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1 author:

Gerd Graßhoff
Humboldt-Universität zu Berlin

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In pursuit of formaldehyde: Causally explanatory models and falsification

Kärin Nickelsen, Gerd Graßhoff

History and Philosophy of Science, University of Bern, Sidlerstrasse 5, 3012 Bern, Switzerland

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ABSTRACT

Falsification no longer is the cornerstone of philosophy of science; but it still looms widely that scientists ought to drop an explanatory hypothesis in view of negative results. We shall argue that, to the contrary, negative empirical results are unable to disqualify causally explanatory hypotheses—not because of the shielding effect of auxiliary assumptions but because of the fact that the causal irrelevance of a factor cannot empirically be established. This perspective is elaborated at a case study taken from the history of plant physiology: the formaldehyde model of photosynthesis, which for about sixty years (1870s to 1930s) dominated the field—despite the fact that in these sixty years all the attempts to conclusively demonstrate even the presence of formaldehyde in plants failed.

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1. Introduction

While for a long time the discussion of "theories" was dominant in the philosophy of science, in the last decades the literature on scientific models, as something in between theories and rules of the thumb, has proliferated enormously.[1] In this paper, we focus on causal models. These models explain sequences of events by spelling out the relevant factors which produce the effects in question and define their relationships to each other. We take the appropriate visual representation of such models to be causal graphs consisting of a network of nodes (which indicate causal factors) and directed edges (which indicate causal relationships). Prime examples of this type of model are biochemical pathways, which perhaps not coincidentally are frequently depicted as graphs by the scientists themselves. Biochemical pathways describe the stepwise development of products out of a series of starting materials; they may take the form of a long chain of reactions or the form of a cycle; they are often very complex, while for many purposes simplified versions do well, since they can be expanded as occasion and knowledge demand (while the absence of a factor in the modelled pathway does not imply the factor's irrelevance). How these pathways are established from experimental results, how they are modified and adapted is, therefore, of tremendous interest if one wants to learn more on the question how scientific models are construed—and under which circumstances they are abandoned.

The latter question is studied in this paper by the example of an episode taken from the long-winded search for the biochemical pathway of photosynthesis. This process in which solar energy is converted into energy that can be used biochemically is fundamental to life on earth, and the way organisms accomplish this task has intrigued scientists for more than two centuries. Yet still around 1900, photosynthesis was basically a black box, the internal mechanism of which was totally obscure. Scientists knew the starting materials and the products of the process, but they had only vague hypotheses of what happened in between.[2] The model which most scientists favoured at the end of the nineteenth century was the

E-mail addresses: nickelsen@philo.unibe.ch (K. Nickelsen), gerd.grasshoff@philo.unibe.ch (G. Graßhoff).

[1] The debate was initiated in the 1960s by studies such as Black (1962) and Hesse (1963), with a strong emphasis on metaphors and analogies. Since then the focus has shifted towards a discussion of, predominantly, the ontology, function and formation of models. Influential in this respect were, among others, the contributions by Cartwright (1983) and Morgan & Morrison (1999). A useful overview is provided, e.g., by Frigg & Hartmann (2006), Bailer-Jones (2009) gives a survey of how models were treated in the history of philosophy of science, as well as an analysis of what a scientific model constitutes (as compared to, for example, a theory).

[2] For surveys of the history of photosynthesis research, see, e.g., Myers (1974), Höxtermann (1992), Huzisige & Ke (1993), Gest & Blankenship (2004), Govindjee & Krogmann (2004) and Nickelsen (2008). See also Govindjee et al. (2005) for a broad collection of historical contributions, tributes and memoirs on the topic. Nickelsen (2009) provides a comprehensive treatment of the history of explanatory models in photosynthesis research in the years from 1840 to 1960.

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formaldehyde model of photosynthesis. Originally suggested in 1870, it dominated the field until the 1930s, that is, for sixty years, although alternative models had always been debated.[3] The puzzling fact is that the model remained dominant despite of the fact that none of the almost innumerable attempts to conclusively demonstrate the presence of the key intermediate—formaldehyde—in the green parts of plants, had ever been successful. From the point of view of traditional philosophy of science, these failures should have counted as an instance of fatal falsification, if ever there was one.

We shall argue that this way of thinking reveals a serious misconception of the nature of the underlying explanatory model. If models of biochemical pathways, such as the photosynthetic production of glucose, are understood as a framework of causal hypotheses (as opposed to simple conditionals), it becomes immediately clear why they cannot be falsified by negative empirical results. This impasse is closely related to Pierre Duhem's well-known non-falsifiability thesis. Duhem drew attention to the fact that it is impossible to test (and reject) a specific hypothesis in isolation, since empirical predictions are always based on an entire system or group of hypotheses, and, on top of that, the derivation requires a number of auxiliary hypotheses concerning the experimental setup. Therefore, the well-targeted falsification of one specific hypothesis is rendered impossible.[4] Despite this powerful criticism, philosophy of science for a long time favoured falsificationism as the best—in fact, the only—way to advance empirical science, in line with the influential suggestions by Karl Popper.[5] This tradition, however, also thought of scientific hypotheses as universal conditionals, whereas we would like to suggest, in contrast, that they are causal hypotheses.

Falsifying a causal hypothesis requires to prove a factor's irrelevance for an effect. However, from the point of view of causal reasoning, this is impossible to do. It would require a *complete* grasp of the causal structures underlying the effect in question and this clearly is something human beings cannot even hope to achieve In contrast to this difficulty, there are well-trodden ways to constructively establish causal hypotheses—which, incidentally, is also far more interesting and useful than the demonstration of what is wrong.

2. Accepted body of knowledge

We shall start by introducing some background to the example discussed in this paper. The well-known equation for oxygenic photosynthesis formulates the process as follows:

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6$$

This equation, which was defined in the nineteenth century, contains the commonly held core assumptions on the processes of photosynthesis that were considered beyond dispute: that carbon dioxide and water (or the combination of these compounds in form of carbonic acid) are the starting materials of the process, and that, in the green cells of plants, they are converted to carbohydrates and oxygen under the influence of light.[6] If one includes some additional knowledge, which is not captured in the equation, the undisputed facts of the process at the end of the nineteenth century were as follows:

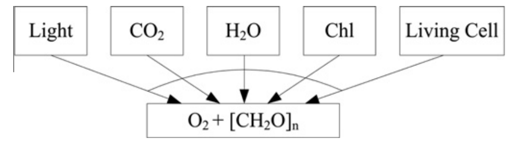

Fig. 1. The elementary one-step model of photosynthesis.

- Carbon dioxide and water are absorbed and act as the starting materials of the process.
- Oxygen and carbohydrates are the products of photosynthesis, and are formed by means of a reductive synthesis from molecules of carbon dioxide.
- Chlorophyll pigments play a crucial role in the process by absorbing light energy and making it chemically available.
- As soon as the cell is damaged, photosynthesis stops; thus, the "living cell", or some then unknown specific aspect of it, presumably the living cell's structure, was also a necessary factor.

This generally accepted body of knowledge on the mechanism of photosynthesis can be summarised using a simple, one-step model, which is visualised in graph form in Fig. 1. The scientists working at the time knew, of course, that more than one step was required to reach the final stage of photosynthesis; however, since they neither agreed on the order of the processes involved in photosynthesis, nor on the question as to which of these processes were light driven and which were not, none of their suggestions can be included in a reconstruction of the body of generally accepted knowledge.

Nobody actually believed that the one-step model represented more than a tiny fraction of the whole picture; but everyone was aware that, in whatever way the more complex model would be drawn up, these basic causal connections had to be accounted for. In the model, molecular oxygen and carbohydrates, the general chemical formula of which is $[CH_2O]_n$, are taken to be the effects of a causal process in which chlorophyll, the cell's structure, carbon dioxide, light and water act as "causally relevant factors", which are similar to John Mackie's INUS conditions: that is, they are necessary, non-redundant parts of a complex group (or bundle) of types of events, framed as "factors", which, as a whole, is a sufficient (albeit not necessary) condition for bringing about the effects in question.[7] The formaldehyde model of photosynthesis, which is dealt with in this paper, was one of the most influential attempts

[3] See Nickelsen (2009), Chapter 1, for a discussion of the model alternatives at the time.

[4] For a recent edition of Duhem's classic "The aim and structure of physical theory", see, e.g., Duhem (1991). Laudan (1990) presents an influential analysis of the notion of "underdetermination" that has often been ascribed to Duhem as one of his major concerns, while Weber (2009) analyses Duhem's critique of crucial experiments and presents an experimentalist's version of the "Inference to the best explanation" as an alternative.

[5] As is well known, Popper brought forward falsifiability as the demarcation criterion of science in his *Logik der Forschung* (1935), which also strongly endorsed the conception of a "hypothetico-deductive" method in science, later widely propagated in, e.g., Hempel (1966). The body of literature on the debate pro and contra falsificationism is enormous; Schilpp (1974) still provides a classic entry into the debate, while O'Hear (1995) encompasses a more recent collection of essays on Popper's philosophy of science. Musgrave (2009) has offered a defense of hypothetico-deductivism without, however, taking into account the specific case of causal hypotheses (as opposed to generalisations such as "all emeralds are green").

[6] This summary equation is still today frequently used in introductory textbooks although it is known to be not quite accurate, neither concerning the quantities nor the qualities of the actual reactants. See for some clarification, from today's point of view, e.g., Walker (2007), pp. 182–183.

[7] On the concept of INUS conditions, see, e.g., Mackie (1974). Mackie's regularity theory of causation was elaborated (and modified by the introduction of "minimal theories") in, e.g., May (1999), which provides a thorough analysis of causal reasoning; in Graßhoff & May (2001), which gives the pertinent definition of causal regularities; and in Baumgartner & Graßhoff (2004), which comprises an introduction into the resulting regularity theory of causation. The latter also provides an accessible introduction to the representation of causal processes in the form of graphs. The extension of this theory to the analysis of experiments is provided, e.g., in Graßhoff, Casties, & Nickelsen (2000). The reconstruction of the discovery of the urea cycle by Hans Krebs and Kurt Henseleit (in 1932) was the first study in which the approach was successfully employed, see, e.g., Graßhoff & May (2003) and Nickelsen & Graßhoff (2008).

to bring forward a more detailed suggestion to explain the biochemical processes underlying photosynthesis.

3. The formaldehyde model of photosynthesis

3.1. The model

The formaldehyde model was first put forward in 1870 by the German organic chemist Adolf von Baeyer (1835–1917).[8] One of the most eminent figures of his time, Baeyer is particularly renowned for his research on the plant dye indigo: Baeyer successfully synthesised this important dye in the test tube in 1880, and by 1883 he had completely elucidated the molecule's structure. (Baeyer was awarded the Nobel Prize in Chemistry in 1905 partly for these achievements.) The core of Baeyer's photosynthesis model comprised the assumptions that the first reduction product of photosynthetic assimilation, which resulted from the photolysis of carbon dioxide in the presence of water, light and chlorophyll, was formaldehyde, and that oxygen was released at the same time.[9] However, after this rather short but influential paper, Baeyer never again contributed anything to the field of photosynthesis research.

It is worth taking a quick look at Baeyer's general preoccupations at this time, since they strongly influenced his photosynthesis model. Around 1870, Baeyer was deeply interested in condensation reactions, achieving a major breakthrough in 1872 when he accomplished the polycondensation of phenol and formaldehyde (the product of which later became famous under the name of "bakelite" as one the first plastics made from synthetic components). Formaldehyde had first been reported in 1855 by the Russian chemist Alexander Mikhailovich Butlerov (1828–86)—although it was conclusively identified only by the German August Wilhelm von Hofmann (1818–92) in 1867—and it had since become a product of central interest in the field of organic chemistry. Baeyer had received Butlerov's work with interest. His attention was drawn in particular to empirical findings that Butlerov presented in 1861: on heating trioxymethylene, a condensation product of formaldehyde, in an alkaline medium, a viscous fluid, which had some of the properties of sugar, was produced.[10] Baeyer took this as the starting point for his theory of carbohydrate synthesis in living plants:

> The general assumption in regard to the formation of sugar and related bodies in the plant is that, under the action of light, carbon dioxide is gradually reduced in the green parts [of a plant] and by subsequent synthesis is transformed into sugar. [. . .] Butlerov's discovery provides the key, and it is indeed surprising that it has up to now been so little utilised by plant physiologists. The similarity that exists between the blood pigment and the chlorophyll has often been referred to; it is also probable that chlorophyll as well as haemoglobin binds carbon monoxide. Now, when sunlight strikes the chlorophyll, which is surrounded by CO_2, the carbon dioxide appears to undergo the same dissociation as at higher temperatures: oxygen escapes and carbon monoxide remains bound to the chlorophyll. The simplest reduction of carbon monoxide is to the aldehyde of formic acid—it only needs to take up hydrogen, $CO + H_2 = COH_2$. Under the influence of the contents of the cells, as well as through the alkalines, this aldehyde is then transformed into sugar. [. . .] Glycerol could, in addition, be formed by the condensation of three molecules and the subsequent reduction of the thus formed glyceric aldehyde.[11]

According to this proposition, the carbon reduction in photosynthesis consisted of in Fig. 2. First, carbon dioxide connects to the chlorophyll, which is shown as [Chl.-CO_2] in the figure; in this state and under the influence of light the carbon dioxide is reduced to carbon monoxide, upon which oxygen escapes. The carbon monoxide forms a complex with chlorophyll [Chl.-CO] and is then reduced further to formaldehyde by the integration of either molecular hydrogen or two atoms of hydrogen from other sources (which were not specified). In subsequent reactions, the formaldehyde was then thought to condensate to carbohydrates—a process that was presumably promoted by the contents of the cell, the influence of which was unknown. For example, Baeyer hypothesised that the first sugar product might still be associated with the components of the cell, and that it would only later be released as sucrose, starch or cellulose.[12]

3.2. The evidence

In the short paper by Baeyer, the quoted passage already comprised all of the evidence he had for the model. First, Baeyer cites a "key" observation by Butlerov: a sugar-like substance can be produced by heating a condensation product of formaldehyde. Generously interpreted, poly-condensated formaldehyde seems to be a causally relevant factor for the formation of sugar-like substances—in other words, there is at least one mechanism of the glucose synthesis (or, at the very least, of the synthesis of something that resembled glucose) that requires formaldehyde as one of the starting materials. Second, Baeyer points to the structural similarity between the leaf-pigment chlorophyll and the blood-pigment haemoglobin. This structural similarity, so Baeyer reasoned, justifies the assumption that chlorophyll undergoes similar reactions, in particular bind carbon monoxide in a complex. And finally Baeyer draws upon the simplicity of the suggested reduction path and of the subsequent carbohydrate formation. As he writes in the paper: "Indeed, it would be difficult to attain the goal so easily through a gradual synthesis following other theories!"[13] Baeyer's suggestion seemed, indeed, rather straightforward:

$$\mathrm{CO} + 2\mathrm{H} \rightarrow \mathrm{COH_2}\ (= \text{formaldehyde})$$
$$\mathrm{n[COH_2]} + 2\mathrm{H} \rightarrow [\mathrm{CH_2O}]_n (= \text{carbohydrates})$$

Put into prose: if carbon monoxide is formed (which, you only need to add two atoms of hydrogen to arrive at formaldehyde. The latter is already very close to the basic unit of carbohydrates (which is [CH_2O]); so to form carbohydrates the formaldehyde only needs to be slightly rearranged and its units multiplied, which takes place during the condensation reactions; whereafter the resulting glyceric aldehyde had to be transformed into a sugar (although Baeyer never explicitly discussed this additional reaction step).

3.3. The reception

Baeyer's theory was eagerly taken up by his contemporaries and succeeding generations of scientists, many of whom regarded this

[8] On Baeyer's life and work see, e.g., Meyer (1906), Willstätter (1929), Schmorl (1952).

[9] See for a discussion of the formaldehyde hypothesis and its reception, e.g., Florkin (1977), pp. 147–151. The model is also treated in Rabinowitch (1945), pp. 255–260, where Baeyer's approach is compared to the competing point of view purported by another eminent German chemist, Justus von Liebig. A detailed comparison of early models of photosynthesis and their construction is given in Nickelsen (2009), Chapter 1.

[10] See Butlerov (1861). The finding and its reception is also discussed in Stiles (1925), p. 194; Florkin (1977), p. 147; and Rabinowitch (1945), p. 255.

[11] Quoted in Stiles (1925), p. 194; also in Florkin (1977), pp. 147–148. For the German original, see Baeyer (1870), pp. 67–68.

[12] Baeyer (1870), p. 68.

[13] Baeyer (1870), p. 68

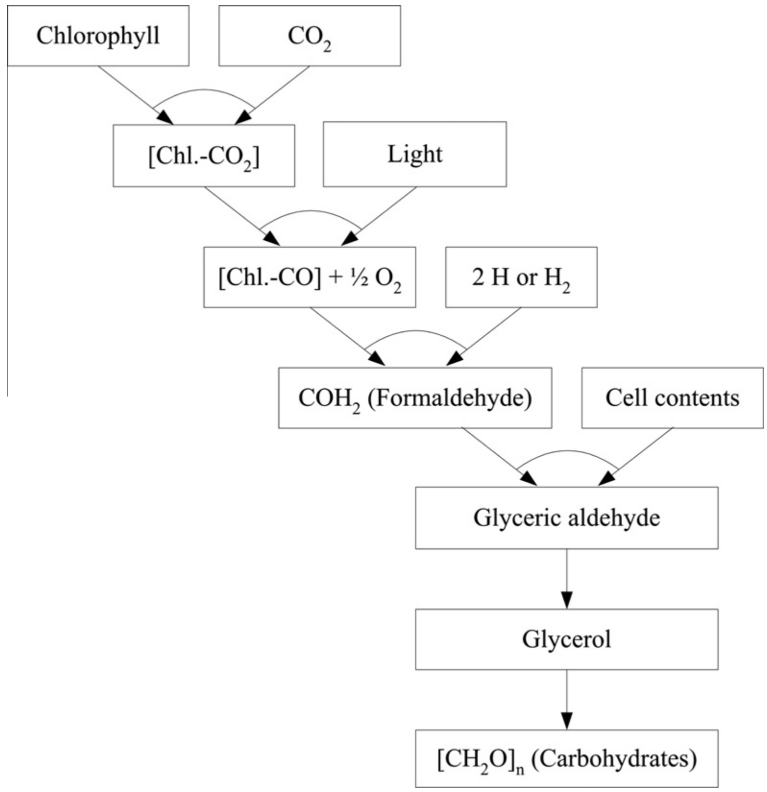

Fig. 2. The processes involved in photosynthesis according to Baeyer's formaldehyde model of 1870.

model as the first experimentally supported proposal to explain carbohydrate synthesis, inside and outside the living plant. In the subsequent years the formaldehyde model was intensely debated, and several modifications were put forward. The possibility of a direct reduction of carbonic acid was discussed; methane was surmised to be an intermediate product between carbon monoxide and formaldehyde; and very soon it was suggested that hydrogen peroxide was also formed in the process, although it was supposed to be immediately removed by the action of the enzyme catalase.[14] Some scientists thought that the reduction of carbonic acid was brought about by hydrogen, either from the decomposition of organic compounds or from a splitting of water by light action.[15] The most sophisticated elaboration of Baeyer's model was provided by Willstätter & Stoll (1918), who not only confirmed the synthesis of glucose via formaldehyde but also the formation of a chlorophyll-carbonic acid complex.

The persuasiveness of Baeyer's hypothesis was not least due to the fact that, under certain conditions, formaldehyde actually was repeatedly found to be formed in artificial systems that contained carbon dioxide, water, and sometimes chlorophyll—for example, the reduction of carbon dioxide caused by magnesium or by silent electric discharge. Some found that ultraviolet light effected the decomposition of carbon dioxide and water.[16] The conditions in question were usually very different from those predominant in the plant—most of the time, they were, in fact, extremely unfavourable for any life-sustaining process to occur. However, the results still seemed to endorse the assumption that there was, in principle, a pathway from carbon dioxide to formaldehyde. This was complemented by findings which demonstrated the occurrence of the second step: the formation of sugars from formaldehyde.[17] The final triumph came when, in 1890, one of Baeyer's former students, the German organic chemist Emil Fischer (1852–1919), succeeded in demonstrating that formaldehyde was, indeed, a possible starting point for the synthesis of the two hexoses, which were thought to be among the major products of photosynthesis (*d*-glucose and *d*-fructose). In addition, one of the pathways that Fischer suggested included glyceric aldehyde as an intermediate, the possible importance of which Baeyer had already hypothesised. At the same time Fischer demonstrated that glycolic aldehyde, which can also be derived from formaldehyde, was another potential intermediate.[18] In view of these findings, even the eminent German plant physiologist Wilhelm Pfeffer (1845–1920), who was the author of the standard plant physiology textbook of the time, admitted that the formaldehyde model of photosynthesis was rather appealing.[19]

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[14] See, e.g., Reinke (1881a, 1881b) (for the direct reduction mechanism); Maquenne (1882) (for the participation of methane); Bach (1893) (for the formation of hydrogen peroxide); Usher & Priestley (1906a), Usher & Priestley (1906b) (for catalase).

[15] See, e.g., Pollacci (1902a, 1902b) and Stoklasa & Zdobnicky (1911) (hydrogen from organic compounds); Löb (1906) and Kimpflin (1908) (hydrogen from the splitting of water).

[16] See, e.g., Fenton (1907) (magnesium); Löb (1906) (electric discharge); Berthelot & Gaudechon (1910), Stoklasa & Zdobnicky (1911) and Baly, Heilbron, & Barker (1921) (ultraviolet light). Among the most influential contenders of these findings are, e.g., Spoehr (1913, 1916), Warner (1914), Ewart (1915), Spoehr & McGee (1923). For a more detailed discussion of the controversy, see Florkin (1977), pp. 148–149, and Stiles (1925), pp. 194–201.

[17] See, e.g., Loew (1886–1889), Fischer (1888, 1890a), Fischer & Passmore (1889), Euler & Euler (1906a, 1906b and in particular Nef (1910, 1913).

[18] See Fischer (1890b, 1890c). For further discussion of these achievements see also, e.g., Schroeder (1917), p. 20 and p. 67. Fischer was deeply influenced by his teacher's work and explicitly related his study of sugar synthesis to Baeyer's formaldehyde hypothesis. Fischer himself later summarised his achievements on sugar synthesis in 1890; see Fischer (1909), p. 22.

[19] See Pfeffer (1897), p. 339; in the original German text Pfeffer used the attribute "*sehr ansprechend*".

This enthusiasm is surprising if one takes into account that it was still an open question whether the general pathway found by Fischer and others was actually instantiated in the plants. It transpired that there was a persistent problem with the formaldehyde model: despite almost innumerable attempts, with the most refined techniques, nobody was able to conclusively detect substantial amounts of formaldehyde—a strong cell poison—in the green parts of plants. Every positive finding was countered by an equally convincing rejection.[20] In view of this situation, and knowing that the model proved false eventually, one wonders whether the scientists of the time should not have realised earlier that they were on the wrong track. It is very tempting to assign this reluctance to drop the formaldehyde model either to psychological immobility, to reverence of Baeyer's authority or to a lack of critical thinking on part of these scientists. However, this seems very implausible in view of the fact that the crowd of supporters included scientists such as the aforementioned Emil Fischer alongside with, for example, Emil Erlenmeyer (1825–1909) and Richard Willstätter (1872–1942), none of whom we would reasonably attest a lack of critical thinking or scientific originality. If these psychological deficiencies were in fact the only way to account for sixty years of biochemical research, we would have to conclude that this whole enterprise (and its eventual success) is, in fact, inexplicable. Instead, we want to argue that, far from being scientifically and psychologically impaired, Baeyer and his successors were following good scientific practice.

4. The justification of explanatory models

4.1. Causal reasoning from experimental results

We mentioned in the introduction that we take explanatory models, such as the formaldehyde model, to be aptly represented by causal graphs: complex (but partial) networks of nodes (causal factors) and directed edges (causal relationships between nodes). The only way to reliably establish causal hypotheses is by conducting difference tests, which are frequently carried out in the form of experiments. A difference test realises two situations which comply with the homogeneity condition: they are appropriately similar in so far as (a) all necessary co-factors are present, so that the causal relevance of the test factor would be discerned; (b) the effect is not brought about by alternative causes. If in these situations an effect E is produced if factor A is realised, while E is not produced if A is absent, one can infer that A is causally relevant for E, in the sense outlined above. In addition to the homogeneity condition, this inference requires acceptance of two more general premises: (i) the principle of causality, which states that there are no effects without causes; (ii) the principle of determinism, which states that the same causes will always produce the same effects (whereby the "causes" also include those factors that sometimes are referred to as the "causal field" or the "background conditions"). If these are conceded, one can from the experimental result mentioned earlier justifiably add a new edge to the causal graph under construction (and perhaps also an additional node).

The truth of the causal inference necessarily hinges on the truth of the homogeneity condition. Establishing the truth of the latter is obviously far from easy but not impossible: the frequent replication of an experiment, that constantly produces the same results, substantially increases the probability that the two situations were, in fact, homogenous; and that realising the test factor A was, in fact, responsible for the production of the effect E.[21] It is very improbable that some hidden factor would consistently influence only those situations in which the test factor A was realised, while leaving the others unaffected, and, hence, misleadingly create the impression that factor A was causally relevant. If the homogeneity condition was violated, the outcome would fluctuate. Thus, fulfilling the homogeneity condition does not require that we are able to spell out all the necessary background conditions; it merely requires that the two situations to be compared are similar in so far that the effect is generated by contribution of the test factor and not by an alternative bundle. It is very probable that we will never know the complete range of necessary factors; we can only try to keep the situations as constant as possible, so that chances are given that with the known factors also the unknown ones are kept unaltered. If the latter was not the case, the experiment will yield inconsistent results; so that all we need to know in order to establish causal relevance is that in situations as similar as possible realising factor A *consistently* produces effect E, which otherwise *consistently* does not materialise.[22]

The puzzling observation is, however, that Baeyer had not done any such difference tests in order to establish his model. This seems to suggest that his hypothesis was mere speculation, which renders its enthusiastic reception all the more confusing.

4.2. Transferring causal knowledge

Let us briefly recall the situation in which Baeyer published his model. The only directly available information on photosynthesis were the starting materials and the products, included in the one-step model outlined above (see Fig. 1). This was a useful prototype, although, as mentioned earlier, it was obviously in need of considerable elaboration. However, attempts to do so were hindered by methodological limitations: the intermediate steps of the process were inaccessible for the conduction of difference tests. (More direct access to the steps of the intermediary metabolism became possible only when, in the 1940s, radioactive tracer molecules were applied to this purpose.[23]) This does not mean, however, that there was *no* difference-test-based knowledge available at all on the possible pathway from the starting materials to the products. It was a general heuristic assumption at the time, that the processes inside an organism should be explained along the lines of processes outside the organism. Around the year 1900, plant physiologists had recognised that further progress in their field of study could only be made if both chemical and physical knowledge were used to complement more phenomenological approaches which used techniques such as gas exchange measurements.[24] Chemists, too, were gradually discovering that the processes in living organisms were an additional, potentially rewarding field of research to which they could usefully contribute.[25] Explaining respiration as a slow combustion process was a powerful example of this way of reasoning that many (physiological) chemists tried to emulate also in other fields of inquiry. Take Baeyer's hypothesis that chlorophyll should bind to

[20] Experimenters who record the identification of formaldehyde in green leaves after illumination include, e.g., Pollacci (1902a, 1902b, 1907), Grafe (1906), Kimpflin (1907), Gibson (1908), Angelico & Catalano (1913), Chodat & Schweizer (1915). Schroeder (1917), on the other hand, provides a forceful rejection of these findings, which, he argued, were either obtained by using flawed methodology or, at the very least, in themselves inconclusive. This perspective finds support by, e.g., Mazé (1920), Rouge (1924) and Sabalitschka & Riesenberg (1924c).

[21] See the literature cited earlier, e.g., May (1999), Graßhoff & May (2001) and Baumgartner & Graßhoff (2004).

[22] The degree of "consistency" required in the outcome as well as the number of consistent replications are matters of disciplinary convention.

[23] For an analysis of the application of tracer methodology for the reconstruction of what later became known as the Calvin–Benson Cycle of photosynthesis, see, e.g., Nickelsen (2009), Chapter 5.

[24] For an emphatic plea along these lines, see, e.g., Pfeffer (1897), pp. 1–7.

[25] See, e.g., Meldola (1906).

carbon monoxide in a complex. In 1870 nobody knew which complexes chlorophyll was able to form because chlorophyll had proven elusive and impossible to isolate. Yet it was known that chlorophyll was structurally similar to haemoglobin, and that the latter easily binds to carbon monoxide. Baeyer's causal link here, thus, was based on the (chemically speaking: very reasonable) assumption that molecules that are structurally similar would undergo similar chemical reactions. The question is whether this line of reasoning was methodologically justified, and how one would characterise it from the point of view of philosophy of science.

One might be tempted to categorise Baeyer's way of thinking as an instance of "analogical reasoning".[26] This recourse to "analogy", however, does not in itself satisfactorily explain the methodology behind the procedure, since notion and its application are notoriously ambigious. A more fruitful approach emerges, however, if one frames the situation in terms of a causal analysis: the underlying assumption was that the process under study (in this case, photosynthesis) fell into the same type (or: class) as other, already well-known processes. Relationships of causal relevance always hold for *types of events*, not only for individual tokens, so that the grouping together of processes into the same type means that they ought to follow the same causal regularities. Thus, Baeyer's reasoning, and his transfer of causal knowledge, was justified on the assumption that the types of events encountered in the test tube were the same as those found *in vivo*, so that the same causal relationships prevailed.

The same line of thinking guided the rest of Baeyer's argument. Baeyer knew a lot about poly-condensation reactions of organic substances, such as formaldehyde—since this was his focus of research interest around 1870, as was mentioned earlier. Baeyer also knew that carbohydrates were structurally composed of a series of molecular units [CH_2O], which were very similar to formaldehyde, and he was familiar with potential intermediate steps of the necessary rearrangement. Based on this knowledge, Baeyer suggested possible links between the established fragments of the process; and then hypothesised that the process inside the plant should operate exactly as the process in the test tube situation outside the plant. The general assumption—that similar products are effected by similar causes and mechanisms—has been a well-proven and in many cases very successful heuristic strategy, even before Sir Isaac Newton (1643–1727) formulated this piece of advice in the form of his first and second Rules of Reasoning, to be found at the beginning of Book Three of his *Principia Mathematica* (1687), where he wrote: "(1) We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances. [...] (2) Therefore to the same natural effects we must, as far as possible, assign the same causes". Of course, this strategy is fallible; after all, the conditions under which carbon dioxide reduction occurred within and outside the organism are dramatically different (in terms of, for example, temperature, pressure or *p*H). To allow for this, additional factors for modelling the processes in the cell were introduced: Baeyer assigned a special function, perhaps of a catalytical nature, to the material constituents of the cell, which would make up for the lack of extreme temperatures etc. in the organism. These factors were no more mysterious than the assumption that water was one of the starting materials. They filled an explanatory gap, and it was usually expected that they would be replaced by more specific factors as advances were made in the subject.

Thus, according to contemporary standards, Baeyer had cobbled together a rather convincing possibility for producing glucose from carbon dioxide. Fischer's finding then demonstrated that there really *was* a pathway from carbon dioxide to glucose via formaldehyde. This compellingly demonstrated that formaldehyde really was causally relevant for the production of glucose. The remaining question was, however, whether this pathway was in fact realised in plants; and the attempts to identify formaldehyde in plants were motivated by the goal to clarify this point.

5. The meaning of negative results

In addition to the attempts to prove formaldehyde's existence in plants, that is, the instantiation of this factor, scientists also tried hard to prove its causal effect on photosynthesis. One can derive from the formaldehyde model the following hypothesis: "Since formaldehyde is a key intermediate in photosynthetic assimilation, the presence of formaldehyde should lead to the photosynthetic formation of glucose (while no glucose should be produced if formaldehyde is absent)." This hypothesis is, of course, a causal one—the question is whether or not formaldehyde is causally relevant to the successful completion of photosynthetic carbon dioxide assimilation. However, since around 1900 it was impossible to realise plants in which formaldehyde was completely present or absent (remember that the very presence or absence of this compound in natural plants was disputed!), the hypothesis was modified in order to determine a quantitative effect: "Since formaldehyde is a key intermediate in photosynthetic assimilation, the *additional* supply of formaldehyde should lead to *increased* photosynthesis rates." This now leads to an obvious experimental set-up: put a plant in a closed system and measure the change in photosynthesis rate when an ample amount of formaldehyde is provided.[27] Space does not permit us to go into the numerous technical difficulties of the experiments that were actually conducted—finding the balance between insignificant supplies of formaldehyde and killing the plant by providing too much of this powerful cell poison was only one of them; going straight to the results, they can be displayed as follows:

Situation	Plant without formaldehyde supply	Plant with formaldehyde supply
Photosynthesis rate	Normal	Normal

The investigated variable was the rate of photosynthesis and the test factor was an additional supply of formaldehyde. What was found was that without formaldehyde, the rate of photosynthesis remained normal, which was not surprising; yet, even with an ample supply of formaldehyde the rate did not change. This is the negative finding in question: a non-change in effect, despite the realisation of a potentially relevant factor. An obvious conclusion from this experiment would be that formaldehyde has no influence on the rate of photosynthesis—hence, that it is causally irrelevant to photosynthetic carbon dioxide assimilation. Obvious though this conclusion may appear, it would in fact be fallacious; and this point of view was clearly shared by the scientists working in the nineteenth century.

If the result of an experiment is negative—in the sense that the situations with or without factors do not differ in outcome—one can draw at least one of the following conclusions:

[26] Cf. Hesse (1963); the term has since been used for a broad range of reasoning practices.

[27] This general approach was practised, e.g., by Baker (1913), Boitreux (1920), Grafe & Vieser (1909, 1911), Jacoby (1919, 1922), Moore & Webster (1913), Sabalitschka & Riesenberg (1924a, 1924b, 1924c).

1. The test factor is, indeed, causally irrelevant.
2. The detection method is flawed or inappropriate.
3. The test factor is causally relevant, but at least one necessary factor of the pertinent (sufficient) bundle of factors was not realised.

The last condition is the decisive one. Even if all the aspects of the experimentation were correctly designed, set-up and carried out, one cannot conclude from an indifferent result, not even from a persistently indifferent one, that the factor being tested is causally irrelevant. The main reason for this lies in the third option outlined above: factors always produce their effects in combination with others, in so-called "bundles" of factors. None of these bundles is necessary for the occurrence of an effect but each of them is sufficient. A causally relevant factor is a necessary part of at least one of these bundles. However, it is always possible that the bundle of factors to which the test factor belongs is not completely realised in the experiment—often because it is not known what most of these factors are. Therefore, experimental outcomes with no difference in the test situations cannot be interpreted in causal terms.

This restriction, however, does not render other causal inferences unreliable. The homogeneity condition requires, as was mentioned earlier, that the test situations of a difference test are appropriately similar in so far as (a) all necessary co-factors are present, so that the causal relevance of the test factor would be discerned; (b) the effect is not brought about by alternative causes. In other words, the two situations can, in actual fact, differ in many respects, but not in terms of fully sufficient bundles. This concept of the homogeneity condition allows a *causal relevance* inference, but not an inference to general *causal irrelevance*. In order to prove that there is no sufficient bundle of factors that the test factor in question (such as formaldehyde) would complete one would need to know *all* the bundles that are able to bring about the effect. But there is no way to ensure that we do have a grasp as complete as that of any natural phenomenon. Hence, it is impossible to falsify causal hypotheses from the negative (that is, unchanging) results of a difference test.

All one can hope to do is to positively establish causal relationships; and if these render an alternative that is explanatorily more powerful, then it makes sense to follow this new modelling option and drop the other. Yet around 1900 there were excellent arguments for believing in the causal relevance of formaldehyde for the synthesis of glucose: notably the *in vitro* experiments carried out by Fischer and others. As long as no alternative path had been established to occur inside or outside the plants, this was the best option at hand.

6. Why the model was dropped eventually

Although the hunting for formaldehyde went on for decades, it did not go on forever. Eventually, the model was dropped; but this was not due to any process of falsification. By the end of the 1930s, two decisive developments had taken place. First, the thermodynamic side of the process had become the subject of study; and it became increasingly difficult to reconcile the formaldehyde model—which was relatively costly, energetically speaking—with the amount of energy available for the process. Even the most vigorous defenders of the model were in trouble to come up with appropriate modifications in view of this new type of data and slowly lost their confidence in the model. Second, rather interesting findings were presented concerning the primary photochemical steps of the process. Evidence accumulated that the light reactions of photosynthesis were of a very peculiar nature, involving photochemical mechanisms that had been unheard of before, such as the cooperation of thousands of chlorophyll molecules in the absorption of light; while at the same time techniques were developed that made it possible to study this part of photosynthesis in more depth.[28]

In their attempt to catch up with this turn of events, researchers lost interest in the formaldehyde model, and so it silently disappeared from the scene. Most research groups that were working on problems of photosynthesis switched their focus to explore the promising new issues. Interest only focused again on the problem of carbohydrate formation when, after 1945, radioactive tracer molecules became broadly available, which allowed people to detect directly the intermediate substances on the way from carbon dioxide to sugar. Formaldehyde, to be sure, was again searched for; and it was again not found; but many of those intermediates that we would expect from today's point of view were equally absent. Even here, negative results did not prove anything. Yet, as time went by, the only possible path toward establishing a factor's causal irrelevance was taken: a sufficient and convincing alternative model was developed that was equally able to explain all available data and was equally in line with accepted chemical knowledge; but without all the difficulties surrounding formaldehyde. Carrying on to believe in the formaldehyde model, under these circumstances, would have been hard to justify; and almost nobody tried to do so.[29]

7. Concluding remarks

How explanatory models of causal processes are construed, modified and eventually abandoned, such as the model of the biochemical pathway of photosynthesis, is one of the central questions of the philosophy of science. Much can be learned about these issues from the reconstruction of actual case studies from the history of science; and one example was given in this paper. With hindsight, the formaldehyde model of photosynthesis was completely flawed. It was far too simplistic; furthermore, featuring a powerful cell poison like formaldehyde, which was never conclusively detected in plants, as one of the core intermediates of photosynthesis seems like a rather eccentric idea. It is, at first glance, difficult to understand why scientists chose to endorse this hypothesis for sixty years instead of dropping it. However, in this paper we argued that there were good reasons at the time to accept the model as a well-founded option, while it was impossible to empirically falsify the hypothesis that formaldehyde was causally relevant for photosynthetic carbon dioxide assimilation.

"Well-founded" was the formaldehyde model in so far as all its causal hypotheses were based on empirical data obtained in difference tests. It is true: none of these tests was carried out in living systems—this was impossible to realise at the time. However, the transfer of causal knowledge from one context to another, from the test tube to the organism, is a very useful and methodologically sound strategy. The underlying assumption is that the causal process to be explained may be of the same type, which justifies at

[28] The interest was sparked by, e.g., the (erroneous) quantum yield for photosynthesis suggested by Warburg & Negelein (1923) who claimed that the release of one molecule of oxygen required no more than 3–5 light quanta. Pioneering experiments that indicated the existence of a "photosynthetic unit" of chlorophyll were published by Emerson & Arnold (1932), while Gaffron & Wohl (1936) elaborated the conceptual interpretation. At the same time, first attempts were made to study photosynthesis based on fluorescence measurements, which turned out to be an extremely promising approach; for the earliest studies, see, e.g., Kautsky, Hirsch, & Davidshöfer (1932), Franck (1935). See also Nickelsen (2009), Chapter 3.

[29] See Nickelsen (2009), Chapter 5, for a comprehensive treatment of the discovery of the path of carbon in photosynthesis, starting with the pioneering experiments by Martin Kamen and Samuel Ruben up to the successful elucidation of the cyclic process achieved in a research team headed by Melvin Calvin and Andrew A. Benson.

least a tentative transfer of knowledge from the one context to the other—provided the contexts can be considered sufficiently similar. In the history of photosynthesis research, this strategy was extremely widespread. Needless to say that not all of these transfer-trials were successful—it is a fallible strategy. But it seems unjust to dismiss this procedure as mere speculation.

Furthermore, although scientists kept to the principal assumptions of the formaldehyde model, in view of the body of positive evidence, Baeyer's original suggestion did not survive the sixty years of its existence unaltered. Several modifications, some of which were mentioned in section 3.3, were brought forward by subsequent generations of scientists. Yet, all of these changes were of a constructive nature, endorsing the possibility of alternative causal links, without claiming to have proven the inaccuracy of the former hypotheses. This behaviour persuasively demonstrates the central role of causal reasoning in science and its implicit application in experimental research. The causal irrelevance of a factor cannot be established; consequently, the best one can hope to do is to *positively* establish causal relationships. For doing so, well-proven and recommendable heuristic strategies exist, such as the difference test and its expansion in form of a four-field test. On the other hand, there is no way to "falsify" an hypothesis on causal relevance, apart from the construction of a sufficient alternative without the factor in question. One cannot possibly exclude that there may be a hitherto unknown bundle of factors in which a test factor would exert causal relevance for the effect in question. Time and again, there are voices requiring more "negative results" of experimental research to be published, in hope to enrich the scientific literature and give advice to others.[30] If one takes the indifferent outcome of a difference test as the typical instance of a "negative result", and fully endulges in the limited significance of these outcomes for any conclusion, the hope for such an enrichment effect seems illusive.

The only conclusion one can draw in view of an indifferent experimental result, such as the experimental findings concerning the impact of formaldehyde on the process of photosynthetic carbon dioxide assimilation, is the insight that somewhere something went amiss: the experimental set-up might be inappropriate, the reading of the measurements may have been flawed—or the partial explanatory hypothesis that (however vaguely) had guided the experiment, was incomplete. Particularly the latter usually will not disconcert the scientist; after all, this is why she keeps on investigating. Pierre Duhem argued in 1914 for similar conclusions. However, as mentioned earlier, his argument mainly rests on the vast number of auxiliary hypotheses that is required to derive empirical predictions from an hypothesis. If experiments fail to agree with the prediction, the result is of limited use because one does not know whether to reject the hypothesis of interest or one of the auxiliary hypotheses. Duhem postulates that, in the end, it is the "bons sense" that enables scientists to decide which hypotheses to reject. The application of causal reasoning as presented here offers a more disciplined approach: There is no inference pattern to demonstrate general causal irrelevance and, hence, to falsify a causal hypothesis; but a single experiment on the assumption of the homogeneity condition can establish causal relevance.

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[30] See, for example, Stephen J. Gould's well-known essay on the topic, Gould (1993); or, more recently, Browman (1999): a theme section coordinated by Howard I. Browman, in which several authors, including philosophers of biology Michael Ruse and David Hull, discuss the epistemic value of negative results. It has to be emphasised, though, that these authors hold widely divergent notions of what counts as a "negative result".

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