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Evidence conforms to conceptions just as often as conceptions conform to evidence.

Ludwik Fleck
[(1935) 1979, p. 28]

The concepts of Ludwik Fleck and their application to the eukaryotic cell cycle

Abstract

The concepts of Ludwik Fleck (1896–1961), a microbiologist, historian, and philosopher of medicine, can be used to analyze the conservative nature of scientific ideas. This is discussed and applied to ideas dominant in the understanding of the eukaryotic cell cycle. These are (a) the G1-phase restriction point as

PUBLICATION INFO	Studia Historiae Scientiarum	e-ISSN 2543-702X ISSN 2451-3202		DIAMOND OPEN ACCESS

CITATION
Cooper, Stephen 2017: The concepts of Ludwik Fleck and their application to the eukaryotic cell cycle. *Studia Historiae Scientiarum* 16, pp. 335–364.
Available online: https://doi.org/10.4467/2543702XSHS.17.013.7714.

RECEIVED: 19.12.2016 ACCEPTED: 12.07.2017 PUBLISHED ONLINE: 18.12.2017	ARCHIVE POLICY Green SHERPA / RoMEO Colour	LICENSE	Crossref

WWW	http://pau.krakow.pl/Studia-Historiae-Scientiarum/; http://www.ejournals.eu/sj/index.php/SHS/

a regulatory element of the mammalian cell cycle, (b) the Rate Change Point proposed to exist in fission yeast, and (c) the proposal that a large number of genes are expressed in a cell-cycle--dependent manner.

Fleck proposed that scientific ideas become fixed and difficult to change because criticisms of current and dominant models are either ignored or turned to support of the current model. The idea of a thought-collective leading to the stability of scientific ideas is a central theme of the theory of Ludwik Fleck.

Keywords: *Ludwik Fleck*, *G0*, *G1*, *Restriction Point*, *Rate-Change Point*, *Eukaryotic Cell Cycle*, *Gene Expression in Cell Cycle*.

Koncepcje Ludwika Flecka i ich zastosowanie do eukariotycznego cyklu komórkowego

Abstrakt

Koncepcje Ludwika Flecka (1896–1961), mikrobiologa, historyka i filozofa medycyny, mogą być użyte do analizowania zjawiska skostnienia idei naukowych. Zagadnienie to omówiono i zastosowano do dominujących koncepcji w rozumieniu cyklu podziału komórek eukariotycznych. Są to: (a) punkt kontrolny fazy G1 (tzw. punkt restrykcyjny) jako element regulacyjny cyklu komórkowego u ssaków; (b) punkt zmiany tempa wzrostu komórek mający występować u drożdży rozszczepkowych (*Schizosaccharomyces pombe*) oraz (c) postulat, że ekspresja znacznej liczby genów jest zależna od fazy cyklu komórkowego.

Fleck zaproponował, że idee naukowe utrwalają się i trudno je zmienić, ponieważ krytyka aktualnych i dominujących modeli jest albo ignorowana, albo przemieniana na poparcie aktualnie obowiązującego modelu. Idea „kolektywu myślowego", prowadząca do stabilizacji idei naukowych, jest centralnym tematem teorii Ludwika Flecka.

Słowa kluczowe: *Ludwik Fleck*, *G0, G1, punkt restrukcyjny, punkt zmiany tempa wzrostu, eukariotyczny cykl komórkowy*, *ekspresja genu w cyklu komórkowym*.

1. Introduction

The Continuum Model of eukaryotic cell-cycle control is now almost 38 years old.[1] This alternative view of the cell cycle[2] was actually generated a number of years earlier based on studies of the bacterial cell cycle.[3] Since its initial proposal, the Continuum Model has not made much headway against what may be called the G1-phase control model of the cell cycle, or better the "Standard Model" of the cell cycle, a model that is current, dominant, and widely-accepted by a broad consensus of researchers in the field of eukaryotic cell-cycle studies. It is important to understand how the Standard Model has remained so dominant despite the success of the alternative Continuum Model view of the cell cycle in explaining myriad published experimental results on the cell cycle. No matter how successful the experimental and theoretical work confirming and supporting the Continuum Model, and no matter how many articles explaining and applying this alternative viewpoint have been published, there appears to be no change in the way people talk about, perceive, or understand, the control of the eukaryotic cell cycle.

Why it is so difficult to effect a change in the consensus viewpoint? Why is the currently dominant view of cell-cycle control impervious to the strongest criticisms? Is it because the current model is right? Is it because the alternative analysis has not been clear or strongly presented? Is it because not enough allies have been enlisted to study and explain the alternative viewpoint?

Recently a friend[4] gave me a copy of a small book with a strange title,[5] written by a person whose name was unknown to me. The book was by Ludwik Fleck, a deceased microbiologist/immunologist of Polish origin, who thought a lot about why scientific ideas are recalcitrant to change. (See photo of Ludwik Fleck, Fig. 1).

This book suddenly illuminated the problem, and explained why it is so difficult to displace a widely held idea, even if that idea may be

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[1] Cooper 1979; 1981.

[2] Cooper, Helmstetter 1968; Helmstetter 1969; Helmstetter, Cooper 1968.

[3] Helmstetter *et al.* 1968; Cooper 1997.

[4] Dr. Lawrence Sturman, Head of the Watson Laboratories of the New York State Health Department in Albany, and a friend since Graduate School.

[5] Fleck 1979.

Fig. 1. Ludwig Fleck, 1896–1961.
Reprinted from: PHILWEB Bibliographical Archive. Theoretical resources off- and on-line; http://philweb.rlwclarke.net/topics/Nature/Fleck/Fleck.jpg

incorrect. As will be seen below, Ludwik Fleck codified and described the processes whereby incorrect theories or ideas persist and are rendered resistant to change or modification. Some of Fleck's concepts are presented here in order to explain why dominant ideas are so resistant to change. The ideas of Fleck will be discussed primarily in the context of some widely believed ideas related to the cell cycle that have been strongly criticized but the criticisms have not been widely recognized.

2. Meeting Ludwik Fleck

Ludwik Fleck is mostly well known today, if one knows him at all, for his book, *Genesis and Development of a Scientific Fact*. This book was published originally in German in 1935[6] and remained relatively unknown – the original printing was merely 640 printed copies and only 200 of these were sold – until it was republished under the urging and mentorship of Thomas Kuhn, who is famous for his seminal book, *Structure of Scientific Revolutions* (1962).[7] The English version of Fleck's book

[6] Fleck 1935.

[7] However, this thesis does not apply to the German-speaking world – cf. footnote 19, below.

was published in 1979[8] with a translation from the original German by Fred Bradley and Thaddeus J. Trenn, with additional editing by Trenn and Robert K. Merton.

Fleck died in Israel in 1961, having emigrated there from his native Poland after World War II. One may ask, "What can Ludwik Fleck contribute to the study of the mammalian cell cycle, since most of our current ideas on the cell cycle are of recent vintage and were developed years after Fleck's book was published as well as years after Fleck's death?" How can Fleck's ideas, published in 1935, be applied to the cell cycle as they were written well before there was any understanding or knowledge of even the most basic concepts of the cell cycle, such as the existence of its different phases. The discussion presented below is an answer to this question, illustrating how Fleck's analysis may be applied to a contemporary scientific debate.

To anticipate the conclusion of this presentation of Fleck's work, the explanations of the difficulty of changing ingrained ideas are not rooted in science, or experiments, or even theories, but are related more to the sociology and psychology of science and thought. This concept will be explained using as examples some simple but problematic aspects of cell-cycle control, such as the restriction point, the rate change point in *S. pombe*, and gene expression at particular times during the division cycle. By concentrating on these simple ideas, I hope to disseminate, and perhaps popularize, some of Fleck's most relevant ideas.

The title of Fleck's book, *Genesis and Development of a Scientific Fact*[9] (hereafter referred to as *GDSF*) is somewhat odd. How can a "fact" develop? Aren't facts solid and immutable? As one commentator is reported saying (from Thomas Kuhn's forward to the translated edition[10]), "How can such a book be? A fact is a fact. It has neither genesis nor development." What Fleck presented in his book is a discussion of the way in which scientific facts do "develop" and change over time. The scientific "fact" that Fleck discussed in his book is the development of ideas regarding the nature of syphilis, and in particular how the Wasserman test affected these ideas. The book is a masterful study of the

[8] Fleck 1979.
[9] Fleck 1935; 1979.
[10] Fleck 1979, p. viii.

historical development of ideas regarding what syphilis was, how it could be recognized, and how, during the 1920's, the Wasserman test, despite numerous problems and confusions, led to an understanding of the nature of syphilis.

Some of Fleck's ideas will be applied to the mammalian cell cycle in order to show the relevance of his ideas to science today. Fleck's analysis is used as a point of reference to understand why particular ideas regarding the cell cycle persist in the collective thought of the field of cell cycle studies, despite, as discussed below, the likelihood that these ideas are incorrect.

3. Who was Ludwik Fleck?

Ludwik Fleck lived through one of the major tragedies of our time, World War II and the associated Holocaust. Fleck was born in Lvov, on the 11th of July, 1896.[11]

The city belonged to the Kingdom of Galicia and Lodomeria, a crownland of the Habsburg Monarchy from the partition of Poland in 1772 until 1804, and then a crownland of the Austro-Hungarian Empire until 1918. Although from 1869 the official language of the educational system in the kingdom was not German but Polish (and Ukrainian to a lesser degree), knowledge of German was quite common among educated people, to whom Fleck also belonged.

He received his medical degree in 1922 from Lvov University, when Lvov still belonged to the reborn Poland. A succession of positions studying typhus and bacteriological problems led Fleck to the study of methods for the diagnosis of infectious disease. In 1927 he was in Vienna working at the State Serotherapeutic Institute. The following year he became head of the bacteriological laboratory of the Social Sick Fund in Lvov until his dismissal in 1935.[12]

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[11] The biographical notes in this section are a short summary of the biographical sketch of Ludwik Fleck given at: Fleck 1979, pp. 149–153 with corrections taken from Schnelle, Cohen (eds.) 1986; Płonka 1994; Sady 2012; Allen 2014; Kokowski 2015; Polska Akademia Nauk 2016; *Wikipedia* 2016, and Davies 2005.

[12] In many works, among others: Fleck 1979, p. 150; Schnelle 1982; Leszczyńska 2006, p. 156; White 2015, p. 141; Erickson 2016, Box 1.4, it is claimed that this dismissal was a result of anti-Jewish measures. However, according to Bożena Płonka-Syroka

Fleck's main area of research was the development of therapeutic sera and diagnostic skin tests. His studies on epidemic typhus fever for which he developed a diagnostic skin test (the exanthin reaction) were internationally confirmed and are mentioned in textbooks.

Besides studies in medical science, Fleck developed an original theory about the thought style of science and "thought collectives" which are fully described in *GDSF*. This book was completed in 1934, and published in 1935 in Switzerland[13] because political conditions in 1935 did not allow a Jew to publish in Germany. The book, despite low sales, was widely discussed and reviewed in journals in Poland, Germany, Austria, Switzerland, France, the Netherlands, Italy, Sweden, and the United States of America.

Among his scientific contributions following the publication of this book was the development of a new method to strengthen the sensitivity of the Wasserman reaction. Fleck also discovered an original method for distinguishing true serological reactions from pseudoreactions. The "fact" discussed in his book relates to the historical development of understanding syphilis and how the Wasserman reaction led to the basic understanding of the etiology and development of this infectious disease.

Fleck's work prior to the commencement of World War II was located in Lvov, which was taken over by the Union of Soviet Socialist Republics in 1939. Lvov is now within the borders of Ukraine. Fleck was director of the City Microbiological Laboratory, and was on the teaching staff of the microbiology department of the State Medical School in Lvov. Until 1941 he also served as head of the microbiology department of the State Bacteriological Institute in Lvov.

During the German occupation of Lvov starting in 1941, Fleck was director of the bacteriological laboratory of the Jewish Hospital. In 1942 Fleck and his family were arrested and he was forced to produce his newly developed typhus vaccine (in 1942) for the German armed forces. He was subsequently deported to the Nazi concentration camp in Auschwitz. At the camp, under duress, Fleck continued to produce

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(1994, p. 49) with this view "it is difficult to agree completely, because at the time one could find people with similar biographies among professors of Jan Kazimierz University in Lvov" (translated by Michał Kokowski).

[13] Fleck 1935.

his vaccine for the German army. In 1944 Fleck was transferred to Buchenwald and again ordered to prepare typhus vaccine.

The nightmare of World War II and his incarceration in concentration camps ended for Fleck on the 11th of April, 1945, when the United States Army liberated Buchenwald. Fleck then returned to Poland where, from October 1945, he served as assistant professor and head of the Institute of Microbiology in the newly founded Marie Curie-Skłodowska University of Lublin. In 1946 he received a *habilitation* and in August 1947 became Associate Professor at this Institute.

During the 1947–1949 period Fleck discovered a new phenomenon related to inflammation, i.e. "leukergy", and Fleck and his students soon published about 40 articles on the subject. This discovery had an immediate impact on the scientific community and in 1949 Fleck received the scientific prize of the city of Lublin for his research in leukergy. In addition to his scientific studies, during the 1948 Nuremberg trials Fleck was asked to render assistance to the prosecution in the case of Krauch, *et al.*

In June 1950, Fleck received the title of Ordinary Professor (the highest scientific title in Poland) and became a full Professor at the Institute of Microbiology Marie Curie-Skłodowska University of Lublin until his appointment in 1952 as director of the Department of Microbiology and Immunology at the Mother and Child State Institute in Warsaw. In 1953 he was awarded the State Scientific Prize of Poland for his research on epidemic typhus fever. Fleck was also elected a corresponding member of the Polish Academy of Sciences in 1954, and a member of the Presidium of this academy in 1955–1957. In 1955 he was invited to the Pasteur Institute in Paris as well as the Medical School in Strassburg to lecture on leukergy. In the following year he was invited to a conference on autoantibodies at the University of Texas.

In 1956, Fleck fell ill with the dangerous Hodgkin's disease. One year later, together with his wife Ernestina, he emigrated to Israel, where their only son, Arieh (Ryszard in Polish) had lived since 1947.[14] Af-

[14] It is claimed in Fleck 1979, p. 152: that "Ever since the end of the war, Fleck had been trying to go to Israel, but it was 1957 before he was allowed to leave Poland in such a way that he could take his wife, Ernestina, with him". However, historical sources say otherwise: his son emigrated to Israel in 1957 against the will of his fa-

ter leaving Poland Fleck joined the Israel Institute for Biological Research at Ness-Ziona as head of the Section of Experimental Pathology, and continued to maintain regular contact with his Polish colleagues and collaborators.

By the beginning of 1961 Fleck was already seriously ill. He died on the 5th of June, 1961 and was buried in Ness-Ziona.

In addition to the monograph discussed here (*GDSF*), Fleck had published over 130 scientific articles in Polish, German, Hebrew, English, French, and Russian. He was a member of many international scientific societies, including the New York Academy of Sciences, the International Haematological Society, and the International Society of Microbiologists.

In recent years there has been a rebirth of study of the ideas of Ludwik Fleck, with many symposia, meetings, and conferences discussing these ideas.[15] In addition, there is a Ludwik Fleck Prize offered annually by the Society for Social Studies of Science for a book related to the study of ideas.[16]

4. The history of "Genesis and Development of a Scientific Fact"

The currently available English translation of Ludwik Fleck's monograph, *Genesis and Development of a Scientific Fact*[17] has been helped by the efforts of Thomas Kuhn to bring the original work (published in German) to a wider audience. In the "Foreword" to the translated edition,[18] Kuhn writes that he had encountered only two people who had read this book aside from himself, and one of them, the renowned mathematician Mark Kac, was a personal friend of Fleck. Kuhn notes that he read this book some time during the years 1949–1950. Kuhn

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ther, and not because of antisemitism, although *antisemitism* was present in Poland in 1957–1958, but for family reasons – cf. Leszczyńska 2006, pp. 164, 169–171; Kokowski 2015, pp. 167–168, 186.

[15] Cf. for example The Ludwik Fleck Center 2005–2011; Płonka-Syroka, Jarnicki, Balicki (eds.) 2015; Conde, Salomon (eds.) 2016.

[16] Society for Social Studies of Science 2017.

[17] Fleck 1979.

[18] Fleck 1979, pp. vii–xi.

specifically points out that two or three years earlier, before encountering Fleck, he experienced his own personal epiphany regarding the historicity of scientific understanding. Kuhn's contribution was directed primarily to understanding the occasional non-cumulative episodes that permeate scientific history and which have been called scientific revolutions. During these years when Kuhn's ideas were developing, it was the serendipitous encounter with a minor footnote in Hans Reichenbach's book, *Experience and Prediction*, that led him to Ludwik Fleck.

Thus, while Fleck was not instrumental in the genesis of Kuhn's ideas (after all, Kuhn was writing about extreme changes in scientific ideas, while Fleck concentrated on why ideas are resistant to change. In a sense, Fleck's work was the obverse of Kuhn's analysis, as it concentrated on the conservative nature of scientific ideas. Yet Fleck's treatment of a particular area of scientific development was actually very supportive of the Kuhnian analysis. Between revolutions in scientific views it is the conservative nature of science that dominates, and it is this aspect of scientific development that is analyzed by Fleck. Thus Fleck's ideas certainly deserve some recognition as part of a new analysis of the nature of the development of scientific ideas.[19]

Kuhn read the book in its original German. Even with his limited language ability, Kuhn drew from Fleck's discussion the key idea that "fact" cannot be rendered completely free from "point of view." One of Fleck's main proposals is that scientific facts cannot be understood without considering the then current mode of thinking or other societal modes of analysis. As an example, in a society where everything in life is associated with the will of "the gods", it would be natural to analyze particular events in nature (e.g., illness) as related to "the will of the gods". The understanding of nature, as revealed by scientific study, is therefore deeply related to the overall thought structure of the society in which the analysis is taking place.

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[19] Moreover "According to [José María] López Piñero [1993], it was a sad episode in the historiography of science that Fleck's work had been presented simply as an early precursor of Kuhn's *The Structure of Scientific Revolutions* and of social construction. […] Fleck's book had had an important impact in the Germanspeaking world at the time of its publication, and in the 1960s it was still a recommended text in history of medicine programmes" (Simon, Herran 2008, p. 3).

5. On the "Tenacity of Systems of Opinion"

It is well accepted, due to the work of Thomas Kuhn, that scientists congregate around a generally accepted idea or a set of opinions that allow them to work together as a group, to communicate ideas within the group, and to develop new ideas based on the common foundational understanding of the group. In Kuhn's terminology, this common understanding is the "paradigm" within which normal science proceeds. Fleck's contribution to this history is not merely a presaging of the concept that commonly accepted ideas are stable and resistant to criticism or alteration, but more important, Fleck proposed *why* these ideas are stable and resistant to change. As Fleck saw the development of ideas, contradictions within the consensus are not only repelled by the current and consensus viewpoint, but these contradictions may even be enlisted as support of an incorrect idea. Rather than a discarding of ideas in the face of contradictory evidence, the ideas may actually be reinforced in the face of the contradictions.

Rather than simply suggesting that even the most objective scientists are subject to inertia or even immobility when core beliefs are challenged, the prescient work of Fleck listed a number of reasons why there is such a resistance to change or such a protection of the commonly or generally held central idea. As Fleck pointed out, this resistance to change is not merely the result of simple passivity or laziness or even mistrust of new ideas; after all, scientists and intellectuals speak again and again of new and exciting ideas. Rather, Fleck pointed out that resistance to change results from an active process that reacts to the criticism.

Fleck denoted four stages in this reaction. It is easiest to get the directness and flavor of Fleck's writing by a direct quote from his book:

> Once a structurally complete and closed system of opinions consisting of many details and relationships has been formed, it offers enduring resistance to anything that contradicts it.
>
> A striking example of this tendency is given by our history of the concept of "carnal scourge" [i.e., syphilitic lesions due to sexual activity] in its prolonged endurance against every new notion. What we are faced with here is not so much simple passivity or mistrust of new ideas

> as an active approach which can be divided into several stages. (1) A contradiction to the system appears unthinkable. (2) What does not fit into the system remains unseen; (3) alternatively, if it is noticed, either it is kept secret, or (4) laborious efforts are made to explain an exception in terms that do not contradict the system. (5) Despite the legitimate claims of contradictory views, one tends to see, describe, or even illustrate those circumstances that corroborate current views and thereby give them substance.[20]

I will now discuss some aspects of the cell cycle and the study of the cell cycle that illustrate how ideas that are problematic or wrong are protected and stabilized against criticism.

6. On the tenacity of the "restriction point"

The restriction point was postulated to exist by Pardee on the basis of a series of experiments described in 1974.[21] The restriction point was proposed as a unique cell-cycle point at which cells come to rest when cells are growth-arrested either by starvation or inhibition. An alternative formulation of the restriction point defines it as a point in the G1 phase, when cells subjected to growth inhibition (usually by serum reduction) can start the S phase if they are past the restriction point, whereas cells prior to the restriction point cannot start another S phase. Subsequent applications of the restriction point phenomenon have enlarged its meaning to include a cell-cycle point from which arrested cells that are allowed to subsequently grow will now form a synchronized culture. The original paper has been cited in thousands of papers, as have many subsequent papers on this phenomenon. But this success at citation does not begin to measure the true impact of the paper. The restriction point has entered that rarified realm of acceptance where no reference is needed, just as today one does not have to cite Watson/Crick when discussing DNA structure or activity. Thus, vast numbers of papers that report cells to cease growing and increase the number of cells with a G1-phase amount of DNA, describe those cells as being

[20] Fleck 1979, p. 27.
[21] Pardee 1974.

arrested at the "restriction point." All papers that report cells being arrested "in G1 phase", or "in G1/G0", or in "G0" are examples of arrest at a restriction point.

Although the notion of a restriction point is now over 40 years old, theoretical and experimental arguments and analyses have been presented that point out that the restriction point does not exist.[22] One may rightly ask how can we know that these arguments are correct? Of course, it is not possible to argue for the absolute truth of these contrarian ideas. But what is clear is that none of the ideas critical of the restriction point concept (and related ideas) has ever been refuted, challenged, disproven, contradicted, or even argued against. Rather, these ideas critical of the restriction point have been generally ignored. I will not review and restate arguments that have been made in numerous papers and supported by numerous experiments; I leave it to the readers of this article to investigate the prior publications. Rather, given that the restriction point is an anthropomorphic construct with a problematic provenance, the important object of the discussion here will be to explore why the restriction point persists as a phenomenon, why it is not critically examined, why it persists as a method to "synchronize" cells, and why it persists as a widely accepted element of cell-cycle control.

The restriction point was proposed to exist at a time when the G1 phase was believed to be the location of the key controlling elements of the cell cycle. This concept was based on numerous papers showing that the G1 phase was the most variable phase, and that the longer a cell's interdivision time, the longer the G1 phase.[23] The simple interpretation developed from this general observation was that the faster a cell could complete its G1-phase control functions, the faster a cell would pass through the division cycle. Slow passage through G1 phase produced a slow growing cell, and fast passage through G1 phase produced a fast growing cell.

Within this intellectual milieu the restriction point fit well as the first identified element in the G1-phase control system. There were other positive aspects of the restriction point model that led to its ready

[22] Cooper 1987b; 1998c; 2002; 2003a; 2003b; 2004a; 2004b; Cooper *et al.* 2006; Cooper, Gonzalez-Hernandez 2009.

[23] Cooper 1979; 1998b.

acceptance. On a scientific and applied level, having a single unique "restriction point" made it conceivable to be able to control cell growth (e.g. cancer cell growth) by regulating passage through the singular "restriction point."

Some particularly sociological and psychological factors also helped. At the time of the proposal of the restriction point Arthur Pardee was famous as a biochemist, bacterial physiologist, bacterial geneticist, and molecular biologist. He had participated in a number of famous discoveries such as the mechanism of feedback inhibition and the pattern of control of enzyme synthesis. He was one of the authors, along with Jaques Monod and Francois Jacob, on the famous PaJaMo paper about the nature of enzyme regulation. When Pardee proposed the restriction point, his well-deserved fame contributed to the ready acceptance of the restriction point proposal. It should also be considered that the logical organization of the original restriction point proposal, along with a rigorous style of analysis that was borrowed from bacterial genetics, led to the immediate acceptance by cell biologists of the restriction point. One should not fault Pardee for this immediate and uncritical incorporation of the restriction point into the canon of cell-cycle-control phenomena. It was the combination of the well-known abilities of Pardee along with the seductive aspect of the discovery of a unique control point that led to the acceptance of the restriction point. The fame of Pardee, through no fault of his own, allowed many in the field of cell--cycle studies to accept Pardee's work without critical analysis. It was only many years later that any critique of the restriction point was presented.[24]

In retrospect, the restriction point phenomenon was interpreted in a completely different way on the basis of experiments with bacteria carried out a few years earlier.[25] The postulated bacterial restriction point(s) were shown to be a result of leakage and not due to any biologically existing "restriction point." Besides experimental work undermining the original proposal of two bacterial restriction points (although they were not called "restriction points"), criteria were proposed for the identification of such restriction points.[26] To briefly recapitulate

[24] Cooper 2003b.
[25] Cooper 1974; Cooper, Weusthoff 1971.
[26] Cooper 1974.

the bacterial analysis, it was proposed that the restriction point is a result of leakage during growth inhibition. Given that no inhibition protocol is perfect, cells closer to the start of S phase will initiate S phase even during a period of inhibition of mass increase. That is because cells closer to S phase require less of additional synthesis to reach some proposed initiation mass or trigger amount in order to initiate S phase. Cells further from S phase require more accumulation during the inhibition period. Experiments with bacteria showed that as the degree of inhibition was varied continuously over a wide range, there was a continuous variation in the fraction of cells able to initiate S phase. Thus, either there were an infinite number of "restriction points" or the restriction point phenomenon was due to leakage.

One of the most fundamental problems when explaining an experimental result with a general model is that if only one possibility is presented or considered, it easily appears as if the given explanation is the only explanation. In contrast, if a particular experiment is presented as trying to decide between two different models, at least one or the other could be excluded as being less acceptable as an explanation of the experimental results. Because the bacterial experiments were not widely known, particularly among researchers studying eukaryotic cells, the relationship of the critique of bacterial restriction points to the eukaryotic restriction point proposal went unnoticed.

Thus we see an application of Fleck's first dictum, that a contradiction to the system appears unthinkable. At a more practical level of scientific thinking, it is not that alternatives are truly "unthinkable" – as all of the alternative ideas are able to be verbalized and visualized without much trouble – but rather that the satisfactory and immediate fit of the restriction point model within the then current and dominant view of G1-phase control of the cell cycle did not allow further exploration of alternatives. In a sense, the initial proposal blinded researchers to alternative explanations. In this sense, the alternative ideas were invisible, and thus unthinkable. The initial "fit" of the restriction point concept to the early data excluded the search for alternative explanations. If the bacterial model were well known (which it wasn't), then further experiments might have been performed (e.g., varying conditions of starvation, growing cells in a wide range of serum concentrations, checking for leakage in growth arrest and mass accumulation, etc.) that could have led to a critical examination of the restriction point model.

One of the ironies of the history of the restriction point in animal cells is that the original postulation of the restriction point emphasized the conclusion that the restriction point is unique. It was the uniqueness of the restriction point (i.e., different arrest conditions arrested cells at the same point) that gave the original postulation its great power. Today, no matter what cells are being studied, when "arrest at a restriction point" is proposed to occur, it is merely assumed that it is the unique "restriction point" proposed by Pardee that is the point at which these cells are now arrested. Whether the cells are aardvark cells or zebra cells, there is no further analysis to demonstrate that one particular restriction point is the same as the restriction point in other cells.

In any case, following the proposal of the restriction point there were many extensions of the restriction point hypothesis. A specific isoleucine restriction point was found, and other restriction points were reported to exist.[27] Of course, none of these findings were ever put in terms of weakening the restriction point hypothesis. The idea might have been that if the world loved and applauded one restriction point, then the world would love other restriction points just as well. Of course the multiplicity of such points should have been taken as an indication that the bacterial model is a better explanation of the restriction point phenomenon and that there was, in actuality, no restriction point. The multiplicity of restriction points would thus be explained as being related to the relative "leakage" associated with each type of arrest condition.

This multiplicity of restriction points fits in with Fleck's second rule, that "… what does not fit into the system remains unseen." It is not that the proliferation of restriction points was not seen, but it was not seen as a contradiction to the basic idea of a unique restriction point. If there are many restriction points, then any one experiment describing arrested cells being at a "restriction point" should note which one of the many points the restriction occurs. Thus the third proposal is also followed here, where the problems with the method are kept secret and ignored.

An even more egregious problem was evident in the original Pardee paper where the cells released from growth arrest were actually known and reported to be unsynchronized. This was evident from the very broad time of initiation of S phases upon re-growth of cells. This

[27] Allen, Moskowitz 1978a; 1978b; Chen, Wang 1984; Wynford-Thomas *et al.* 1985.

phenomenon has disappeared from consideration. Thus the very basic experiments that led to the original proposal of the restriction point were not supportive of the restriction point idea.

The fourth proposal, that "…laborious efforts are made to explain an exception in terms that do not contradict the system…" is evident in explanations of why cells described as "synchronized" do not exhibit synchronized divisions or even synchronized patterns of DNA contents. This troubling experimental fact is dismissed with the explanation that one would not expect to see discreet synchronous divisions because of the variability of interdivision times of mammalian or eukaryotic cells. Recent experiments from the laboratory of Charles Helmstetter[28] on cells synchronized with the eukaryotic membrane-elution method ("baby machine") show that this proposal is inadequate and unsatisfactory. Mammalian cells can be synchronized by selection to produce a culture that exhibits a number of clear synchronized divisions (Fig. 2).

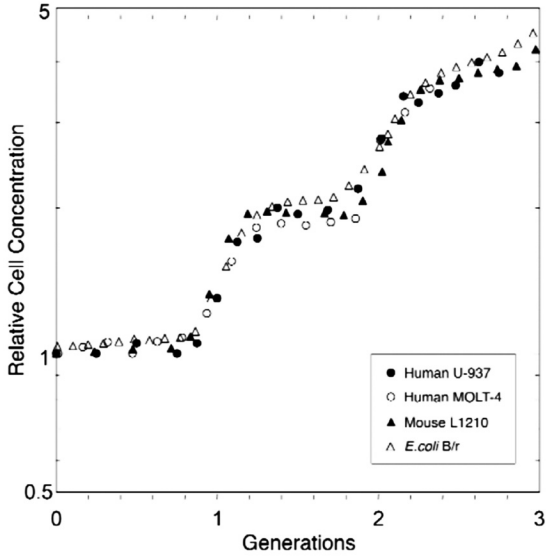

Fig. 2. Synchronized divisions of three different mammalian cell lines and bacteria. The absolute times for each cell type varies, but the experimental results are normalized to generation time so that the synchrony curves overlap (from Helmstetter *et al.* 2003, p. 43, fig. 2).

[28] Thornton, Eward, Helmstetter 2002; Cooper 2002b; Helmstetter *et al.* 2003.

It is far better to conclude from the absence of synchronized divisions or the absence of synchronized passage through DNA patterns of the cell cycle that the cells are not synchronized and the cells are not arrested at a restriction point.

7. On the Rate Change Point in Fission Yeast

A recent critical examination of the Rate Change Point (RCP) in fission yeast (*Schizosaccharomyces pombe*) provides a telling example. The RCP is a point in mid-cell-cycle where there is observed to be a change in the growth rate of cell. The RCP was proposed to exist by experiments performed by Paul Nurse (later to become a Nobel Laureate) and Murdoch Mitchison (recognized as the founding father of cell cycle analysis of fission yeast) based on microscopic analysis of the growth of cells. Suffice it to note that the RCP has been cited in an enormous number of papers and is believed to exist in fission yeast with essentially no published critical analysis of this phenomenon.[29]

A paper published by Stephan Baumgärtner and Iva M. Tolić-Nørrelykke[30] examined a large number of cells and proposed, again, the existence of a RCP. However, when the actual data of Baumgärtner and Tolić-Norrelyke were re-examined, it was clear that there was absolutely no evidence for a Rate Change Point.[31] This critical re-examination of the data supporting an RCP showed that a combination of flawed plotting (rectangular plot rather than semi-logarithmic plot) and the aggregation of results from different cells gave the incorrect conclusion supporting the existence of a Rate Change Point.

8. On Cell-Cycle Dependent Gene Expression

The study of how cells pass through the division cycle is a central activity of current cell biology. The widely-accepted model of the eukaryotic cell cycle is that cells express numerous genes at specific points

[29] Mitchison, Nurse 1985.
[30] Baumgärtner, Nørrelykke 2009.
[31] Cooper 2013.

in the cell cycle. Microarray experiments on human cells,[32] *S. cerevisiae*,[33] *S. pombe*,[34] as well as prokaryotes such as *Caulobacter*,[35] have led to the proposal that there are sequential peaks of expression of numerous genes at different times during the cell cycle.

There have been criticisms of the current model based on re-examinations of published data,[36] experiments on growing cells,[37] problems with the logic of the current model,[38] and problems with experimental approaches to studying the cell cycle.[39] Furthermore, even if mRNAs were preferentially expressed at specific times during the cell cycle, such expression can only lead to negligible changes in protein level during the cell cycle.[40] The problem is further exacerbated by the use of normalization of the original data which obscures the often small changes in mRNA variation during the cell cycle.[41]

The problem of what cellular element initiates the expression of a gene at a particular time and what cellular element initiates the expression of that control element has rarely been considered.[42] At the other end of cyclical expression, expression must cease at a particular time and there must be additional controls affecting the length of the initiation stimulus. This problem has been termed the "Russian doll" problem as the existence of a specific time of gene expression, as well as a time of cessation of gene expression during the cell cycle, leads to an infinite regression of initiations and cessations of initiations.[43]

This is one more application of the ideas of Fleck to the persistence, over many years, of an idea that is incorrect.

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[32] Cho *et al.* 2001.

[33] Spellman *et al.* 1998.

[34] Oliva *et al.* 2005; Peng *et al.* 2005; Rustici *et al.* 2004.

[35] Laub *et al.* 2000.

[36] Shedden, Cooper 2002b; 2002c.

[37] Cooper *et al.* 2007.

[38] Cooper 2012.

[39] Cooper 1998c; 2002a; 2002c; 2003a; 2003b; 2004a; 2004b; Cooper *et al.* 2006; Cooper, Chen, Ravi 2008; Cooper, Gonzalez-Hernandez 2009.

[40] Cooper *et al.* 2007.

[41] Cooper 2015.

[42] Cooper *et al.* 2007; Cooper 2012.

[43] Cooper 2012.

9. Thought Collectives and the Tenacity of Scientific Opinion

The other major conceptual contribution of Fleck is the concept of a "thought collective" (*Denkkollektiv*) or a "thought community" (*Denkgemeinschaft*). A thought collective is not related to an enforced belief system, but is rather a descriptive term describing the common views held voluntarily by a group of scientists regarding the fundamental beliefs of the group.

It is the thought collective that may be considered most closely related to the "paradigm" model of Thomas Kuhn. A paradigm that describes or regulates a particular field of study is the belief system within which "normal" science proceeds. New ideas are added to the paradigm and the paradigm is enlarged over time. But there is no change in the basic paradigm stemming from these new ideas. Revolutions in science occur, according to Kuhn, when the then current paradigm is unable to account for results that challenge the basic paradigm.

Thus a Kuhnian paradigm is essentially conservative, as it conserves the foundational and fundamental belief systems of the scientific group. Similarly, Fleck's thought collective is conservative because only by keeping ideas relatively invariant and constant is communication between its members facilitated. If the ideas of a scientific field were always in flux, communication would be both difficult and confusing. But it is this conservative aspect that prevents critical ideas that undermine the current belief system from being given a full hearing. As Fleck so presciently wrote (in *GDSF*):

> Besides such fortuitous and *transient* thought collectives there are *stable* or comparatively stable ones (italics in *GDSF*). These form particularly around organized social groups. If a large group exists long enough, the thought style becomes fixed and formal in structure. Practical performance then dominates over creative mood, which is reduced to a certain fixed level that is disciplined, uniform, and discreet. This is the situation in which contemporary science finds itself as a specific, thought-collective structure (*denkkollektives Gebilde*) (Fleck 1979, p. 103).

And later on Fleck continues:

> A special feeling of dependence therefore dominates all communication of thought within a collective. The general structure of a thought collective entails that *the communication of thoughts within a collective, irrespective of content or logical justification, should lead for sociological reasons to the corroboration of the thought structure* (*Denkgebilde*) (italics in *GDSF*; Fleck 1979, p. 106).

The restriction point is an idea that illustrates, in a clear fashion, the dominance of collective belief over experimental evidence. As has been pointed out before, the easy acceptance of a particular belief system allows new work to be readily described, readily assimilated and readily applauded by the collective group of scientists that share the core beliefs of the group. That the restriction point, based on experiments that should have had an alternative explanation, and which appears to be a concept that needs expulsion from the current view of the cell cycle, maintains such a hold on the field is a wonderful example of how a collective thought of the group prevents an alteration of the basic ideas of the group.

10. Lessons from Ludwik Fleck

As one can see, the ideas of Ludwik Fleck are not specific to some particular field. Rather, Fleck's ideas apply across an entire spectrum of thought processes where there is a group aspect to the intellectual process. As ideas become ingrained within the group they take on a life of their own. The origins of particular ideas are forgotten. Problems with the ideas are overlooked. New and uncomfortable ideas are not received easily by the group because of the quite wrenching effect it might have on the cohesive thought processes of the group.

If the only application of Fleck's ideas were to the area or phenomena discussed here, i.e. the restriction point and the RCP, then the ideas of Fleck would have a very narrow and limited application. But over the years I have heard many researchers bemoan the same problem that I have discussed here as related to a particular idea within their field. Thus one may suspect that Fleck's ideas have a wider application, and it is probable that others may take heart from the ideas presented here.

It is just part of the human condition and human thought. It is not that one has not tried hard enough, or not worked hard enough, or not published enough. One must just acknowledge the conservative nature of thought structures. They do not change readily because if they did, we would have chaos. But on the other hand, the result of stability is sometimes inertia and immobility. And we must always be wary of stability that prevents new and even better ideas from displacing the current and comfortable ideas of the thought collective.

11. Closing thoughts

It is not the purpose of this discussion to prove that the widely accepted and widely used restriction point concept is wrong, or that the rate change point does not exist, or that cycle-dependent gene expression is a problematic proposal. That has been done in other papers.[44] The purpose of this discussion is simply to show that Ludwik Fleck has codified various ideas as to why incorrect ideas persist and are maintained by a group or collective consciousness. It is hoped that these ideas are at a minimum interesting, and perhaps even helpful and inspiring.

It should also be noted that a number of works on Ludwik Fleck have been published and should be consulted for further information on this original thinker.[45]

12. Acknowledgements

Dr. Lawrence Sturman was instrumental in bringing me the work of Ludwik Fleck. Bernard Banet was helpful in understanding the life and thought of Ludwik Fleck. I thank Michael Kokowski for his help in improving this paper. Comments may be sent to cooper@umich.edu.

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[44] Cooper 1979; 1981; 1987a; 1987b; 1991; 1998a; 2000; 2002a; 2003b; 2004a; 2004b; 2005; 2012; 2013; Cooper *et. al.* 2006; Cooper, Chen, Ravi 2008.

[45] For example: Schnelle 1983; Schnelle, Cohen 1986; Löwy (ed.) 1990; 2000; Egloff (ed.) 2005; The Ludwik Fleck Center 2005–2011; Leszczyńska 2006; 2009; Sady 2012; Allen 2014; Kokowski 2015; Płonka-Syroka, Jarnicki, Balicki (eds.) 2015; Jarnicki 2015; 2016; Conde, Salomon (eds.) 2016.

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