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A New Conception of Equality of Tautologies

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ABSTRACT. It is well-known that there are "hard" and "simple" tautologies, but in the capacity of the logical functions they all are equal to each other. In our opinion this thesis is not entirely correct. We suggest a new conception of equality of tautologies, with the help of the notion of φ-determinative conjunct, which was defined in [1] for every tautology φ.

KEYWORDS: φ-determinative conjunct, minimal determinative disjunctive normal form, equality of tautologies.

1. Introduction

In this paper we would like to discuss a conceptual question: in what case two tautologies can be considered as equal. Let φ and ψ be propositional formulae (logical functions) and let each of them depend on the propositional variables $p_1, p_2, \ldots, p_n$. It is well-known that φ and ψ are equal iff for every $\sigma = (\sigma_1, \ldots, \sigma_n)$ $(\sigma_i \in \{0,1\},\ 1 \leqslant i \leqslant n)$ $\varphi(\sigma_1, \ldots, \sigma_n) = \psi(\sigma_1, \ldots, \sigma_n)$. By this conception all tautologies are equal to each other. In our opinion this thesis is not entirely correct.

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In fact, the tautology $\varphi_k = (p_1 \supset (p_2 \supset (p_3 \supset \ldots \supset (p_k \supset p_1)\ldots)))$ is very "simple". It is easy to notice that (i) if the value of p_1 is 1, then, because of its second occurrence, the value of φ is equal to 1 without taking into consideration the values of the remaining variables, and (ii) if the value of p_1 is 0 then the value of φ is 1 because of the first occurrence of p_1. So, only the variable p_1 is "important" in this formula, while the other variables are absolutely unimportant. In some tautologies several variables are "important", and there are also tautologies where nearly all variables are "important". It is natural that such tautologies are "harder" (some examples of "hard" tautologies will be adduced below). In [1] the notion of φ-determinative conjunct was defined. Using this notion we suggest a new definition of equality of tautologies according to which two tautologies can be considered as equal iff they have the same "hardness".

2. Preliminary

This paper deals exclusively with classical propositional logic. We shall use the generally accepted concepts of unit Boolean cube (E^n), logical function, propositional formula, tautology, conjunct, and disjunctive normal form (DNF).

The particular choice of language for the representation of propositional formulae does not matter for our analysis. However, because of technical reasons we assume that our language contains the propositional variables p_i $(i \geqslant 1)$, the logical symbols $\neg$, &, $\vee$, $\supset$ and the parentheses (,). Note that some of the parentheses can be disregarded in generally accepted cases.

It is well-known that every propositional formula is a presentation of a specific logical function and every logical function can be represented by means of different propositional formulae and, particularly, by different DNFs.

In some cases we shall identify the propositional formula with the logical function, which is presented by this formula.

Two given formulae $\varphi(p_1, p_1, \ldots, p_n)$ and $\psi(p_1, p_1, \ldots, p_n)$ are considered as equal, according to the usual terminology, iff they present the same logical function, i.e. for each $\sigma^n = (\sigma_1, \ldots, \sigma_n) \in E^n$ $\varphi(\sigma_1, \ldots, \sigma_n) = \psi(\sigma_1, \ldots, \sigma_n)$.

We call *replacement-rule* the following trivial equalities for each proposi-

tional formula A:

$$0\&A = 0,\ A\&0 = 0,\ 1\&A = A,\ A\&1 = A,\ A\&A = A,\ A\&\bar{A} = 0,\ \bar{A}\&A = 0$$
$$0\vee A = A,\ A\vee 0 = A,\ 1\vee A = 1,\ A\vee 1 = 1,\ A\vee A = A,\ A\vee\bar{A} = 1,\ \bar{A}\vee A = 1$$
$$0\supset A = 1,\ A\supset 0 = \bar{A},\ 1\supset A = A,\ A\supset 1 = 1,\ A\supset A = 1,\ A\supset\bar{A} = \bar{A},\ \bar{A}\supset A = A$$
$$\bar{0} = 1,\ \bar{1} = 0,\ \overline{\overline{A}} = A.$$

Let φ be a propositional formula and let $\{p_1, p_2, \ldots, p_n\}$ be the set of its distinct variables. For some $\sigma^m = (\sigma_1, \ldots, \sigma_m) \in E^m$ $(1 \leqslant m \leqslant n)$ the conjunct $K = p_{i_1}^{\sigma_1}\&p_{i_2}^{\sigma_2}\&\ldots\&p_{i_m}^{\sigma_m}$ is called *φ-determinative* if the assignment of values σ_j to each p_{i_j} $(1 \leqslant j \leqslant m)$ induces the value (1 or 0) for φ, without taking into consideration the values of the remaining variables [1], i.e. if the value for φ is obtained using the above replacement-rule after the assignment of the value σ_j to p_{ij}. It is obvious that for $m = n$ every conjunct $K = p_{i_1}^{\sigma_1}\&p_{i_2}^{\sigma_2}\&\ldots\&p_{i_n}^{\sigma_n}$ for each $\sigma^n = (\sigma_1, \ldots, \sigma_n) \in E^n$ is φ-determinative. The case for $m < n$ is more interesting.

EXAMPLE

Let $\varphi = (p_1\&p_2) \supset (p_3 \vee (\bar{p}_4\&p_5))$.
It is easy to check that the following conjuncts are φ-determinative:

$$\mathscr{K}_1 = p_1^0, \mathscr{K}_2 = p_2^0, \mathscr{K}_3 = p_3^1, \mathscr{K}_4 = p_4^0\&p_5^1, \mathscr{K}_5 = p_1^0\&p_2^1\&p_3^0\&p_4^1\&p_5^1$$

but the conjuncts $\mathscr{K}_6 = p_1^1\&p_3^0$, $\mathscr{K}_7 = p_3^0\&p_5^1$, $\mathscr{K}_8 = p_2^1$ are not φ-determinative.

It is well-known that every logical function φ can be represented by different DNFs: minimal, short, dead etc. In each of these DNFs some parameter (number of occurrences of variables, number of conjuncts, etc.) has its minimal value. It is important to note that *every conjunct from every* DNF φ *is φ-determinative*.

3. Notion of $\mathscr{D}_\varphi^{min}$. Equality of tautologies

According to the traditional view of equality of propositional formulae, mentioned at the beginning of this paper, all tautologies must be equal to each other. In our opinion this thesis is not entirely correct. Here we suggest a new conception of equality of tautologies based on the notion of φ-determinative conjunct.

In the ordinary terminology we call variables and negated variables *literals*; the conjunct $\mathscr{K}$ can be represented simply as the sets of literals and is called *clause* (no clause contains both a variable and the negation of that variable). A formula in DNF can be expressed as a set of clauses $\{\mathscr{K}_1, \mathscr{K}_2, \ldots, \mathscr{K}_\ell\}$.

The *elimination-rule* (ε-rule) infers $\mathscr{K}' \cup \mathscr{K}''$ from clauses $\mathscr{K}' \cup \{p\}$ and $\mathscr{K}'' \cup \{\bar{p}\}$, where $\mathscr{K}'$ and $\mathscr{K}''$ are clauses and p is a propositional variable.

We would like to say that the conjunct K is deduced from the DNF $\mathscr{D}$ if there is a finite sequence of clauses such that every clause in the sequence is one of the clauses of $\mathscr{D}$ or is inferred from earlier clauses in the sequence by ε-rule, and the last clause is $\mathscr{K}$.

DNF $\mathscr{D}$ is called *full* (tautology) if the empty conjunct (Λ) can be deduced from $\mathscr{D}$.

The minimal number of the usages of ε-rule in the deduction of Λ from full DNF $\mathscr{D}$ is called *complexity* of $\mathscr{D}$ and denoted by $C(\mathscr{D})$.

Let φ be some tautology.

A full DNF $\mathscr{D}$ is called *φ-determinative* if every conjunction of $\mathscr{D}$ is φ-determinative. Any φ-determinative DNF $\mathscr{D}$ with minimal complexity is called *minimal determinative* DNF for φ and denoted by $\mathscr{D}_\varphi^{min}$. It is natural to take the value of $C\left(\mathscr{D}_\varphi^{min}\right)$ as characterizing the complexity of validity of the formula φ.

EXAMPLES

1. Let $\alpha_k = p_1 \supset (p_2 \supset (\ldots \supset (p_{k-1} \supset (p_k \supset (\bar{p}_k \supset p_1)))\ldots))$, with $k \geqslant 2$.

   It is easy to check that the following DNF are α_k-determinative:

   $$\mathscr{D}_1 = \{p_1; \bar{p}_1\}, \quad \mathscr{D}_2 = \{p_k; \bar{p}_k\}, \quad \mathscr{D}_3 = \{p_1 p_2; p_1 \bar{p}_2; \bar{p}_1\},$$

   but only $\mathscr{D}_1$ and $\mathscr{D}_2$ are minimal determinative for α_k and $C(\mathscr{D}_1) = C(\mathscr{D}_2) = 1$.

2. Let

   $$\begin{aligned} \beta_\ell \;=\; & (p_1 \supset p_2) \supset ((p_2 \supset p_3) \supset \\ & (\ldots \supset ((p_{\ell-1} \supset p_\ell) \supset (p_1 \supset p_\ell))\ldots)) \end{aligned}$$

   with $\ell \geqslant 3$.

   $\mathscr{D}_{\beta_\ell}^{min} = \{p_1 \bar{p}_2; p_2 \bar{p}_3; \ldots; p_{\ell-1} \bar{p}_\ell; \bar{p}_1; p_\ell\}$ and $C\left(\mathscr{D}_{\beta_\ell}^{min}\right) = \ell$.

Note that the problem of the construction of $\mathscr{D}_{\varphi}^{min}$ is unfortunately *NP*-hard (this follows from the results proved in [2] and [3]).

Let the size (the number of all symbols) of a formula φ be denoted by $|\varphi|$.

The following statements about $\mathscr{D}_{\varphi}^{min}$ are proved in [1] and [2]:

1. If every φ-determinative conjunct contains at least m literals for any tautology φ, then $C\left(\mathscr{D}_{\varphi}^{min}\right) \geqslant 2^m$.

2. For every tautology φ of size n, $C\left(\mathscr{D}_{\varphi}^{min}\right) \leqslant 2^n$.

3. For sufficiently large n, sequences of tautologies φ_n of size n are described, such that $C\left(\mathscr{D}_{\varphi_n}^{min}\right)$ are of order $n, n^2, n^3, \ldots, n^{\left[\frac{n}{2}\log_n 2\right]}$.

PROOF SKETCH

1. If every φ-determinative conjunct contains at least m literals, then every φ-determinative DNF $\mathscr{D}$ must contain at least 2^m conjuncts.
2. It is obvious that if φ is a tautology of size n, then the number of the distinct variables of φ is less than n, and if full $\mathscr{D}$ is the canonic DNF, i.e. every clause of $\mathscr{D}$ contains the literals of all variables, then $C(\mathscr{D}) \leqslant 2^n$, hence $C\left(\mathscr{D}_{\varphi}^{min}\right)$ is also less than 2^n.
3. Let $\varphi_{s,m}$ be the formula $\bigvee\limits_{(\sigma_1 \ldots \sigma_s) \in E^s} \bigwedge\limits_{j=1}^{m} \bigvee\limits_{i=1}^{s} p_{ij}^{\sigma_i}$. It is not difficult to notice that $\varphi_{s,m}$ are tautologies for every $s \geqslant 1$ and $1 \leqslant m \leqslant 2^s - 1$, therefore the tautologies

$$\varphi_{s,1}, \varphi_{s,s}, \varphi_{s,s^2}, \varphi_{s,s^3}, \ldots, \varphi_{s,s^{[(s-1)\log_s 2]}}$$

can be considered to form a sequence of the kind described above.

The notion of $C\left(\mathscr{D}_{\varphi}^{min}\right)$ is useful also for the evaluation of proof complexity. In particular, this notion is used in [1] and [2] in order to prove the following results:

1. For sufficiently large n, there are sequences of tautologies φ_n of size n such that their proof-complexities (the steps of proof and/or the size of proof) in "weak" proof systems of classical propositional logic (like resolution system, cut-free sequent system) are of order $n, n^2, n^3, \ldots, n^{\left[\frac{n}{2}\log_n 2\right]}$.

2. Every tautology φ can be proved inside a Frege system (the most natural calculus for propositional logic) in less than $c_1 \cdot C\left(\mathscr{D}_{\varphi}^{min}\right)|\varphi|$ steps and in less than $c_2 \cdot C\left(\mathscr{D}_{\varphi}^{min}\right)|\varphi|^2$ size, where c_1 and c_2 are constants, and therefore, as above, for sufficiently large n, there is the sequence of such tautologies φ_n of size n, for which the upper bounds of Frege proof complexities are of order $n, n^2, n^3, \ldots, n^{\left[\frac{n}{2}\log_n 2\right]}$.

All the above results suggest that the value of $C\left(\mathscr{D}_{\varphi}^{min}\right)$ is important for the validity (derivability) of a tautology φ.

So, we can notice that $C(\mathscr{D})$ may be "small" (as in the case of α_k and β_ℓ in Examples 1. and 2.) and can be "large" (for $\varphi_{s,2^s-1}$). We can choose $k = \ell = s(2^s-1)$ so that the number of variables of tautologies α_k, β_ℓ and $\varphi_{s,2^s-1}$ will be equal to each other, but α_k, β_ℓ are "simple" and $\varphi_{s,2^s-1}$ is very "hard".

Taking into consideration the above-mentioned arguments, we suggest the following definition of equality of tautologies:

> **Definition.** The tautologies φ and ψ are strongly equal if every φ-determinative conjunct is also ψ-determinative and vice versa.

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[3] M. ALEKHNOVICH, S. BUSS, Sh. MORAN, T. PITASSI, "Minimum propositional proof length is *NP*-hard to lineary approximate", *Journal of Symbolic Logic*, 66, 2001, pp. 171–191.

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The Sink and the Murder Scene: Rise and Fall of a Causal Model for AIDS Pathogenesis

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ABSTRACT. AIDS pathogenesis has been challenging researchers for more than two decades. The topic of this paper is an important episode in the history of AIDS science, concerning one of the most influential and discussed attempts to explain the onset of AIDS as an effect of HIV infection. The rise of the so-called "sink model" of AIDS pathogenesis is outlined on the background of the knowledge and anomalies emerging in AIDS research in the Nineties. Then a reconstruction is offered of the appraisal of the model against further experimental evidence, ultimately leading to the overcoming of the model itself and to a "paradigm shift" towards alternative views currently under scrutiny.

KEYWORDS: AIDS, causal model, HIV, paradigm shift, pathogenesis, sink model

1. Introduction

Although a remarkable body of relevant knowledge has been collected over the years, AIDS pathogenesis has been challenging researchers for more than two decades. In what follows we will focus on an important episode in the history

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of AIDS: the proposal and overcoming of an account of AIDS pathogenesis, the "sink model", which has been widely influential and discussed. A brief exposition of the historical background and problem situation is given at first, followed by a reconstruction of the model and of its appraisal against evidence. Finally, further and more recent developments are outlined, which both shed new light on old issues and open up novel problems in research on the pathogenesis of AIDS.

2. Backstage: A brief history of AIDS research

The birth of AIDS research dates back to the beginning of the Eighties. Starting from 1980 a new mysterious pathological condition killing previously healthy persons was observed in the United States and soon recorded by the epidemiological surveillance federal agency CDC (Centers for Disease Control). First patients suffered from an unusually severe form of Kaposi's sarcoma and from opportunistic infections, such as *Pneumocystis Carinii* pneumonia. They especially included young homosexual males from big urban areas (Los Angeles and New York City)[1] and intravenous drugs users,[2] but soon other populations were identified as involved in the epidemic (such as hemofiliacs and infants).[3]

Susceptibility to opportunistic infections suggested a pathological lack of immunocompetence and was readily associated with lymphocytopenia observed in patients' blood.[4] This connection guided the first official definition of the newly observed clinical phenomenon as a *syndrome*, i.e., a condition which manifests itself as a collection of symptoms due to an underlying pathological condition, *immunodeficiency*, which is *acquired*, namely non-congenital.[5] Early aetiological hypotheses have been directed to the causal role of an infectious agent, at first suggested on the basis of epidemiological data,[6] as well as towards non-infectious pathogenic factors possibly associated with behavioral phenomena.[7] The former line of thought encouraged virus hunters: viruses were major candidates for aetiology given that antibiotics were clearly unable

[1] CDC (1981a; 1981b; 1981c); Friedman-Kien (1981); CDC (1982a; 1982b).

[2] CDC (1982c).

[3] CDC (1982d; 1982e; 1982f).

[4] CDC (1981a); Gottlieb *et al*. (1981); Masur *et al*. (1981); Siegal *et al*. (1981).

[5] CDC (1982g).

[6] CDC (1982a; 1982h; 1982i); Auerbach *et al*. (1984).

[7] Durack (1981); CDC (1982a; 1982b); Goedert *et al*. (1982); Marmor *et al*. (1982); McManus *et al*. (1982); Jaffe *et al*. (1983); Newell *et al*. (1984).

to control the disease and that, despite routine screening for bacteria in blood products, there was evidence of possible transfusion-associated AIDS.[8]

In 1983 and 1984 scientific reports by Luc Montagnier's, Robert Gallo's and Jay Levy's research teams appeared announcing the isolation of a newly discovered virus in AIDS patients, then still labeled LAV (Lymphoadenopathy Associated Virus),[9] HTLV-III (Human T-Lymphotropic retroVirus type III),[10] or ARV (AIDS-Related Virus).[11] The virus was found to target a family of immune system cells (T-lymphocytes) whose depletion was typically observed in AIDS patients' blood, and a decisive element of the chemical basis for this tropism was soon identified in the CD4 surface receptor.[12] Moreover, some *in vitro* cytopathic activity was observed.[13] Finally, several studies reported a strong association between infection by the virus and the clinical symptoms of AIDS.[14]

In a couple of years the viral approach in AIDS research was shaped in its essential lines and rapidly gained wide acceptance. In 1986 HIV (Human Immunodeficiency Virus) was established as a unifying label, partly as the widespread recognition of a causal link between the virus and the disease.[15] The same year, the HIV-AIDS research programme was authoritatively established by the influential volume *Confronting AIDS*, a survey of knowledge and a blueprint for action published by the US National Academy of Sciences' Institute of Medicine.[16] Prepared by a panel consisting of prominent virologists, clinicians, public health experts, and social scientists, the book encapsulated the official body of knowledge about AIDS at the time as centred around *three* main theses. First, the committee concluded that the isolation of HIV and later research "led to its definitive identification as the cause of AIDS".[17] Secondly, HIV is consid-

[8] CDC (1982i); Curran *et al*. (1984).

[9] Barré-Sinoussi *et al*. (1983); Montagnier *et al*. (1984).

[10] Popovic *et al*. (1984); Gallo *et al*. (1984).

[11] Levy *et al*. (1984).

[12] Dalgleish *et al*. (1984); Klatzmann *et al*. (1984).

[13] Levy *et al*. (1984); Montagnier *et al*. (1984); Popovic *et al*. (1984).

[14] Kitchen *et al*. (1984); Sarngadharan *et al*. (1984); Salahuddin *et al*. (1985); Ou *et al*. (1988); Darby *et al*. (1989).

[15] Coffin *et al*. (1986).

[16] USA Institute of Medicine (1986).

[17] *Ibid*., p. 39. The statement of the causal link between HIV-infection and the development of AIDS has been meant to imply that the increase in the probability of the occurrence of the disease provided by the occurrence of the infection *appoximates that from 0 to 1*: on one hand, HIV-infection is seen as a strictly *necessary* condition for AIDS, i.e., $p(\text{AIDS}|\text{not-HIV}) = 0$; on the other hand, it is considered as a *typically sufficient* condition, i.e., $p(\text{AIDS}|\text{HIV}) >> 50\%$. This is, I think, no overstatement of the prevailing position. For HIV as *necessary* see, for instance, Blat-

ered a pathogenic agent *newly* introduced in human populations in the last decades and *recently* spread worldwide. In fact, one of the most powerful factors driving AIDS research at its beginnings and contributing to the elaboration of the viral approach has been the quest for an answer to the obvious question: "Why AIDS *now*?" and, although the details of the microbiological mutations and inter-specific breakthrough allegedly leading to the epidemic have been and somehow remain debated, a "new disease, new agent" principle has been explicitly invoked.[18] Moreover, and finally, unprotected sexual intercourse and blood exchange are identified as typical ways of transmission of the infection, and hence of the disease. As a consequence, unsafe sex and shared usage of needles (common in intravenous drug consumption) are classified as major at risk behaviors for AIDS.

Meanwhile, AIDS epidemics were being registered in Europe[19] and Africa[20] and the AIDS case-definition was being importantly adjusted and expanded.[21] Moreover, a different but related retrovirus, called "HIV type 2" or simply "HIV-2", was isolated in West Africa and also found to be associated with AIDS disease.[22]

Then, between the end of the Eighties and the beginning of the Nineties, some researchers, notably Peter Duesberg and Robert Root-Bernstein, challenged essentially all the basic tenets of HIV-AIDS research and claimed that their acceptance had been premature and not well founded.[23] Duesberg, in particular, presented a partially renewed and extended version of early views, according to which different AIDS-related pathological conditions are produced by the exposition to non-infectious factors which severely damage the organism on chemical grounds, such as drugs consumption and malnutrition.[24] Mainstream HIV-AIDS researchers and distinguished scientific commentators have

tner, Gallo, and Temin (1988); Weiss and Jaffe (1990); Weiss (1993). Acquired immunodeficiency without HIV-infection has been classified as a separate clinical condition of unknown origins in need of further inquiry (see Fauci, 1993). For p(AIDS|HIV), see Weiss (1993) and Smith (1998).

[18] Gallo and Montagnier (1988); DeVita, Hellman, and Rosenberg (1997, pp. 5-6).

[19] Thomsen *et al*. (1981); Downs *et al*. (1987).

[20] Bayley (1984); Piot *et al*. (1984); Van de Perre *et al*. (1984); Serwadda *et al*. (1985); Quinn *et al*. (1986); Quinn *et al*. (1987).

[21] CDC (1985; 1987). Also see CDC (1992).

[22] Clavel *et al*. (1986); Clavel *et al*. (1987).

[23] Duesberg (1987; 1988); Root-Bernstein (1993). An epistemological analysis of this background controversy on the role of HIV in AIDS has been presented in Crupi (2000).

[24] Duesberg (1992); Duesberg and Rasnick (1998); Duesberg, Koehnlain, and Rasnick (2003).

repeatedly and vigorously rejected the criticisms[25] and the alternative views[26] of dissenters and have insisted on the necessity of continuous efforts to fully understand the pathogenetic processes involved in HIV infection in order to block more and more effectively its harmful consequences.[27]

In what follows, I will mostly focus on one particular attempt in this direction, which represents a remarkable episode in the history of AIDS research.[28]

3. The central paradox of AIDS pathogenesis

The guiding commitments of HIV-AIDS research constitute an original convergence of insights emerged in contemporary virology between the Sixties and Seventies. First, the suggestion of the existence of "slow viruses", i.e., viruses responsible for pathological conditions arising long after infection.[29] HIV has been clearly taken as being a slow virus in this sense.[30] Second, the involvement of viruses in the pathogenesis of some forms of cancer;[31] and third, the birth of human retrovirology.[32] HIV is itself a retrovirus, and among AIDS-defining conditions there are oncological pathologies, some of which are thought of as being virus-induced.

As far as pathogenetic mechanisms are concerned, however, early hypotheses have been quite traditional. Many well-known viral diseases develop because the agent causes target host cells' death as a consequence of active infection, the typical case being that of direct cell-destruction by cytolysis during the productive phase of the viral life cycle. From the beginning, it was clear that AIDS patients lacked immunocompetence and, as we have already seen, two specific kinds of experimental data drew much attention from the researchers:

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[25] Blattner, Gallo, and Temin (1988); Weiss and Jaffe (1990); Cohen (1993); Maddox (1993a; 1995a); O'Brien and Goedert (1996).

[26] Ascher *et al*. (1993); Maddox (1993b); Schechter *et al*. (1993); Darby *et al*. (1995); Maddox (1995b).

[27] For a last statement of this position, see the Durban Declaration 2000.

[28] For more extensive treatments of the history of AIDS, see Epstein (1996), Grmek (1990), and Hellman (2001, ch. 10).

[29] Gajdusek, Gibbs, and Alpers (1965).

[30] See, for instance, Levy (1993, p. 185).

[31] Emmelot and Bentvelzen (1972); Tooze (1973).

[32] Blattner (1990).

(D.1) it turned out that disease progression is associated with loss of CD4+ T-lymphocytes in blood; and

(D.2) HIV was found to exhibit a strong tropism for these very immune system cells and to display some cytopathic activity against them.

Taken together, these data seemed to suggest a natural framework for pathogenesis, which can be summarized in two basic assumptions:

(B.1) the pathogenetically crucial consequence of infection is that HIV enters CD4+ T-cells and destroys them;

(B.2) this causes a general CD4+ lymphocytopenia, which progressively impairs physiological immune system functions, thus exposing the organism to classical opportunistic infections and other AIDS-related pathologies.

Over the years, a wide range of different mechanisms for CD4+ T-cells' destruction in AIDS have been considered and investigated (including cytolysis, formation of syncytiae, induction of apoptosis, and various immune and autoimmune host responses), and evidence has been reported of damages occurring in immune system cells of AIDS patients quite independently from active infection.[33] However, even if some alternative accounts have been proposed,[34] the most influential approach to pathogenesis has been for long the acceptance of the working hypothesis that the major event in AIDS is the destruction of immune system cells, largely due to active infection by HIV and causing their subsequent depletion.[35]

Yet this point of view had to face a serious anomaly: according to early estimates, mainly based on blood sample measurements, the ratio of actively infected T-cells, even in clinically compromised individuals, was *very low*. Figures ranged from a minimum of about 1 out of 10^5 to a maximum of about 1 out of 10^3.[36] On the basis of these numbers, the primary focus on direct cytopathic mechanisms did not allow a convincing account of immunological collapse even assuming that *all* actively infected cells are invariably killed *in vi-*

[33] For reviews and further references, see Weiss and Jaffe (1990), Levy (1993), Stevenson (2003).

[34] Ascher and Sheppard (1988); Nowak *et al*. (1991); Habeshaw, Hounsell, and Dalgleish (1992); Sheppard and Ascher (1992a, b); Adleman and Wofsy (1993); Margolick *et al*. (1993); Margolick *et al*. (1995).

[35] Fauci (1987; 1988).

[36] Harper *et al*. (1986); Schnittmann *et al*. (1989).

vo by HIV. As a consequence, a "HIV hunting" phase started. Ingenuity, determination and improvements in observational techniques yielded two partially encouraging results. First, it turned out that the virus was biologically active and significantly more widespread in lymphoid tissues.[37] Second, by ultrasensitive methods of detection (such as PCR) it was estimated that large quantities of viral RNA – and, therefore, high levels of "free floating" viral particles (viral load) – were present in plasma.[38]

The latter results, dating the beginning of the Nineties, were readily received as good news for research in AIDS pathogenesis[39] and soon incorporated into pathogenetical hypotheses and speculations.[40] Yet, according to these studies (as well as more recent ones),[41] even in lymphoid tissues actively infected T-cells are typically no more than 1 out of 100 – *still not enough* to be reconciliated with the then prevailing trends in AIDS pathogenetical research given the regenerative capacity of the immune system. Moreover, the overwhelming majority (~99.9%) of detected "free" viral particles appeared to be defective, i.e., unable to successfully infect cells.[42]

This puzzling state of affairs – i.e., evidence of low levels of active HIV infection despite substantial loss of immunocompetence and of circulating CD4+ T-cells in AIDS patients – has been labeled the "central paradox of HIV infection"[43] and has represented a major challenge in the study of AIDS pathogenesis. Some have observed that, assuming the view that AIDS is mainly caused by infection-mediated killing of immune system cells by HIV, it seems one is facing a "murder scene with more bodies than bullets".[44]

This was the situation when one of the most significant episodes in the history of the viral programme took place.

4. The sink model

In January 1995 David Ho's and George Shaw's research teams published two articles on *Nature* and shaped the "sink model" of immune cells "dynamics" in

[37] Pantaleo *et al*. (1991); Embretson *et al*. (1993); Pantaleo *et al*. (1993).
[38] Piatak *et al*. (1993).
[39] Cohen (1993); Maddox (1993a); Temin and Bolognesi (1993).
[40] See Pantaleo, Graziosi, and Fauci (1993); Weiss (1993).
[41] Haase *et al*. (1996); Chun *et al*. (1997).
[42] Piatak (1993); Sheppard, Ascher, and Krowka (1993).
[43] Sheppard, Ascher, and Krowka (1993).
[44] Ascher *et al*. (1995). Also see Anderson, Ascher, and Sheppard (1998).

AIDS pathogenesis.[45] Here is a summary reconstruction of the proposal, based on Ho *et al*.'s paper.

AIDS seems to be characterized by a pathological dynamics in immune cells populations. In its final stage, in particular, it develops through a severe decrease in counts of circulating CD4+ T-lymphocytes, which supposedly reflects a more general depletion (see statement **B.2** in paragraph 3). If x denotes the total number of CD4+ and t a time-variable, then dx/dt will be the rate of change of CD4+ levels in the organism. Then let P and K be, respectively, the rate of cell production and that of cell death. The basic equation of Ho's *et al*.'s model states that

(E) $dx/dt = P - K$.

This simply means that the rate of change of CD4+ T-cell total count is a function of cell production rate and cell death rate. According to the standard view, in the final stage of AIDS dx/dt typically assumes consistently negative values. However, before that, a long period of "incubation" or "latency" occurs during which CD4+ levels appear relatively stable. Suppose we idealize the incubation period as a "steady state" in which

(S) $dx/dt = 0$.

Clearly, **(E)** along with **(S)** imply that in the steady state $P = K$, but what is their value? The viral aetiology grounding the HIV-AIDS research programme suggests that there should be some biologically damaging activity by HIV leading to the final collapse of the immune system. As a consequence, Ho *et al*. conjecture that the value of K during the incubation period, modelled by the steady state, is *not the purely physiological cell death rate*. If so, it follows from **(E)** that the relatively constant levels of CD4+ in the incubation period must in fact be a surface effect of an underlying abnormal turnover induced by HIV infection.

The experimental intervention reported in the paper consisted in the administration to previously untreated patients, starting from time t_0, of a then new powerful kind of drugs (protease inhibitors) contrasting viral replication. Blood samples measurements obtained soon after t_0 suggested that HIV was indeed effectively being halted, showing a relatively unsurpring steep decrease of viral load. If HIV typically kills CD4+ T-cells by infecting them, one would reasonably expect fewer and fewer of them being killed, and therefore overall CD4+

[45] Ho *et al*. (1995); Wei *et al*. (1995).

levels to rise, i.e., $dx/dt > 0$ soon after t_0. Now consider the following important auxiliary assumptions:

(A.1) blood sample measurement are highly representative of *overall* CD4+ T-cell population;

(A.2) P remains constant before and soon after t_0, i.e., cell production rate is not influenced by drug administration.

(A.1) directly excludes major effects of *redistribution* among different compartments of the CD4+ T-lymphocytes pool; in particular, it excludes that an increase observed in the blood compartment be *compensated* by a decrease somewhere else (e.g., in lymphoid tissues). Moreover, since it is commonly estimated that overall CD4+ population is about $0{,}5 \bullet 10^2$ times CD4+ population in blood, **(A.1)** implies that increase in CD4+ levels in blood at any given time should approximately amount to the increase in overall levels (i.e., dx/dt) divided by $0{,}5 \bullet 10^2$.

On the other hand, **(A.2)** states that, after t_0, $dx/dt > 0$ *only because* K drastically drops down, i.e., because, by having halted HIV, fewer and fewer CD4+ T-cells are being killed. Assuming that soon after t_0 K virtually reduces to 0, by **(A.2)** the model implies that dx/dt soon after t_0 approximates P (i.e., overall CD4+ production rate). In particular, **(A.2)** implies that the increase in CD4+ levels soon after t_0 quite faithfully reflects the rate of cell production that, *before* t_0, was required to compensate for the HIV-induced cell destruction and keep CD4+ levels stable. Thus, **(A.1)** and **(A.2)** together imply that increase in CD4+ levels in blood soon after t_0, estimated by blood sample measurements, should amount to about P divided by $0{,}5 \bullet 10^2$, where P, in turn, equals K in the steady state (by **(E)** and **(S)** above).

By statistical analysis on raw data from 18 patients, Ho *et al*. estimated that, soon after t_0, CD4+ increase in blood is on average $3{,}51 \bullet 10^7$ per day, and used this figure to fix the value of parameter P in the model at $1{,}8 \bullet 10^9$ per day ($3{,}51 \bullet 10^7$ times $0{,}5 \bullet 10^2$). This number is meant to provide a measure of CD4+ turnover rate (daily production and destruction) in the steady state, that is, in the "incubation" or "latency" period in untreated HIV infection, when the virus is active and undisturbed.

According to the sink model, then, CD4+ T-cells dynamics during the incubation period is in fact characterized by a very high turnover consisting in continuous virus-mediated cell-destruction compensated by an ongoing effort of replenishment by the immune system. And here is the suggestion proposed in the often quoted last paragraph of the paper:

> The CD4+ T-lymphocytes depletion seen in advanced HIV infection may be likened to a sink containing a low water level, with the tap and drain both equally wide open. As the regenerative capacity of the immune system is not infinite, it is not difficult to see why the sink eventually empties.[46]

The sink model implies that the development of AIDS is backed by continuous CD4+ T-lymphocyte destruction and suggests that it is precisely this process that leads, through exhaustion, to the final depletion of this crucial population of cells. The proposal of this model offered a concrete, although still partial and tentative, insight as to the mechanisms leading to the collapse of the immune system.

5. Theory and evidence

The sink model drew much attention within as well as without the community of researchers. The *Time*, for instance, awarded David Ho with the title of Man of the Year in 1996. According to the magazine, "his pioneering experiments with protease inhibitors helped clarify how the virus ultimately overwhelms the immune system".[47] And in 1997 some critics defined the rise of the sink model as "spectacular", while complaining "that there is hardly any visible debate over this versus alternative theories" in the viral pathogenesis of AIDS and noting that, after the appearance of the model, previously well-known approaches seem to "have been fading away rather silently".[48]

Remarkably, commenting on the "new view" of HIV infection soon after the publication of the 1995 papers, the then editor of *Nature* John Maddox claimed that the "central paradox" had for the first time a plausible solution. In fact, assuming a mechanism of killing by infection as driving HIV infection to overt AIDS (and this assumption, although not explicitly involved, certainly inspired the construction of the sink model) along with a typically very short time-lag from cell-infection to cell-killing, there might be some hope of explaining why so few infected cells are detected and how, if so few are found to be infected, the virus can possibly destroy the immune system: large amounts of the CD4+ population in the blood at any given time may have been freshly created and not yet infected. In Maddox's words:

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[46] Ho *et al*. (1995, p. 126).
[47] *Time*, 30 Dec. 1996.
[48] Grossman and Herberman (1997a, p. 936).

> In essence, the new developments resolve the paradox by showing that the T-cells in an infected person's blood are likely to have been created only in the few days previously. There will not have been time enough for more than a small proportion of them to have become infected, while those that harbour virus will be killed off very soon. So the scarcity of T-cells from which virus can be recovered in test-tube experiments is consistent with the assertion that the immune system is in overdrive from the onset of infection by HIV.[49]

First reactions among AIDS researchers, collected in the "Scientific Correspondence" section of the May 1995 issue of *Nature*, were by and large less enthusiastic. On the whole, critics did not question the experimental data reported by Ho's and Shaw's research teams, but were apparently reluctant to recognize those very results as genuinely supporting the sink model against other possible interpretations of the same data. Accordingly, substantial and recurrent doubts were raised about the assumptions involved, a major target being statement **(A.1)** above (see paragraph 4). In absence of direct evidence of T-lymphocytes' abnormal replication rates – so the argument run – increasing levels of T-cells counts in blood can well, and even more plausibly, be explained as an effect of redistribution from different compartments, in particular from lymphoid tissues into circulation.[50] This alternative reading amounts to a straight rejection of **(A.1)**: in this perspective, Ho *et al.*'s blood samples measurement were clearly *not* representative of overall T-cell population, since increase in blood levels did not reflect a more general proliferation, but rather was *compensated* by a decrease in other compartments harbouring T-cells.

However, the sink model shared at least one of the typical features of good and promising scientific hypotheses: it provided new empirically testable predictions on the basis of which its acceptance or rejection could be rationally evaluated. Although the sink model has been widely discussed, it seems plausible that its value had to be ultimately assessed by its capability to bear *additional* and *confirmed* empirical content.[51] The following are two particularly straightforward consequences (predictions) of the model:

(P.1) due to their rapid loss and the necessity of their ready replacement required to sustain the observed constant levels at the steady state, CD4+

[49] Maddox (1995b, p. 1).
[50] Dimitrov and Martin (1995); Mosier (1995); Sprent and Tough (1995).
[51] See Popper (1963) and Lakatos (1978).

production rate in naïve (untreated) HIV-positive patients should be higher than in HIV-negative controls;

(P.2) as a direct consequence of the suppression of viral replication by effective antiretroviral therapy in HIV-infected subjects, CD4+ T-cells should live, on average, significantly longer.

Several methods for investigating immune cells dynamics and testing the empirical predictions of the model have been devised and employed.[52] Arguably, this process culminated in 1999 with the publication on *Nature Medicine* of a sophisticated experimental study by Hellerstein and collegues, reporting results obtained by a research team based in San Francisco.[53] The observational technique involved allows "direct" monitoring of *in vivo* cell dynamics in humans. The procedure runs as follows. First, glucose or water are administred (either intravenuosly or orally) which have been labeled by means of deuterium, a safe and stable isotope of hydrogen which is incorporated in dividing cells by DNA synthesis. Then peripheral blood (or tissue) samples are obtained at various points in time, cell populations of interest (for instance, CD4+ T-lymphocytes) are purified, and isotopic enrichment of cellular DNA is assessed. By mathematical analysis, the time-dependence of the fraction of labeled DNA can be determined and this, in turn, allows the calculation of dynamically relevant data, such as production rate and survival time.

The 1999 CD4+ labeling study clearly showed both **(P.1)** and **(P.2)** empirically incorrect: CD4+ production rate has *not* been found to be significantly higher in naïve HIV-positive subjects than in healthy seronegative controls, and CD4+ survival time in HIV-positive previously untreated subjects was *not* significantly extended after 12 weeks of effective antiretroviral therapy. As the authors point out, even if "a definitive biological interpretation of the [...] results cannot be made at present", "some models [...] can be excluded".[54] In particular, according to AIDS researcher Giuseppe Pantaleo, commenting on the paper, the reported outcomes virtually "put an end to four years of exciting (although often harsch) debate about the CD4+ T-lymphocyte production/ destruction hypothesis"[55] – i.e., the sink model.

[52] Wolthers *et al*. (1996); Fleury *et al*. (1998); Sachsenberg *et al*. (1998); Zhang *et al*. (1998); Wolthers *et al*. (1999).

[53] Hellerstein *et al*. (1999).

[54] *Ibid*., p. 86.

[55] Pantaleo (1999).

6. Shifting the paradigm? From killing by infection to chronic immune activation

The construction of the sink model has been a major, and possibly the last, upshot of the view of AIDS as a relatively traditional viral disease mainly driven by the cytopathic activity of HIV. Beyond the observations quoted in the previous paragraph and directly discorfirming the sink model, a growing body of evidence has shown general limitations of this view. In particular, a serious problem has been the demonstration that in AIDS patients a different family of T-lymphocytes, called CD8+, which do *not* represent a natural target for HIV infection, suffer from abnormalities in biological behavior and population dynamics which are strikingly similar to those affecting CD4+ T-cells.[56] Worse still maybe, even among CD4+ T-cells, a major cell-killing process, i.e., apoptosis, predominantly occurs in *uninfected* cells.[57]

Some observers have identified a paradigm shift in recent research on AIDS pathogenesis.[58] The rise and fall of the sink model seems, in fact, to have come along with, and even to have stimulated, a fundamental change in perspective. A proposal which is gaining attention and consensus sees in an abnormal and chronic immune activation the crucial process associated with progression to AIDS,[59] and much recently reported experimental evidence seems to fit in a quite natural way into this framework but not into more traditional views. According to this emerging perspective, a crucial step is the inclusion into AIDS pathogenetical models of a more accurate and sophisticated version of our current knowledge of physiological immune system processes. Both CD4+ *and* CD8+ circulating T-lymphocytes include functionally distinct subpopulations. Essential components are represented by a large subset of long-lived "resting" cells consisting in pools of so-called "naïve" and "memory" cells, which regenerate and reproduce in a slow and relatively stable fashion. Upon antigenic exposure, a portion of (both naïve and memory) resting cells become activated, thereby starting a process of rapid proliferation and differentiation into so-called "effector" cells over a period of days or weeks. A large majority of activated cells typically die soon by activation-induced apoptosis, while a small fraction meets the pool of long-lived memory cells and serves as a persistent

[56] See, for instance, Roederer (1998); Hazenberg *et al*. (2000); Kovacs *et al*. (2001); Lempicki *et al*. (2000); McCune *et al*. (2000).

[57] Finkel (1995).

[58] Grossman *et al*. (2002); Silvestri and Feinberg (2003).

[59] Grossman and Herberman (1997b); Grossman *et al*. (2002).

reservoir for subsequent antigen-induced activation. It has been repeatedly reported that HIV-infected persons typically exhibit abnormal, chronic and up-regulated levels of immune system activation.[60]

Focussing on pathological immune activation as the basic process underlying progression to AIDS is providing researchers with several new insights, and gathers into a unified framework a cluster of intriguing experimental results. For instance, a marked preferential biological activity by HIV in activated CD4+ T-cells has been reported.[61] Consistent with these data, the immune activation approach suggests that it is precisely increased immune activation that sustains high HIV replication and viral load levels in (untreated) progression to AIDS. In other words, "activation is the machine driving virus production".[62] Moreover, the fact that antiretroviral theraphy may impact very quickly on viral load without immediately increasing average survival time of T-cells[63] suggests that, even if HIV is cytopathic *in vivo* to some extent, T-cells' death in HIV infection occurs largely independent of HIV. Rather, it may reflect apoptosis in a pathologically expanded population of activated T-cells. On the same basis, the finding of a typical susceptibility to apoptosis in circulating CD8+ cells and, in general, uninfected "bystanders" in HIV infection and AIDS can be quite simply explained. In fact, in a further labeling study in 2003, Hellerstein and collegues reported that in HIV/AIDS untreated patients the absolute number of circulating short-lived activated CD4+ cells is significantly higher than in healthy controls, while the number of circulating long-lived "resting" cells is drastically lower.[64]

Many aspects of the interplay between the immune activation model and experimental evidence are currently under scrutiny. Here I just would like to point out that the paradigm shift (assuming it is indeed occurring) has substantial, and partly puzzling, consequences on both old issues and further directions of inquiry. As a major example of the former case, it should be noticed that, from the standpoint of the new approach, inferring the basic pathogenetical hypotheses **(B.1)** and **(B.2)** from initial data **(D.1)** and **(D.2)** (see paragraph 3) seems to have taken AIDS research on a blind alley for years. For instance, AIDS researcher Mario Roederer has claimed that, contrary to the interpretation prevailing in the early times, "the fact that HIV uses CD4 as its primary receptor

[60] Gougeon *et al.* (1996); Giorgi *et al*. (1999); Sousa *et al*. (2002); Hunt *et al*. (2003).
[61] Roederer *et al*. (1997); Spina *et al*. (1997); Woods *et al*. (1997).
[62] Grossman *et al*. (2002, p. 321).
[63] Hellerstein *et al*. (1999); Kovacs *et al*. (2001).
[64] Hellerstein *et al*. (2003).

and that CD4+ T-cell numbers decline during AIDS are only an *unfortunate coincidence* that have led us astray from understanding the immunopathogenesis of this disease".[65] In fact, the very idea of an *overall* depletion of CD4+ T-cells as the hallmark of AIDS has been called into question in favour of the statement of a "*selective* depletion of 'resting' naïve and memory cells"[66] on the basis of the recent observation that, at least during asymptomatic infection, in an allegedly reliable animal model of AIDS CD4+ (and CD8+) T-cells' total counts seem actually to *increase*.[67]

As far as future prospects are concerned, it is fair to say that a satisfactory account of two crucial links in the causal chain from HIV infection to AIDS *via* immune activation still fail: in a recent review, while promoting the paradigm shift, Silvestri and Feinberg point out that "we still lack an explanation of why HIV appears to be uniquely powerful in inducing a chronic state of immune activation [...], and why the HIV-induced immune activation is so disruptive of the proper overall functioning of the immune system".[68] In view of documented observations that AIDS-like immune activation may occur without HIV infection[69] and that effective clinical improvement in AIDS patients on antiretroviral treatment can obtain despite evidence of modest inhibition of HIV replication,[70] investigation on these "missing links" seems a particularly urgent task for future research.

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[65] Roederer (1998, p. 146, emphasis added).
[66] Grossman (2003).
[67] Sopper *et al*. (2003).
[68] Silvestri and Feinberg (2003, p. 823).
[69] Kalinkovich *et al*. (1998).
[70] Deeks *et al*. (2002).

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Reply to Hudson: "Howson on Novel Confirmation"

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ABSTRACT. In a recent paper in this journal Robert G. Hudson (2006) criticises a discussion originally by me, later elaborated in a jointly authored work with Allan Franklin, of an example due to Maher (1988) which Maher used to motivate a Bayesian solution to the prediction-versus-accommodation problem. Hudson extends his critique to an explanation by us why we thought that Mendeleev's discovery of the Periodic Table of the chemical elements was not susceptible to the same analysis as that we gave of Maher's example. In what follows I shall rebut his charges and show that they rest on a mixture of inattention to the text and some elementary logico-mathematical errors.

Maher's example contrasts two scenarios. In one, call it A, a subject, call him/her Pat, predicts the outcomes of 100 tosses of a coin. In the other, B, Pat waits to be informed of the outcomes of the first 99 tosses before "predicting" the entire 100. In assessing the confidence one should have in Pat's predictive powers one might want to consider the possibility that (s)he possesses some reliable method of prediction, and we shall in particular consider the possibility that he has some such method whose reliability is perfect. Following the notation in Howson and Franklin (1991), which Hudson adopts together with our own formulas, let us call that hypothesis m. Let h be Pat's prediction of the sequence of 100 outcomes (so h specifies the values of a 100-member sequence of Hs and Ts), and let e describe the result of the first 99 tosses, which we suppose are as described in h.

Intuitively, we are inclined to feel that in case A Pat's having genuinely predicted e lends quite strong support to m and thereby enhances the probability of Pat's prediction of the 100^{th} outcome. In case B, on the other hand, e provides no such support either to m or to the prediction of the 100^{th} outcome. Using a rather complex argument, Maher concluded that this intuition can be repre-

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sented within the Bayesian theory of prior and posterior probabilities. Franklin and I presented a rather simpler way of doing this,[1] whose elegance is extolled by Hudson simultaneously with his declaring that the way we use it is "confused" (an allegation he repeats several times). In what follows I will show that Hudson's charges are without foundation, and that his own presentation is vitiated by inattention to our text – a text which I think I can fairly say went to extreme lengths in attempting to avert any risk of misunderstanding – combined with elementary errors of logic and understanding.

The formal Bayesian argument proposed in Howson (1988) to support the intuitive discrimination between the two cases, and repeated in more detail in Howson and Franklin (1991), is very simple. Take case A first. Let $h(100)$ be Pat's prediction of the 100th outcome. Given e, $h(100)$ is clearly equivalent to h, and so we can represent $P(h(100)|e)$ simply as $P(h|e)$. Using some simple bits of probability theory and assuming that $P(m\&e)$ and $P(\neg m\&e)$ are nonzero, we now expand $P(h|e)$ as follows:

(0) $\quad P(h|e) = P(h|m\&e)P(m|e) + P(h|\neg m\&e)P(\neg m|e).$

I now quote from Howson and Franklin (the reason for the explicit quotation will be apparent very shortly), "that the subject predicted h is now part of the background information relative to which P [...] is computed [...] [so] m entails h" (1991, p. 576). Letting K_A describe this background, we therefore have $K_A \Rightarrow (m \rightarrow h)$ (read "$\Rightarrow$" as "entails"). It follows that $P(h|m\&e) = 1$. Hence

(1) $\quad P(h|e) = P(m|e) + P(h|e\&\neg m)P(\neg m|e).$

Also, we can take $P(e|\neg m)$ to be very small, while $P(e|m)$ is 1. Assuming $P(m)$ is not completely negligible, it follows by a standard Bayes Theorem argument that $P(m|e)$ is close to 1 and $P(\neg m|e)$ is close to 0. Hence $P(h|e)$ is also close to 1.

In case B things are very different. I quote again from Howson and Franklin:

> The background information can now be represented by the statement:
> "The subject was informed of the outcomes of the first 99 flips of the coin, and asserts the conjunction of these with the prediction that the 100th will be a head".
> The background information does not specify what the outcomes of the first 99 flips were, and so m does not entail h or e relative to that information (although $e\&m$ entails h) (1991, *ibid.*).

[1] Though it replicates that in Howson (1988).

The background information, K_B, is specified in this way because we want to be able to represent the possibility that whatever the outcomes of the first 99 tosses are, Pat will incorporate that data into his/her own information stock as a basis for the prediction of the outcome of the 100th toss. Without any loss of generality, therefore, we can represent Pat abstractly as an input-output device $M(x)$, where x is the data, which, for a specific value, e.g. e, of x determines Pat's prediction as $M(e)$. Since m just says "Pat = $M(x)$ is reliable whatever the value of x", while e records one such value, it is quite reasonable to set $P(e|m) = P(e|\neg m)$, from which it follows that $P(m|e) = P(m)$. Also, since e entails e and m entails that $h(100)$ is a head, we have that $K_B \Rightarrow (m\&e) \rightarrow h$, whence $P(h|e\&m) = 1$. Thus from (0) we infer

(2) $\quad P(h|e) = P(m) + P(h|e\&\neg m)P(\neg m),$

which is approximately equal to $P(h|\text{chance}\&e)$ if $P(m)$ is small.

It might seem pedantic to spell out again what is being assumed in each of the two cases A and B, and we did so in order that the reader could check from themselves that the derivations of (1) and (2) are in order. Hudson, however, affects to find our account "confused" on the ground that

> in their presentation of SCENARIO (A), *there is no mention of what the background specifies as to the exact outcomes predicted by the subject* – and still m is taken to entail h (and thus e). Indeed, given how Howson and Franklin define and use the symbols m, h and e, it does not matter whether the background information specifies what the outcomes are; m entails h (and so e), in any case, for given that the subject has reliable advance information about the outcomes of the 100 flips she will correctly predict h, whether in SCENARIO (A) or SCENARIO (B), that is, whether she was informed about the outcomes of the first 99 flips or not (Hudson 2006, p. 93; my italics).

Hudson has obviously not read carefully, or not understood, what we said, and said I think very clearly, and as a result every single assertion in this quotation is false. But there is worse to come, for he proceeds next to find fault with the plausible claim that, given the circumstances quoted above from our paper, $P(e|m) = P(e|\neg m)$ and hence $P(m|e) = P(m)$:

> But again, given the meaning assigned to m, $P(e|m)$ is surely much larger than $P(e|\neg m)$. However, it is still the case that $P(m|e) = P(m)$ (*Ibid.*).

The first sentence, we know, is false, while the second shows that Hudson cannot perform elementary computations in the probability calculus which, assum-

ing P(h), P(m) are nonzero, is easily seen to pronounce that *it is impossible for P($e|m$) to be larger than P($e|\neg m$) and for P($m|e$) to be equal to P(m)*. The first conjunct states that, considered as indicator variables, e and m are positively correlated,[2] while the second states that they are independent. Hudson's conclusion that he has derived (2) "in more obvious fashion" (*ibid*., p. 94) is thus absurd, and the conclusions he wishes to draw from his "derivation" are all invalidated by it.

His dismissal of our argument that the Mendeleev case is radically dissimilar to the coin-tossing example is one such conclusion. Note that (0) is valid for all m, h and e, assuming the unconditional probabilities are all nonzero, and hence we could let m be Mendeleev's theory of the Periodic Table. What Franklin and I had pointed out in our joint paper was that this substitution destroys the asymmetry present in the two possible scenarios of the Maher example, since now m entails h and we immediately obtain (1) in any event, with the straightforward Bayesian corollary that if P($e|\neg T$) is small, as it arguably was, there being no alternative explanation around at the time, we could expect P($h|e$) to be considerable just for that reason. Hudson's comment about us that

> a Bayesian analysis of the issue, using their own formalism (understood properly), leads to the opposite conclusion [to theirs] (*ibid*., p. 97; Hudson's parentheses)

is therefore not only offensive but simply wrong.

It will be clear, I hope, that Hudson has badly misrepresented what Franklin and I say. Thus it is highly ironic that Hudson himself brings an explicit charge of misrepresentation against me, claiming that I misrepresent the views of John Worrall, my own colleague at LSE, and that I do so moreover by quoting from one of Worrall's own publications! The quotation in question from Worrall, which Hudson reproduces, is this:

> of the empirically accepted logical consequences of a theory those, and only those, used in the construction of the theory fail to count in its support (Worrall 1978, p. 48).

[2] The familiar Bayesian difference measure of support of h by e, i.e. the difference P($h|e$) – P(h), is easily seen to be proportional to the degree of correlation between the indicator variables **h** and **e** (these take the value 1 on states for which the corresponding proposition is true, and 0 on states for which it is false).

Fairly unequivocal, one might think, except for the ambiguous phrase "used in the construction of the theory". What exactly does "used" mean? In general it is difficult to give any clear answer, though there is one situation which occurs commonly in science where the meaning is relatively clear, and that is where a theory has adjustable parameters and the data fix the values of one or more of them. Indeed, in Howson (1990) I discuss an example Worrall uses to support his claim in the paper from which the quotation was taken, the use of Mercury's anomalous perihelion – anomalous for CGT, classical gravitation theory – to fix an appropriate parameter in CGT, like the density of a dust cloud, say, to account for the anomaly. I showed, as a simple exercise in the probability calculus, that if two rival theories h and $h(a)$ both predict e, but e fixes the parameter a in $h(x)$, then, using the familiar Bayesian support measure given by the difference between posterior and prior probabilities, two interesting features are seen: (i) the posterior probability of $h(a)$ is equal to the *prior* probability of $h(x)$, and (ii) the ratio of the support of h to $h(a)$ is equal to $[\mathrm{P}(h)/\mathrm{P}(h(x))].\mathrm{P}(e)^{-1}$. To be precise, it is easy to show, given a mild independence assumption, that if $S(h,e)$ signifies the support of $h(a)$ by e given by the difference between posterior and prior probabilities, then

$$S(h,e) = P(h(x))P(\neg e).$$

This simple decomposition of $S(h,e)$ in the circumstances cited is an important feature of the difference measure (and one as far as I am aware unknown before I exhibited it). It accords very closely with the intuition that a hypothesis whose parameters have been adjusted to the data should be exactly as probable given the data as the prior probability of the unadjusted hypothesis, and that there should be a bonus of support to the genuinely predictive hypothesis if both it and $h(x)$ start out with equal priors. In this case of the rivals above we see that the bonus will be exactly equal to $\mathrm{P}(e)^{-1}$, so the more unlikely a priori the prediction is to be true the more support accrues proportionately to the predictive hypothesis.

It follows that Hudson's claim that "[Howson] hasn't adequately explained what evidential value there is in prediction *per se*" (2006, p. 99) is as far from the truth as his other charges. If the hypothesis with free parameters and its genuinely predicting rival start off equal, we see from the result above that the latter gets more support than the former once its parameters have been fixed to allow it to make the same predictions. In other words, there *is* a virtue in prediction per se, but it can be dominated by the prior implausibility of the predicting hypothesis. Indeed, depending on the prior probabilities of h and $h(x)$,

the accommodating hypothesis $h(a)$ could turn out to be *more* supported than $P(h)$. Hudson thinks this is wrong and that the predictive hypothesis should never receive less support than the accommodating one, but a little thought should convince anyone that this must be wrong. For an extreme example, suppose that $P(h) = 0$ and $P(h(x)) > 0$. If the prior probability of the predictive hypothesis is actually zero then it should not garner any support, while the accommodating hypothesis might, depending on the circumstances, pick up some. I point out in Howson (1988) that such a case is modelled where there are enough computers outputting different sequences of 1 and 0: one of these machines is certain to predict the 99 coin tosses, though there is a zero prior probability that it has a reliable algorithm for predicting coin tosses in general.

Let us now return to the Worrall quotation above. That it is incorrect is easily seen from the following simple example. I take all the balls, each black or white, out of an urn, and I discover that there are r white and s black. I accordingly evaluate the parameter x in the hypothesis $h(x)$: "The proportion of white balls in the urn is x" as $x = r/(r + s)$. Would anyone seriously deny that the hypothesis $h(r/(r + s))$ is maximally supported by the data (it is actually *entailed* by it)? Yet this is what Worrall's assertion implies. We can, incidentally, gauge the quality of Hudson's scholarship by noting that his claim that I misrepresent Worrall is based on the ground that Worrall might have wanted to qualify it in the context of an example *different* from the one he himself used as evidence for that assertion, namely the alleged fact that "Mercury's perihelion [advance] is not regarded as supporting classical theory", although it is predicted by versions of that theory (Worrall 1978, p. 48). In passing, we can see rather clearly that the conclusion Worrall draws from this observation (that the consequences used in the construction of a theory do not support it) is in fact a *non sequitur*: that the data implied by $h(a)$ do not support $h(x)$ – which is effectively what Worrall notes – does not imply that they do not support $h(a)$ itself (which is what he concludes). As I have shown above, in general the data *will* support $h(a)$.

Hudson's objections against me are both unscholarly and without foundation. I hope, nevertheless, that some of the other conclusions that have emerged from this note will be of more positive interest.

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Aims and contents

L&PS – Logic and Philosophy of Science is an on-line philosophical journal sponsored by the Department of Philosophy of the University of Trieste (Italy). The journal promotes both theoretical and historical research in the philosophy of science and logic, without excluding any particular cultural perspective.

Topics welcomed by the journal include:

– the theory of scientific knowledge and the analysis of the general methodological problems of science (such as scientific discovery, causation, scientific inference, induction and probability, the structure of scientific theories and their relations with empirical data);
– the methodological and foundational problems of the different sciences, from the natural, to the biomedical, to the social sciences;
– the problems related to the historical development of logic, in all its branches, and to the role of logical methods both in the general methodology of science and in the foundations of empirical and mathematical sciences;
– the philosophical problems raised by the development of the cognitive sciences and the philosophy of mind, with particular attention to those results that are relevant for the analysis of scientific practice;
– the epistemological problems related to Artificial Intelligence, robotics, virtual reality, and artificial life;
– the problems in the sociology and the history of science that are relevant to the philosophical investigation of science;
– the problems related to the ethics of science;
– the questions related to the historical and conceptual development of the philosophy of science and logic;
– the problems of the philosophy of language, with particular attention to those results that are relevant for logic and philosophy of science.

The journal will appear twice a year (in March and in September), and one of these issues will be usually devoted to a special topic.

Information for the authors

Papers submitted to the journal must be written either in Italian or in English, and must be accompanied by a short summary in English (and also in Italian for the articles written in Italian). All papers will be evaluated by anonymous referees.

In order to promote critical discussion and exchange among scholars, the journal is willing to publish reports on work in progress, to be submitted and evaluated according to the criteria already mentioned above.

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