theoretical approach to the concept of independence. "Ohne die Annahme einer ... Unabhängigkeit der ... Dinge voneinander ... wäre physikalisches Denken ... nicht möglich." [26]. In other words, the existence or the occurrence of an event  $A_t$  at the Bernoulli trial  $t$  need not but can be independent of the existence or of the occurrence of another event  $B_t$  at the same Bernoulli trial  $t$ . Mathematically, independence[45, 49] in terms of probability theory is defined as

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \quad (2.15)$$

In a narrower sense, the *conditio sine qua non* relationship concerns itself at the end only with the case whether the presence of an event  $A_t$  (condition) enables or guarantees the presence of another event  $B_t$  (conditioned). As a result of these thoughts, another question worth asking concerns the relationship between the independence of an event  $A_t$  (a condition) and another event  $B_t$  (conditioned) and the necessary condition relationship. To be confronted with the danger of bias and equally with the burden of inappropriate conclusions drawn, another fundamental question at this stage is whether it is possible that an event  $A_t$  (a condition) is a necessary condition of event  $B_t$  (conditioned) even under circumstances where the event  $A_t$  (a condition) (a necessary condition) is independent of an event  $B_t$  (conditioned)? This question is already answered more or less to the negative [14]. An event  $A_t$  which is a necessary condition of another event  $B_t$  is equally an event without which another event ( $B_t$ ) could not be, could not occur and implies as such already a kind of a dependence. Thus far, **data which provide evidence of a significant *conditio sine qua non* relationship between two events like  $A_t$  and  $B_t$  and equally support the hypothesis that  $A_t$  and  $B_t$  are independent of each other are more or less self-contradictory and of very restricted of none value for further analysis.** In fact, if the opposite view would be taken as plausible, contradictions are more or less inescapable.

**Definition 2.4 (Necessary Condition [*Conditio sine qua non*]).**

Scientific knowledge and objective reality are deeply interrelated. As mentioned at the start of the article, the specification of necessary conditions has traditionally been part of the philosopher's investigations of different phenomena. Behind the need of a detailed evidence it is justified to consider that philosophy as such has certainly not **a monopoly on the truth** and other areas such as medicine as well as other sciences and technology may transmit truths as well and may be of help to move beyond one's selfenclosed unit. Seemingly **the law's concept of causation** justifies to say few words on this subject, to put some light on some questions. Are there any criteria in law for deciding whether one action or an event  $A_t$  has caused another (generally harmful) event  $B_t$ ? What are these criteria? May causation in legal contexts differ from causation outside the law, for example, in science or in our everyday life and to what extent? Under which circumstances is it justified to tolerate such differences as may be found

to exist? To understand just what is the law's concept of causation it is useful to know how the highest court of states is dealing with causation. In the case *Hayes v. Michigan Central R. Co.*, 111 U.S. 228, the U.S. Supreme Court defined 1884 *conditio sine qua non* as follows: "... **causa sine qua non – a cause which, if it had not existed, the injury would not have taken place**". [43] The German Bundesgerichtshof für Strafsachen stressed once again the importance of *conditio sine qua non* relationship in his decision by defining the following: "**Ursache eines strafrechtlich bedeutsamen Erfolges jede Bedingung, die nicht hinweggedacht werden kann, ohne daß der Erfolg entfiel**"[23] Another lawyer elaborated on the basic issue of **identity and difference between cause and condition**. Von Bar was writing: "Die erste Voraussetzung, welche erforderlich ist, damit eine Erscheinung als die Ursache einer anderen bezeichnet werden könne, ist, daß jene eine der Bedingungen dieser sein. Würde die zweite Erscheinung auch dann eingetreten sein, wenn die erste nicht vorhanden war, so ist sie in keinem Falle Bedingung und noch weniger Ursache. Wo immer ein Kausalzusammenhang behauptet wird, da muß er wenigstens diese Probe aushalten . . . **Jede Ursache ist notwendig auch eine Bedingung eines Ereignisses; aber nicht jede Bedingung ist Ursache zu nennen.**"[1] Von Bar's position translated into English: *The first requirement, which is required, thus that something could be called as the cause of another, is that the one has to be one of the conditions of the other. If the second something had occurred even if the first one did not exist, so it is by no means a condition and still less a cause. Wherever a causal relationship is claimed, the same must at least withstand this test. . . Every cause is necessarily also a condition of an event too; but not every condition is cause too.* Thus far, let us consider among other the following in order to specify necessary conditions from another, probabilistic point of view. An event (i. e.  $A_t$ ) which is a necessary condition of another event or outcome (i.e.  $B_t$ ) must be given, must be present for a conditioned, for an event or for an outcome  $B_t$  to occur. A necessary condition (i. e.  $A_t$ ) is a requirement which must be fulfilled **at every single Bernoulli trial t**, in order for a conditioned or an outcome (i.e.  $B_t$ ) to occur but it alone does not determine the occurrence of an event. In other words, if a necessary condition (i. e.  $A_t$ ) is given, an outcome (i.e.  $B_t$ ) need not to occur. In contrast to a necessary condition, a 'sufficient' condition is the one condition which 'guarantees' that an outcome will take place or must occur for sure. Under which conditions we may infer about the unobserved and whether observations made are able at all to justify predictions about potential observations which have not yet been made or even general claims which may go even beyond the observed (*the 'problem of induction'*) is not the issue of the discussion at this point. Besides of the principal necessity meeting such a challenge, a necessary condition of an event can but need not to be at the same Bernoulli trial t a sufficient condition for an event to occur. However, theoretically it is possible that an event or an outcome is determined by many necessary conditions. Let us focus to some extent on what this means or in other words how much importance can we attribute to such a special case. *Example.* A human being cannot live without oxygen. A human being cannot live without water. A human being cannot live without a brain. A human being cannot live without kidneys. A human being cannot live without ... et cetera. Thus far, even if oxygen is given, if water is given, if a brain is given, without functioning kidney's (or something similar) a human being will not survive on the long run. This example is of use to reach the following conclusion. Although it might seem somewhat paradoxical at first sight, **even under circumstances where a condition or an outcome depends on several different necessary conditions it is particularly important that every single of these necessary conditions for itself must be given otherwise the conditioned (i.e. the outcome) will not occur.** Finally, mathematically, the necessary condition (SINE) relationship, denoted by  $p(A_t$

$\leftarrow B_t$ ) in terms of probability theory, is defined as

$$\begin{aligned}
 p(A_t \leftarrow B_t) &\equiv p(a_t) + p(b_t) + p(d_t) \\
 &\equiv \frac{N \times (p(a_t) + p(b_t) + p(d_t))}{N} \\
 &\equiv \frac{a + b + d}{N} \\
 &\equiv +1
 \end{aligned} \tag{2.16}$$

**Definition 2.5 (The  $\tilde{\chi}^2$  goodness of fit test of a necessary condition relationship).**

The data as obtained by investigations can vary extremely across studies as well as among and within individuals. Some (experimental) studies may support a hypothesis of a *conditio sine qua non* relationship between two factors while other may fail on the same matter. An appropriate study design is of essential importance for a successful execution of research. However, each design has its own strengths and weaknesses, and the data achieved need not to guarantee to arrive at correct conclusions. Besides of all, under some known circumstances, testing hypothesis about the *conditio sine qua non* relationship  $p(A_t \leftarrow B_t)$  is possible by the chi-square distribution (also chi-squared or  $\tilde{\chi}^2$ -distribution), first described by the German statistician Friedrich Robert Helmert [34] and later rediscovered by Karl Pearson[54] in the context of a goodness of fit test. The  $\tilde{\chi}^2$  goodness of fit test of a *conditio sine qua non* relationship[12, 13] with degree of freedom (d. f.) of d. f. = 1 is calculated as

$$\begin{aligned}
 \tilde{\chi}^2_{\text{Calculated}}(A_t \leftarrow B_t | B) &\equiv \frac{(a - (a + c))^2}{B} + \\
 &\quad \frac{((b + d) - \underline{B})^2}{\underline{B}} \\
 &\equiv \frac{c^2}{B} + 0 \\
 &\equiv \frac{c^2}{B}
 \end{aligned} \tag{2.17}$$

or equally as

$$\begin{aligned}
 \tilde{\chi}^2_{\text{Calculated}}(A_t \leftarrow B_t | A) &\equiv \frac{(d - (c + d))^2}{\underline{A}} + \\
 &\quad \frac{((a + b) - A)^2}{A} \\
 &\equiv \frac{c^2}{\underline{A}} + 0 \\
 &\equiv \frac{c^2}{\underline{A}}
 \end{aligned} \tag{2.18}$$

and can be compared with a theoretical chi-square value at a certain level of significance  $\alpha$ . It has not yet been finally clarified whether the use of Yate's[65] continuity correction is necessary at all.

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**Definition 2.6 (The expected Chi-Square value of a cell.).**

Chi-square is a statistical test commonly used to compare observed data with data we would expect to obtain according to a specific hypothesis. Historically, the chi-square distribution (also chi-squared or  $\tilde{\chi}^2$ -distribution), first described by the German statistician Friedrich Robert Helmert [34] was rediscovered later by Karl Pearson[54] in the context of a  $\tilde{\chi}^2$  goodness of fit test. One of the assumptions of the Chi-square test is not that the observed value in each cell is greater than 5 but that the expected value in each cell is greater than 5. The expected Chi-Square value of **the cell a** of the table 3 is calculated as follows:

$$E(a) \equiv \frac{(A \times B)}{N} \quad (2.19)$$

In other words, for each cell (i. e. a, b c, d), its row (A, A) marginal is multiplied by its column (B, B) marginal, and that product is divided by the sample size (N).

		Conditioned B <sub>t</sub>		
		TRUE	FALSE	
Condition	TRUE	a	b	A
	A <sub>t</sub>	FALSE	c	d
		B	<u>B</u>	N

**Table 3.** Two by two table and Chi square

**Definition 2.7 (The left-tailed p Value of the conditio sine qua non relationship).**

The left-tailed (lt) p Value [17] of the conditio sine qua non relationship can be calculated as follows.

$$\begin{aligned} pValue_{lt}(A_t \leftarrow B_t) &\equiv 1 - e^{-(1-p(A_t \leftarrow B_t))} \\ &\equiv 1 - e^{-(c/N)} \end{aligned} \quad (2.20)$$

A low p-value indicates statistical significance.

Table 4 provides an overview of the definition of the necessary condition.

		Conditioned B <sub>t</sub>		
		TRUE	FALSE	
Condition	TRUE	p(a <sub>t</sub> )	p(b <sub>t</sub> )	p(A <sub>t</sub> )
	A <sub>t</sub>	FALSE	<b>+0</b>	p(d <sub>t</sub> )
		p(B <sub>t</sub> )	p( <u>B</u> <sub>t</sub> )	+1

**Table 4.** The two by two table of a necessary condition relationship

**Definition 2.8 (Fisher's exact one sided right tailed test of a necessary condition relationship).**

Under some circumstances, a certain sampling distribution of a test statistic (like necessary condition relationship) is only approximately equal to the theoretical chi-squared distribution and a chi-squared goodness of fit test[15, 16] might provide only approximate significance values. In point of fact, if **the expected values calculated** are too low or below 5, Fisher’s Exact Test is an alternative to a chi-square test and it is more appropriate to consider the use Fisher’s Exact test in place of chi-square test especially for 2×2 tables. Fisher’s exact test is used especially when sample sizes are small, but the same is valid for all sample sizes. However, Fisher’s exact test can be used even for tables that are larger than 2×2.

Sir Ronald Aylmer Fisher (1890 – 1962) published an exact statistical significance test (“*Fisher’s exact test*”) [28] for the analysis of contingency tables *valid for all sample sizes*.

**The null hypothesis of Fisher’s Exact test is that the rows and the columns of the 2 × 2 table are independent, such that the probability of a subject being in a particular row is not influenced by being in a particular column.** Table 5 provides an overview of the foundation of Fisher’s Exact test.

		Conditioned B <sub>t</sub>		
		TRUE	FALSE	
Condition A <sub>t</sub>	TRUE	a	b	A
	FALSE	c	d	<u>A</u>
		B	<u>B</u>	N

**Table 5.** Two by two table and Fisher’s exact test

Fisher’s exact test is a conservative test which is based on the hyper geometric distribution and not on the calculation of probabilities from a distribution (as in t-tests or chi-square). The hyper geometric (HGD) probability mass function is given by

$$\begin{aligned}
 p_{\text{HGD}}(X = a) &\equiv \left( \frac{\binom{A}{a} \times \binom{N-A}{B-a}}{\binom{N}{B}} \right) \\
 &\equiv \left( \frac{\binom{A}{a} \times \binom{A}{c}}{\binom{N}{B}} \right)
 \end{aligned}
 \tag{2.21}$$

Fisher’s exact test can be used on more robust data sets too. Consider sampling a population of size N that has B objects with O and B with O. Draw a sample of A objects and find a objects with O (see table 6).

		Sampling a population		
		O	<u>O</u>	
In Sample (Not In Sample)	YES	a	b	A
	NO	c	d	<u>A</u>
		B	<u>B</u>	N

**Table 6.** Two by two table and Fisher’s exact test II

Then there are

$$\binom{N}{A} \quad (2.22)$$

possible samples. Of these,

$$\binom{B}{a} \quad (2.23)$$

is the number of ways of choosing O in a sample of size B, while

$$\binom{B}{b} \quad (2.24)$$

is the number of ways of choosing not-O or O in a sample of size

$$N - B = \underline{B} \quad (2.25)$$

Because these are independent, there are

$$\binom{B}{a} \times \binom{B}{b} \quad (2.26)$$

ways of choosing a Os and b not-Os.

Therefore, the probability of choosing a

$$\begin{aligned} Os &\equiv \frac{\binom{B}{a} \times \binom{B}{b}}{\binom{N}{A}} \\ &\equiv \frac{B!}{a! \times c!} \times \frac{\underline{B}!}{b! \times d!} \\ &\equiv \frac{N!}{A! \times \underline{A}!} \\ &\equiv \frac{B! \times \underline{B}! \times A! \times \underline{A}!}{N! \times a! \times b! \times c! \times d!} \end{aligned} \quad (2.27)$$

which is Fisher's exact test formula given usually. In order to calculate the significance of the observed data, i.e. the total probability of observing data as extreme or more extreme if the null hypothesis is true, we have to calculate the P value of a one-tailed test.

The *one sided right tailed (rt) P Value* under conditions of the validity of the hyper-geometric[30, 42, 53] distribution (HGD) is calculated according to the following formula[18, 56].

$$pValue(HGD)_{rt}(X \geq a) \equiv 1 - \sum_{t=0}^{a-1} \left( \frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \quad (2.28)$$

### Definition 2.9 (Causal relationship k).

The history of the denialism of causality in Philosophy, Mathematics, Statistics, Physics et cetera is very long. We only recall David Hume's (1711-1776) account of causation and his inappropriate reduction of the cause-effect relationship to a simple habitual connection in human thinking or

Immanuel Kant's (1724-1804) initiated trial to consider causality as nothing more but a '*a priori*' given category [48] in human reasoning and other similar attempts too. It is worth noting in this context that especially Karl Pearson (1857 - 1936) himself has been engaged in a long lasting and never-ending crusade against causation too. **"Pearson categorically denies the need for an independent concept of causal relation beyond correlation ... he exterminated causation from statistics before it had a chance to take root"** [51] At the beginning of the 20<sup>th</sup> century notable proponents of **conditionalism** like the German anatomist and pathologist David Paul von Hansemann [32] (1858 - 1920) and the biologist and physiologist Max Richard Constantin Verworn [63] (1863 - 1921) started a new attack [47] on the principle of causality. In his essay "Kausale und konditionale Weltanschauung" Verworn [63] presented "an exposition of 'conditionism' as contrasted with 'causalism,' [61] while ignoring cause and effect relationships completely. **"Das Ding ist also identisch mit der Gesamtheit seiner Bedingungen."** [63] However, Verworn's goal to exterminate causality completely out of science was hindered by the further development of research. The history of futile attempts to refute **the principle of causality** culminated in a publication by the German born physicist Werner Karl Heisenberg (1901 - 1976). Heisenberg put forward an illogical, inconsistent and confusing uncertainty principle which opened the door to wishful thinking and logical fallacies in physics and in science as such. Heisenberg's unjustified reasoning ended in an act of a manifestly unfounded conclusion: **"Weil alle Experimente den Gesetzen der Quantenmechanik und damit der Gleichung (1) unterworfen sind, so wird durch die Quantenmechanik die Ungültigkeit des Kausalgesetzes definitiv festgestellt."** [33] while 'Gleichung (1)' denotes Heisenberg's uncertainty principle. Einstein's himself, a major contributor to quantum theory and in the same respect a major critic of quantum theory, disliked Heisenberg's uncertainty principle fundamentally while Einstein's opponents used Heisenberg's Uncertainty Principle against Einstein. After the End of the German Nazi initiated Second World War with unimaginable brutality and high human losses and a death toll due to an industrially organised mass killing of people by the German Nazis which did not exist in this way before, Werner Heisenberg visited Einstein in Princeton (New Jersey, USA) in October 1954 [50]. Einstein agreed to meet Heisenberg only for a very short period of time but their encounter lasted longer. However, there were not only a number of differences between Einstein and Heisenberg, these two physicists did not really love each other. "Einstein remarked that the inventor of the uncertainty principle was a 'big Nazi'..." [50] Albert Einstein (1879 - 1955) took again the opportunity to refuse to endorse **Heisenberg's uncertainty principle** as a fundamental law of nature and rightly too. Meanwhile, Heisenberg's uncertainty principle is refuted [5-7] for several times but still not exterminated completely out of physics and out of science as such. In contrast to such extreme anti-causal positions as advocated by Heisenberg and the **Copenhagen interpretation of quantum mechanics**, the search for a (mathematical) solution of *the issue of causal inferences* is as old as human mankind itself ("*i. e. Aristotle's Doctrine of the Four Causes*") [36] even if there is still little to go on. It is appropriate to specify especially the position of D'Holbach [41]. D'Holbach (1723-1789) himself linked cause and effect or causality as such to changes. **"Une cause, est un être qui en met un autre en mouvement, ou qui produit quelque changement en lui. L'effet est le changement qu'un corps produit dans un autre ..."** [41] D'Holbach infers in the following: **"De l'action et de la réaction continuelle de tous les êtres que la nature renferme, il résulte une suite de causes et d'effets .."** [41] With more or less meaningless or none progress on the matter in hand even in the best possible conditions, it is not surprising that authors are suggesting more and more different

approaches and models for causal inference. Indeed, the hope is justified that logically consistent *statistical methods of causal inference* can help scientist to achieve so much with so little. One of the methods of causal inference in Bio-sciences are based on the known *Henle*[35] (1809–1885) - *Koch*[44] (1843–1910) *postulates* [24] which are applied especially for the identification of a causative agent of an (infectious) disease. However, the pathogenesis of most chronic diseases is more or less very complex and potentially involves the interaction of several factors. In practice, from the ‘pure culture’ requirement of the Henle-Koch postulates insurmountable difficulties may emerge. In light of subsequent developments (PCR methodology, immune antibodies et cetera) it is appropriate to review the full validity of the Henle-Koch postulates in our days. In 1965, Sir Austin Bradford Hill [40] published nine criteria (the ‘*Bradford Hill Criteria*’) in order to determine whether observed epidemiologic associations are causal. Somewhat worrying, is at least the fact that, Hill’s “... fourth characteristic is *the temporal relationship of the association*” and so-to-speak just a reformulation of the ‘*post hoc ergo propter hoc*’[2, 64] logical fallacy through the back-door and much more than this. It is questionable whether association as such can be treated as being identical with causation. Unfortunately, due to several reasons, it seems therefore rather problematic to rely on Bradford Hill Criteria carelessly. Meanwhile, several other and competing mathematical or statistical approaches for causal inference have been discussed [2–4, 8–10, 21, 25, 27, 37–39, 46, 51, 57, 59, 66] or even established [2–4, 8–10]. Nevertheless, the question is still not answered, is it at all possible to establish a cause effect relationship between two factors while applying only certain statistical [58] methods? Nonetheless, mathematically, the causal relationship [2–4, 8–10] between a cause  $A_t$  and an effect  $B_t$ , denoted by  $k(A_t, B_t)$  in terms of probability theory, is defined *at each single*[60] *Bernoulli trial*  $t$  as

$$\begin{aligned}
 k(A_t, B_t) &\equiv \frac{\sigma(A_t, B_t)}{\sigma(A_t) \times \sigma(B_t)} \\
 &\equiv \frac{p(A_t \cap B_t) - p(A_t) \times p(B_t)}{\sqrt{(p(A_t) \times (1 - p(A_t))) \times (p(B_t) \times (1 - p(B_t)))}}
 \end{aligned}
 \tag{2.29}$$

where  $\sigma(A_t, B_t)$  denotes the co-variance between a cause  $A_t$  and an effect  $B_t$  *at every single Bernoulli trial*  $t$ ,  $\sigma(A_t)$  denotes the standard deviation of a cause  $A_t$  at the same single Bernoulli trial  $t$ ,  $\sigma(B_t)$  denotes the standard deviation of an effect  $B_t$  at same single Bernoulli trial  $t$ .

Table 7 provides an overview of the definition of the causal relationship  $k$ .

		Effect $B_t$		
		TRUE	FALSE	
Cause $A_t$	TRUE	$p(a_t)$	$p(b_t)$	$p(A_t)$
	FALSE	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
		$p(B_t)$	$p(\underline{B}_t)$	+1

**Table 7.** The two by two table of the causal relationship  $k$

However, even if one thinks to recognise the trace of Bravais [22] (1811-1863) - Pearson’s (1857-1936) “*product-moment coefficient of correlation*”[29, 52] inside the causal relationship  $k$  [2–4, 8–10]

both are completely different. According to Pearson: “*The fundamental theorems of correlation were for the first time and almost exhaustively discussed by B r a v a i s (‘Analyse mathématique sur les probabilités des erreurs de situation d’un point.’ Mémoires par divers Savans, T. IX., Paris, 1846, pp. 255-332) nearly half a century ago.*”[52] Neither does it make much sense to elaborate once again on the issue causation[20] and correlation, since both are not identical [58] nor does it make sense to insist on the fact that “*Pearson’s philosophy discouraged him from looking too far behind phenomena.*”[31] Whereas it is essential to consider that the causal relationship  $k$ , in contrast to Pearson’s product-moment coefficient of correlation[52] or to Pearson’s phi coefficient[55], is defined at every single Bernoulli trial  $t$ . This might be a very *small* difference. However, even a small difference might determine a difference. However, in this context and in any case, this small difference *makes*[11] the difference.

**Definition 2.10 (Fisher’s exact test and the causal relationship  $k$ ).**

Under some circumstances, the significance of a causal relationship  $k$  can be tested by Fisher’s exact statistical significance test (“*Fisher’s exact test*”) [28] for the analysis of contingency tables too.

**The null hypothesis of Fisher’s Exact test** is that a cause and an effect as illustrated by the  $2 \times 2$  table 8 are independent.

		Effect $B_t$		
		TRUE	FALSE	
Cause $A_t$	TRUE	a	b	A
	FALSE	c	d	<u>A</u>
		B	<u>B</u>	N

**Table 8.** Fisher’s exact test and causation

The observed data are determined by several factors one of which is the study design too. In order to evaluate the significance of the observed data, i.e. the total probability of observing data as extreme or more extreme if the null hypothesis is true, it is necessary to calculate a P value i. e. of a one-tailed test.

The *one sided right tailed (rt) P Value* under conditions of the validity of the hyper-geometric[30, 42, 53] distribution (HGD) is calculated according to the following formula[18, 56].

$$pValue(HGD)_{rt}(X \geq a) \equiv 1 - \sum_{t=0}^{a-1} \left( \frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \quad (2.30)$$

The *one sided left tailed (lt) P Value* under conditions of the validity of the hyper-geometric[30, 42, 53] distribution (HGD) is calculated according to the following formula.

$$pValue(HGD)_{lt}(X \leq a) \equiv \sum_{t=0}^a \left( \frac{\binom{A}{t} \times \binom{N-A}{B-t}}{\binom{N}{B}} \right) \quad (2.31)$$

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## 2.2. *Axioms*

### 2.2.1. Axiom I. Lex identitatis

$$+ 1 = +1 \quad (2.32)$$

### 2.2.2. Axiom II. Lex contradictionis

$$+ 0 = +1 \quad (2.33)$$

### 2.2.3. Axiom III. Lex negationis

$$\neg \times 0 = 1 \quad (2.34)$$

where  $\neg$  denotes (logical) negation.

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### 3. Results

Findings of a study sample are very often extrapolated to a larger population while the results of such a study may deviate extremely from the truth. Bias has the potential to affect scientific investigations and to distort the conclusion drawn. A study labelled with a (systematic) error can lose validity in relation to the degree of the study bias. The presence of study bias is universal since it is most unlikely to completely eliminate bias. Nonetheless, some study designs are more prone to bias. Therefore, it is necessary to recognise and to minimise bias for both, the investigators and the reader in order to limit the misinterpretation and the misuse of data. In this context, very often thought experiments are used in physics but are of use in Bio-sciences too. In other words, even bio-scientific practice has room for thought experiments which are meanwhile basically devices of a any scientific investigation. In the following some new insights (theorems) in the light of view data observed by thought experiments according to a special study design will be provided.

#### **Theorem 3.1 (Oxygen and human being alive).**

A systematic difference between study measurements and the true population values may be due to chance and other factors. Under many circumstances such bias results from very poor study design too. While confounding can be controlled to some extent at the analysis stage bias due to study design cannot be corrected at the analysis stage. However, it is possible and necessary to recognise bias very precisely especially at the analysis stage. In general it is known that sufficient amount of gaseous oxygen and the survival of human beings is a confirmed human knowledge. Therefore, a secured relationship like the relationship between gaseous oxygen and the survival of human beings is appropriate enough to re-investigate the influence of study design on the quality of the conclusions drawn.

#### **Claim.**

Null-hypothesis: Oxygen is a necessary condition of human survival.

Alternative hypothesis: Oxygen is not a necessary condition of human survival.

#### **PROOF.**

Chance is difficult to be eliminated entirely. However, chance can be minimised by increasing the size of a study or through replication of measurements et cetera. This study (thought experiment) has been able to measure the following data.

**Table 9.** Oxygen and human being alive.

		Human being alive		
		YES	NO	
Oxygen	YES	50	25	75
	NO	0	50	50
		50	75	125
Causal relationship k =		0,6667		
p Value right tailed (HGD) =		0,0000		
p (SINE) =		1,0000		
$\tilde{\chi}^2$ (SINE   B <sub>t</sub> ) =		0,0000		
$\tilde{\chi}^2$ (SINE   A <sub>t</sub> ) =		0,0000		
p Value (SINE) =		0,0000		
p (IMP) =		0,8000		
$\tilde{\chi}^2$ (IMP   A <sub>t</sub> ) =		8,3333		
$\tilde{\chi}^2$ (IMP   B <sub>t</sub> ) =		8,3333		
p Value right tailed (HGD) =		0,0000		
p Value (IMP) =		0,1813		
p (SINE∩IMP) =		0,8000		
$\tilde{\chi}^2$ (SINE∩IMP) <sub>1</sub> =		8,3333		
$\tilde{\chi}^2$ (SINE∩IMP) <sub>2</sub> =		8,3333		
p Value right tailed (HGD) =		0,0000		
p Value (SINE∩IMP) =		0,1813		
p (EXCL) =		0,6000		
$\tilde{\chi}^2$ (EXCL   A <sub>t</sub> ) =		33,3333		
$\tilde{\chi}^2$ (EXCL   B <sub>t</sub> ) =		50,0000		
p Value (EXCL) =		0,3297		
p(IOI)=		0,2000		
p(IOU)=		0,0000		

The right tailed p Value is calculated as follows:

$$\begin{aligned}
 pValue_{rt}(X \geq 50) &\equiv 1 - \sum_{t=0}^{50-1} \left( \frac{\binom{75}{t} \times \binom{125-75}{50-t}}{\binom{125}{50}} \right) \\
 &\equiv 0,0000000000
 \end{aligned} \tag{3.1}$$

#### QUOD ERAT DEMONSTRANDUM.

*Remark 3.1.* The data of study before support the null-hypothesis **without** gaseous oxygen **no** human survival ( $k = +0,6667$ ; p Value right tailed (HGD)  $< 0,00001$ ; p (SINE) = 1,0000;  $\tilde{\chi}^2$  (SINE | B<sub>t</sub>) = 0,  $\tilde{\chi}^2$  (SINE | A<sub>t</sub>) = 0; p Value (SINE) = 0). The study bias is under control with an index of unfairness (IOU) of p(IOU)= 0 and an index of independence (IOI) of p(IOI)= 0,2. In the same respect, the

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conditio per quam relationship (IMP) is not significant and the exclusion relationship (EXCL) is not significant too. In other words, the null-hypothesis: **without** gaseous oxygen **no** human survival cannot be rejected.

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**Theorem 3.2 (Oxygen and human being alive).**

The relationship between sufficient amount of gaseous oxygen and the survival of human beings can be taken as validated human knowledge. It is precisely because of this possible to re-investigate once again this relationship by a study while a certain study design is assured to analyse the influence of a study design on the conclusion drawn.

**Claim.**

Null-hypothesis: Oxygen is a necessary condition of human survival.

Alternative hypothesis: Oxygen is not a necessary condition of human survival.

**PROOF.**

In this context, the following data and statistical results were achieved by a study performed.

**Table 10.** Oxygen and human being alive.

		Human being alive		
		YES	NO	
Oxygen	YES	50	1	51
	NO	0	49	49
		50	50	100

  

Causal relationship k =	0,9802
p Value right tailed (HGD) =	0,0000
p (SINE) =	1,0000
$\tilde{\chi}^2$ (SINE   $B_t$ ) =	0,0000
$\tilde{\chi}^2$ (SINE   $A_t$ ) =	0,0000
p Value (SINE) =	0,0000
p (IMP) =	0,9900
$\tilde{\chi}^2$ (IMP   $A_t$ ) =	0,0196
$\tilde{\chi}^2$ (IMP   $B_t$ ) =	0,0200
p Value (IMP) =	0,0100
p(IOI)=	0,0100
p(IOU)=	0,0100

---

The right tailed p Value is calculated as follows:

$$\begin{aligned}
 pValue_{rt}(X \geq 50) &\equiv 1 - \sum_{t=0}^{50-1} \left( \frac{\binom{51}{t} \times \binom{100-51}{50-t}}{\binom{100}{50}} \right) \\
 &\equiv 0,0000000000
 \end{aligned} \tag{3.2}$$

**QUOD ERAT DEMONSTRANDUM.**

*Remark 3.2.* It is noteworthy that the study before has been able to reproduce the relationship between oxygen and human survival ( $k = +0,9802$ ; p Value right tailed (HGD)  $< 0,00001$ ; p (SINE) = 1,0000;

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$\tilde{\chi}^2 (\text{SINE} | \underline{B}_t) = 0$ ,  $\tilde{\chi}^2 (\text{SINE} | \underline{A}_t) = 0$ ; p Value (SINE) = 0) in an impressive manner while the index of unfairness (IOU) is  $p(\text{IOU})=0,0100$  and the index of independence (IOI) is  $p(\text{IOI})= 0,0100$ . In other words, the null-hypothesis: **without** gaseous oxygen **no** human survival cannot be rejected. However, the data of this study are equally self-contradictory too.

The data of the study do support the conclusion too that gaseous oxygen is a sufficient condition of human survival or in other words **if** gaseous oxygen **then** human being is alive ( $k = +0,9802$ ; p Value right tailed (HGD)  $< 0,00001$ ;  $p(\text{IMP}) = 0,9900$ ;  $\tilde{\chi}^2 (\text{SINE} | \underline{A}_t) = 0,0196$   $\tilde{\chi}^2 (\text{SINE} | \underline{B}_t) = 0,02$ ; p Value (SINE) = 0,01) which is contrary to facts. This obvious shortcoming has resulted from the study design which demanded that  $p(\text{IOI}) \equiv p(\text{IOU}) \equiv 0,01$ . In order to address such a serious problem effectively, the design of a certain study should assure an  $p(\text{IOI}) + p(\text{IOU}) \sim 0,5$  or an  $p(\text{IOU}) < 0.25$ .

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**Theorem 3.3 (Oxygen and human being alive).**

Another study (thought experiment) has investigated the relationship between gaseous oxygen and human survival.

**Claim.**

Null-hypothesis: Oxygen is a necessary condition of human survival.

Alternative hypothesis: Oxygen is not a necessary condition of human survival.

**PROOF.**

The following data and statistical results were achieved by this thought experiment.

**Table 11.** Oxygen and human being alive.

		Human being alive		
		YES	NO	
Oxygen	YES	1	49	50
	NO	0	50	50
		1	99	100
Causal relationship k =		0,1005		
p Value right tailed (HGD) =		0,5000		
p (SINE) =		1,0000		
$\tilde{\chi}^2$ (SINE   $B_t$ ) =		0,0000		
$\tilde{\chi}^2$ (SINE   $A_t$ ) =		0,0000		
p Value (SINE) =		0,0000		
p (EXCL) =		0,9900		
$\tilde{\chi}^2$ (EXCL   $A_t$ ) =		0,0200		
$\tilde{\chi}^2$ (EXCL   $B_t$ ) =		1,0000		
p Value (EXCL) =		0,0100		
p(IOI)=		0,4900		
p(IOU)=		0,4900		

The right tailed p Value is calculated as follows:

$$\begin{aligned}
 pValue_{rt}(X \geq 1) &\equiv 1 - \sum_{t=0}^{1-1} \left( \frac{\binom{50}{t} \times \binom{100-50}{1-t}}{\binom{100}{1}} \right) \\
 &\equiv 0,5000000000
 \end{aligned} \tag{3.3}$$

**QUOD ERAT DEMONSTRANDUM.**

*Remark 3.3.* As in the previous investigation, this investigation has confirmed the relationship between oxygen and human survival ( $k = +0,1005$ ; p Value right tailed (HGD)  $< 0,5000$ ; p (SINE) = 1,0000;  $\tilde{\chi}^2$  (SINE |  $B_t$ ) = 0,  $\tilde{\chi}^2$  (SINE |  $A_t$ ) = 0; p Value (SINE) = 0). The index of unfairness (IOU) is p(IOU)=0,49 and the index of independence (IOI) is p(IOI)= 0,49. In other words, the null-hypothesis:

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**without** gaseous oxygen **no** human survival cannot be rejected. However, the data even this study are self-contradictory too.

The data of the study formally support the conclusion too that gaseous oxygen **excludes** human survival and vice versa which is contrary to facts ( $p(\text{EXCL}) = 0,9900$ ;  $\tilde{\chi}^2(\text{EXCL} | A_t) = 0,02$ ,  $\tilde{\chi}^2(\text{EXCL} | B_t) = 1,0$ ;  $p \text{ Value}(\text{EXCL}) = 0,01$ ). In other words human beings and gaseous oxygen cannot exist together which is obviously an erroneous conclusion. However, there are several specific reasons to explain such an illogical conclusion.

Just to name a few, a  $p(\text{IOI}) \sim 0,5$  indicates data which are potentially biased and inappropriate for analysis of an exclusion relationship. The causal relationship  $k$  is  $k = +0,1005$  and positive. Among other things, a positive causal relationship ( $k > 0$ ) is mathematically not compatible with a significant exclusion relationship. In addition to the aforementioned arguments, there are other reasons why study design may lead to fallacious conclusions. The data of the study support the Null-hypothesis: **without** gaseous oxygen **no** human survival. However, Fisher's exact right tailed test supports the assumption too that gaseous oxygen and human survival are independent of each other ( $p \text{ Value right tailed (HGD)} < 0,5000$ ) which is again a very unpleasant contradiction. Such a contradiction must be brought to bear to its full extent in this sensitive area and must not be ignored. In general, a purely mechanical application of statistical methods does not seem to be sufficiently enough to end up at sustainable logical conclusions. The quality of data analysed is at least as important as the statistical methods used to analyse the data. However, the quality of data cannot be assumed, the quality of data need to be assured among other by an appropriate study design and should be checked again when data are analysed. Even if it may be potentially extremely difficult to understand how to cope with an appropriate statistical analysis of data, this is not impossible. Due to an insufficient study design, a necessary condition can be establish sometimes even if a causal relationship  $k$  is not significant especially under circumstances where  $p(\text{IOU}) > 0,25$ . However, mathematically it is not possible to bring a negative causal relationship ( $k < 0$ ) into line with a necessary condition. And of course we must take a very careful look to the potential danger as associated with a inappropriate study design to master the implied challenges with extremely great care and sensitivity.

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#### 4. Discussion

What if ...? What is not, but could have been or would have been is still not. In particular, may be it will be but at this present moment in time it is still not. Reasoning about possibilities which are remote from the way objective reality actually is might reveal a wealth of puzzles and insights. However, we are slightly more enlightened if we recognise too how the things really are. Classical logic is dealing with conditions in its own special way. For example, from the truth of a conjunction, it can be inferred that each component given at the same (point in space-time) or Bernoulli trial  $t$  is true (if “ $A_t$  and  $B_t$ ” is true, then “ $A_t$ ” is true and “ $B_t$ ” is true). Independent of this fact, probability theory is able to deal with conditions too as outlined in this publication. To arrive at correct study conclusions depends many times on the logical structure of a study too. Dependent on the statistical methodology used, the patient groups being compared should be comparable to avoid comparison bias. Sometimes, groups are not comparable even before a study (selection bias). The *conditio sine qua non* relationship is very resistant against comparison and selection bias. It is possible to compare even very old human beings with newborn children. Example. Air is a necessary condition for humans, independently whether the same are young or old, with risk factors or without risk factors et cetera.

#### 5. Conclusion

The *conditio sine qua non* relationship is mathematised using the framework of classical logic and probability theory.

#### Supporting Information

None.

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#### Conflict of interest

No conflict of interest to declare.

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