Journal of the History of Biology (2009) 42:495–527
DOI 10.1007/s10739-008-9169-5

The Laboratory Technology of Discrete Molecular Separation: The Historical Development of Gel Electrophoresis and the Material Epistemology of Biomolecular Science, 1945–1970

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Abstract. Preparative and analytical methods developed by separation scientists have played an important role in the history of molecular biology. One such early method is gel electrophoresis, a technique that uses various types of gel as its supporting medium to separate charged molecules based on size and other properties. Historians of science, however, have only recently begun to pay closer attention to this material epistemological dimension of biomolecular science. This paper substantiates the historiographical thread that explores the relationship between modern laboratory practice and the production of scientific knowledge. It traces the historical development of gel electrophoresis from the mid-1940s to the mid-1960s, with careful attention to the interplay between technical developments and disciplinary shifts, especially the rise of molecular biology in this time-frame. Claiming that the early 1950s marked a decisive shift in the evolution of electrophoretic methods from moving boundary to zone electrophoresis, I reconstruct various trajectories in which scientists such as Oliver Smithies sought out the most desirable solid supporting medium for electrophoretic instrumentation. Biomolecular knowledge, I argue, emerged in part from this process of seeking the most appropriate supporting medium that allowed for discrete molecular separation and visualization. The early 1950s, therefore, marked not only an important turning point in the history of separation science, but also a transformative moment in the history of the life sciences as the growth of molecular biology depended in part on the epistemological access to the molecular realm available through these evolving technologies.

Keywords: Arne Tiselius, electrophoresis, experimental practice, laboratory, material epistemology, molecular biology, Oliver Smithies

Introduction

Gel electrophoresis, a technique that separates charged molecules on a gel platform under the influence of an electric field, enables scientists to work with biological substances that they cannot normally see without the aid of an external tool. Today, the method is carried out widely in the laboratories of genetics, biochemistry, biomedical science, and many other allied fields of molecular biology. Yet, given its importance in biomolecular studies, its historical development has hitherto received limited attention from historians of science and technology.[1] Most of those who have written about its history are themselves experts in separation science. As a result, these narratives have often been written for specialized scientific journals, in broad strokes, and with emphases that highlight the author's own research orientation or contribution to some aspects of electrophoretic instrumentation.[2] This paper, then, attempts to offer a more nuanced and complex understanding of the historical development of gel electrophoresis from the 1940s to the 1960s by bringing into better visibility the kind of non-linear, multi-faceted story that the primary sources themselves reveal.

A valuable entry point to this story is an article published in 1988 by the historian of science Lily Kay on the history of the solution-based electrophoretic apparatus first developed in the 1930s by Arne Tiselius, the 1948 Chemistry Nobel Laureate.[3] In that piece, however, Kay's goal was to substantiate her argument, articulated more fully in her *Molecular Vision of Life*, that the Rockefeller Foundation had played a significant role in the rise of molecular biology in the 1930s and 1940s.[4] She showed that the Rockefeller Foundation initiated the "molecularization" of biology by encouraging the study of vital processes through

[1] For example, Morange, 1998, a rare work of synthesis in the historiography of molecular biology, only touches on the development of the early electrophoretic apparatus by Arne Tiselius in the 1930s and then briefly mentions electrophoresis again in a later part of the book in the context of genetic engineering, but does not address how this particular laboratory instrumentation evolved in between, especially when electrophoretic instrumentation looked very different at those two points in time. Given the importance of electrophoresis on a solid supporting medium in the research of molecular genetics and various biomedical sciences, I was surprised to find that its historical development has received so little interest from historians of biology in particular. See e.g. the essays in de Chadarevian and Kamminga, 1998; Gaudillière and Rheinberger, 2004.

[2] See e.g. Bier, 1959; Kekwick and Pedersen, 1974; Grabar, 1980; Hjertén, 1988, 2002, 2003; Vesterberg, 1989, 1993; Lewontin, 1991; Putnam, 1993; Rilbe (Stockholm), 1995; Smithies, 1995; Virtanen et al., 1995; Kyle and Shampo, 2005; and Rocco, 2005.

[3] Kay, 1988. On Tiselius' influential work, see Tiselius, 1937.

[4] Kay, 1993.

physical, chemical, and mathematical techniques.[5] According to Kay, the Rockefeller Foundation's financial assistance in building the Tiselius electrophoretic apparatus at selective prestigious American research institutions like Princeton, Columbia, Cornell, Harvard, Yale, and Stanford, among others, represents one of the ways in which the birth of molecular biology was galvanized by the importation of skills, both technical and cognitive, from the physical sciences in the 1930s and 1940s.[6] In other words, Kay zeroed in on the historical development of the Tiselius apparatus and inferred from it the larger intellectual and institutional patterns of the life sciences during those two decades.

My project builds on Kay's study in two ways: in terms of chronology and in terms of extending the recently growing historiographical thread that explores the relationship between modern laboratory practice and the production of scientific knowledge.[7] In contrast to her work, however, this paper does not concentrate on one specific scientific instrument, but brings together various paths that scientists had taken in order to improve the laboratory operation of gel electrophoresis.

[5] Like most of the literature in the history of biology, I use the terms "molecularization" and "molecular revolution" interchangeably in this paper to refer to the increasing focus of scientific studies centered on small and large molecules alike over the course of the twentieth century, especially in the life sciences. See Kay, 1993; Olby, 1990. Susan Wright, 1994, has introduces the term "molecular politics" to refer to the debates stimulated by genetic engineering in the 1970s. And Hans-Jörg Rheinberger, 1995, uses the term "molecularization" in a slightly different way to refer more specifically to the increasing role of genetics in medicine.

[6] On the importation of skills from the physical sciences to the life sciences, see also Cairns, Stent, and Watson, 1966; Fleming, 1968; Yoxen, 1979; Abir-Am, 1982; Fuerst, 1982; Kay, 1985; and Keller, 1990. On the other side of the debate about the role of physical science in biology, see Schaffner, 1974; Judson, 1980. By redirecting to attention of historians of science to Europe more generally and France in particular, Jean-Paul Gaudillière, 2002, demonstrates that the physical sciences were not the sole "colonizer" of the life sciences, but that *medical* research policy was equally, if not more, significant in the orientation of biology towards a molecular vision of life. On the important role of medicine in the history of molecular biology, see also de Chadarevian and Kamminga, 1998. Abir-Am first described molecular biology as the result of the physical sciences' "colonization" of the life sciences: see Abir-Am, 1982, p. 350.

[7] On the growing body of literature that explores the relationship between laboratory culture and the production of biological knowledge, see Elzen, 1986; Kay, 1988, 1993; Zallen, 1992; Rabinow, 1996; Lenoir, 1997, esp. chap. 9; Rasmussen, 1997; Rheinberger, 1997, 2001; de Chadarevian and Kamminga, 1998; Creager, 2002, 2006; Kohler, 2002, chaps. 4 and 5; Gaudillière and Rheinberger, 2004; Max Planck Institute Workshop, 2006; and Max Planck Institute Conference, 2006. See also Pickering, 1995; Baigrie, 1996; Galison, 1997; Cetina, 1999; Baird, 2004; and de Chadarevian and Hopwood, 2004. Almost all of these works and my analysis concentrate solely on the development of science in Europe and North America.

Accordingly, I do not frame my analysis around a single research problem in biomolecular science. Instead, what I attempt to flesh out is the larger historical transformation from the Tiselius free-solution equipment to contemporary gel electrophoresis – a historical transformation from which we can draw insights concerning the nature of scientific instrumentation and knowledge acquisition. Thus, a central tenet of my study is to probe, quoting Davis Baird, "how the material dimensions of science and technology do epistemological work."[8]

As a result of our diverging chronological focus and approaches to the topic of electrophoresis, Kay and I also arrive at very different interpretations of the role of the Rockefeller Foundation in the history of molecular biology. It is interesting to note, for instance, that Tiselius' initial interest in building his electrophoretic apparatus was accompanied by his interest in separating blood serum proteins.[9] Yet, in Kay's analysis, the Rockefeller Foundation's lavish financial support of the development of the early Tiselius electrophoretic apparatus and in the wartime research projects in immunochemistry (especially at Caltech) are treated as seemingly unrelated, however profound, historical influences on the life sciences, except from an institutional point of view. However, as I will demonstrate with more nuance in one of the following sections below, when we turn to the *material epistemology* of science, paying closer attention to the practical motivations behind why scientists used their available tools and conducted their experiments the way they did, it becomes evident that not only did the evolution of electrophoresis intersect with immunochemical studies in significant ways around the 1950s, but the Rockefeller Foundation's influence on the life sciences had also functioned at a level deeper than institutional and funding patterns.[10]

[8] Baird, 2004, p. 11.

[9] See Tiselius, 1937. For the importance of blood serum research in biomedicine during the 1940s and the immediate postwar years, see Kay, 1989, 1993; Creager, 1998; de Chadarevian, 1998; and Gaudillière, 2002. These works are important because they demonstrate how trajectories of scientific research are often shaped by the larger social and political environment of a particular historical moment.

[10] Although in "Molecular Biology and Pauling's Immunochemistry" (1989) and *Molecular Vision of Life* (1993), Kay emphasizes that her discussion centers on both the institutional and intellectual trends of the life sciences in the 1930s and 1940s, for the "intellectual" part of her story, she only explores how the various research projects in serological genetics and immunochemistry at Caltech were connected to the Rockefeller Foundation's program in molecular biology through the *general idea* of "large protein molecules." She does not explicate this connection from the perspective of laboratory practice, which to me is an important aspect of any intellectual exercise in biomolecular science, so I have purposefully left out the word "intellectual" when referring to her argument in this sentence.

To be sure, it should be emphasized that, rather than refuting Kay and others' assessment of the role the Rockefeller Foundation played in the history of molecular biology, my more immediate goal is to direct historians' attention toward an under-acknowledged layer of the historical processes through which biomolecular knowledge was shaped and reshaped. To bring in an even more poignant example, the particular distinction between the *moving boundary* method that characterizes the early Tiselius apparatus and the *zone* method that characterizes the later gel electrophoretic systems falls outside of Kay's interest but plays a central role in my historical argument. Whereas the former electrophoretic procedure does not separate molecules into absolute "zones," the latter gives complete molecular segregation. Hence, with the moving boundary method in the 1930s and 1940s, scientists were still unable to visualize fully separated molecules after performing electrophoresis: they had to rely on the difference between the non-overlapping and the overlapping regions on the migration path of the molecules in order to determine their properties quantitatively.

The decisive shift in the evolution of electrophoretic methods from moving boundary to zone electrophoresis that occurred around 1950 coalesced from the efforts of scientists in different disciplines, from physical chemistry to immunology, as they sought out the most desirable stabilizing medium for electrophoretic instrumentation. Between the mid-1940s and late 1960s, researchers tried, among other substances, silica jelly, agar jelly, filter paper, pectin gel, cellulose acetate, starch grain, starch gel, and eventually polyacrylamide gel, which quickly became the staple medium for gel electrophoresis due to its functional versatility. Over the course of this period, scientists also promoted new ways of conceptualizing the electrophoretic system itself, such as "zone electrophoresis," "molecular-sieve electrophoresis," and "two-dimensional electrophoresis." Above all, at any given stage in this period, the reciprocal influence between experimental practice and scientific ideas defined both the limitations and possibilities of biomolecular studies, and, conversely, both the constraints and potentials of biomolecular investigation framed the interplay between its laboratory instrumentation and scientific understanding.

My paper lays out several separate historical strands of electrophoresis development, and shows how these trajectories came together by the 1960s. I argue that modern biomolecular knowledge, insofar as it frequently relies on discrete molecular separation and visualization, emerged in part from the broader historical process of seeking the most appropriate supporting medium for gel electrophoresis. The early 1950s

marked not only an important turning point in the history of separation science, but also a critical juncture in the history of the life sciences as the growth of molecular biology depended largely on the epistemological access to the molecular realm available through these evolving laboratory technologies. While the discovery of the DNA structure, the breaking of the genetic code, and the statement of the central dogma received headline attention during the forging of the ''molecular revolution'' in the 1950s and 1960s, the development of gel electrophoresis took on a background seat where it slowly, silently, but substantially transformed the possible horizon of biological research.

Early Developments in Discrete Molecular Separation after the Tiselius Apparatus

Already in the mid-1940s, knowing what the early electrophoretic apparatus developed by Tiselius was able to accomplish, scientists studying the chemical and physical properties of amino acids recognized the instrument's inability to offer discrete molecular visualization. Accordingly, several physical chemists and biochemists proposed potential adjustments that would overcome this major limitation of the Tiselius apparatus. For instance, around this time, A. H. Gordon, working with R. Consden and Archer J. P. Martin at the Wool Industries Research Association in Leeds, England, attempted to develop a method of ionophoresis through which complete separations of amino acids and lower peptides could be obtained in a slab of silica jelly.[11] Normally, in the absence of compartment diaphragms, the presence of a density gradient would prevent convection of the electrolyte under the influence of an electric field. In the Tiselius apparatus, they correctly observed, because ''the density gradient is provided by the substances under investigation, complete separation into separate bands cannot be obtained.''[12] In order to deal with this problem, they proposed using a rectangular slab of silica jelly that was swamped with electrolyte throughout so that ''the substances being analyzed can move independently and separate into discrete bands.'' They continued: ''Since the movement of the bands is proportional to the time of running, and their widening by diffusion is only proportional to the square

[11] The difference between ''ionophoresis'' and ''electrophoresis'' will be discussed further in a later part of this paper. For convenience, the reader can think of the former as specifically referring to the separation of small molecules (e.g. nucleic acids).

[12] Consden, Gordon, and Martin, 1946, p. 33.

root of the time, substances having relatively small differences in mobility can be separated from one another."[13]

Previous experimental methods would not allow two substances with small differences in mobility at a given pH to be separated in a diaphragm cell.[14] On the other hand, with their newly proposed method of using silica jelly as an inert supporting medium, which eliminated the necessity of a diaphragm altogether, Gordon's research team was able to separate glutamic acid from aspartic acid at neutrality by taking advantage of their small difference in ion mobility. Similarly, as another example, they also reported their successful separation of a wool hydrolysate into basic, neutral, and acidic fractions at neutral pH.[15] Gordon, Consden, and Martin's work on ionophoresis in silica jelly, therefore, exemplifies a two-fold process by which chemical scientists searched for a stabilizing medium that would allow amino acids to be separated into discrete bands, while simultaneously relying on their prior awareness of the laboratory constraints associated with Tiselius' well-known free solution technique. In this instance, the Tiselius instrument functioned as a material entity that not only carried scientific knowledge, but also facilitated the possible emergence of new laboratory approaches to biomolecular science.

This epistemic property of the Tiselius apparatus quickly compelled Gordon to apply the same underlying laboratory principle that he had used for amino-acids separation to protein separation. In September 1949, with B. Keil and K. Sebesta in the Department of Organic Chemical Technology at Technical University in Prague, Gordon published a brief article in *Nature* that opened with the following remark: "The ease with which ionophoretic separations of amino-acids and lower peptides can be carried out in a rectangular slab of silica jelly suggested that a similar technique might be useful for separating the proteins."[16] They soon found that silica jelly was an inappropriate substance for column stabilization, because it did not allow macromolecules like hemoglobin to migrate freely when subjected to an electromotive force. However, they did discover that "a 1 per cent agar jelly, on the other hand, was found to allow the protein to migrate." After testing with various colored proteins, they reported that agar jelly

[13] Consden, Gordon, and Martin, 1946, p. 33.

[14] Martin and Synge, 1945.

[15] Consden and Gordon, 1950. In order to appreciate better the place of this particular study in a longer timeframe in which the authors worked as partners throughout the 1940s, see also Consden et al., 1944, 1946, 1947, 1948, 1949.

[16] Gordon et al., 1949, p. 498.

could in fact "permit the migration of molecules as large as that of haemocyanin (mol. Wt. 8,500,000)."[17] In addition to hemoglobin and haemocyanin, they were able to electrophorese other large molecules including ferritin, pepsin, egg white proteins, and human plasma proteins.[18] Gordon's switch from silica jelly to agar jelly as the main solid supporting medium for molecular separation brings to light, once again, the ways in which scientific instrumentation mediates the production of new laboratory knowledge based on the ideas already encapsulated in the existing scientific tools.

Even though the treatment of agar jelly as the inert substance for electrophoretic stabilization provided absolute separation and visualization of macromolecules, this technique brought with it an inherent disadvantage. As noted by Gordon's research team, "the chief disadvantage involved in the use of agar is the difficulty of its complete removal from the substances under investigation at the end of the experiment."[19] The difficulty with taking away entirely the agar content (itself mobile under the influence of an electric field) from the substances being analyzed suggests that this method would be unsuitable for preparative purposes, if perhaps a little more ideal for analytic uses. Still, the issue of agar contamination shows that existing laboratory practice (e.g., ionophoresis with silica jelly) not only initiates the possible emergence of a new scientific approach (e.g., electrophoresis with agar jelly); besides this advantage, it also generates a whole set of unprecedented practical problems that would become associated with the new approach. The problem of agar contamination was not really a problem at all until researchers, based on their experience from using silica jelly for the ionophoresis of amino acids, started to experiment with agar jelly for the electrophoresis of large molecules.

Arne Tiselius, the Filter Paper Method, and Zonal Electrophoresis

While presenting on the topic of electrophoresis as part of his 1948 Nobel lecture, Arne Tiselius did not refer to the term "zone electrophoresis," nor did he mention such a concept in passing.[20] But 2 years later, he coined "zone electrophoresis" in the title of an article that he published in *Acta Chemica Scandinavica*, footnoting it with the

[17] Gordon et al., 1949, p. 498.
[18] Gordon et al., 1950.
[19] Gordon et al., 1949, p. 499.
[20] Tiselius, 1964.

following statement: ''It seems practical to distinguish between 'boundary electrophoresis' as performed in the common moving boundary apparatus, and 'zone electrophoresis' where the migration of more or less completely separated zones is studied, usually by application of some immobilizing medium to prevent convection.''[21] In fact, no one in the scientific community used the phrase ''zone electrophoresis'' prior to the publication of this 1950 article: it did not, for example, appear in the series of articles that Gordon had written on the usage of silica and agar jelly as supporting media for the absolute separations of amino acids and proteins. Even though Gordon and his collaborators were obviously already thinking about the same notion of discrete biomolecular separation in the mid-1940s, and they indeed constantly used the word ''zone(s)'' all the way through the end of the 1940s, it was only after Tiselius' reference to it in the title of his 1950 article that the term ''zone electrophoresis'' started to gain wide currency among scientists studying the physical and chemical properties of macromolecules.

While Gordon and his collaborators experimented with agar jelly in the late 1940s, Arne Tiselius worked with other physical chemists and biochemists at his Institute of Biochemistry at the University of Uppsala to develop an adequate procedure of zonal electrophoresis using filter paper strips. One of the first partners with whom Tiselius tried using paper strips for the separation of serum proteins was H. D. Cremer. In 1950, Tiselius and Cremer identified two distinct advantages in this filter paper technique over Tiselius' earlier moving boundary method: (1) discrete protein zones could be visualized by staining the paper strip with bromphenol blue after separation; and (2) only 3–4 mg of protein were needed as opposed to the 200 mg required for the free solution procedure.[22] Soon, Henry Kunkel from the Rockefeller Institute for Medical Research in New York came to Uppsala and helped Tiselius to improve the filter paper method. Together, they minimized disturbing factors such as evaporation, heating, buffer concentration gradients, and pH changes in the electrode vessels to a significant degree. The collaboration with Kunkel resulted in Tiselius' first formal English publication of this simplified filter paper electrophoretic method.[23] Around 1950, apart from the work being carried out at Tiselius' Uppsala laboratory, a handful of other scientists had also begun

[21] Haglund and Tiselius, 1950, p. 957.

[22] Cremer and Tiselius, 1950.

[23] Kunkel and Tiselius, 1951.

looking into the electrophoresis of protein components with a filter paper support.[24]

Nonetheless, the term "zone electrophoresis" really gained popularity only after Tiselius had clarified its meaning in relation to his filter paper technique. On the one hand, he did acknowledge that even before receiving his Nobel Prize in Chemistry in 1948, scientists with different disciplinary background and research agendas, building on his earlier moving boundary apparatus, were already trying out a variety of supporting media in order to electrophorese molecules into absolute zones. On the other hand, Tiselius credited himself and his associates at the Uppsala Institute of Biochemistry entirely for "propos[ing] the term zone electrophoresis for the type of experiment in which a separation into zones is achieved."[25] With respect to the earlier studies on gel ionophoresis conducted under the direction of Gordon, Tiselius said that "Zone electrophoresis, particularly in gels, has also been called 'ionophoresis' as one of its first applications was with low molecular weight substances (amino acids, peptides), but as the zone methods now have found wide application also with protein and other large molecular weight material, this term does not seem adequate as a name for migration experiments in supporting media."[26] In other words, Tiselius' filter paper approach to macromolecular electrophoresis directly supported his consolidation of the neologism "zone electrophoresis," which rendered his own filter paper procedure as more favorable than the ones proposed by previous scientists.

Perhaps Tiselius had also overemphasized the importance of his filter paper method through the way he presented the rising popularity of zone electrophoresis around his time. After reviewing a series of historical attempts of molecular separation that employed different kinds of solid support, he correctly suggested that filter paper strips were one of the most recent and successful stabilizing media applied to zonal electrophoresis.[27] It was only with reference to this specific medium, however, that he mentioned its distinct advantage of "providing a micro-method and requires only a very simple apparatus."[28] Here, Tiselius failed to note explicitly that earlier methods, such as the one proposed by Gordon in which agar jelly was employed, also had the advantage of offering smaller, and thus more convenient, laboratory

[24] Wieland and Fischer, 1948; Turba and Enenkel, 1950; Durrum, 1950.

[25] Tiselius, 1953, p. 30. See also Arne Tiselius, "Introduction," in Bier, 1959, p. xviii.

[26] Tiselius and Flodin, 1953, p. 461.

[27] Tiselius, 1953, pp. 29–30.

[28] Tiselius, 1953, p. 30.

practices that would promote the wide usage of the procedure of electrophoresis in biomolecular studies in general. Certainly, in comparison to the electrophoretic instrument that he had built earlier, which spanned five feet in height and twenty feet in length, his filter paper apparatus was less complex and expensive to construct. Still, others' early attempts with ground glass wool, for instance, or Gordon's experimenting with agar jelly, also provided a simpler form of electrophoretic instrumentation.[29]

Additionally, much like filter-paper electrophoresis, Gordon's separation system that used agar gel as the main stabilizing material required a much lower concentration of the substance being studied than the amount necessary for operating the early Tiselius apparatus. Regardless of Tiselius' implicit or explicit intention when discussing zone electrophoresis around 1950, the filter paper method that he and his colleagues had come up with exemplified only one of the many ways by which the scientific community reacted to his early moving-boundary equipment. Henceforth, this five-foot tall apparatus acted simply as a laboratory carrier of scientific knowledge, prompting *many different* consequential experimental attempts that reshaped biomolecular science through its changing material dimension.

The Birth of Immuno-Electrophoresis: Unifying Immunochemistry and Gel Electrophoresis

Stamped with prestige throughout the late 1930s and the 1940s, the huge Tiselius apparatus stimulated a series of subsequent empirical endeavors to find a solid supporting medium suitable for the complete separation of biological molecules. By the early 1950s, these parallel pursuits converged in a distinct way that gave rise to a new laboratory practice in biomedical science called the ''immuno-electrophoretic method.'' The birth of this new technique indicates the significance of immunochemical studies in the evolution of electrophoretic instrumentation.[30]

Pierre Grabar and his student Curtis Williams at the Insitut Pasteur in Paris first introduced this method in a 1953 preliminary paper, ''Method Permitting the Combined Study of the Electrophoretic and Immunochemical Properties of a Mixture of Proteins: Applications to

[29] Coolidge, 1939.

[30] It is certainly true that in some respects, there are continuities from Tiselius's classic demonstration of his huge apparatus with which he separated serum proteins into alpha, beta, and gamma globulin.

Blood Serum,'' which they published in the French Journal *Biochimica et Biophysica Acta*.[31] Two years after this brief introductory report, a richer exposition of this technique appeared in the same journal, now with the term ''immuno-electrophoretic method'' included in the title. There Grabar and Williams summarized the procedure in the following way:

> Firstly, electrophoresis of the substance to be studied is carried out in a 1.5–2% agar gel in a veronal buffer solution of $\Gamma/2 = 0.05$ and with a drop in potential of 3–4 V/cm in the gel. Then the precipitating immune serum is diffused perpendicularly to the electrophoretic migration axis. Each constituent of the mixture studied gives an independent specific precipitation band, which can be distinguished owing to its immunological specificity and defined by its relative electrophoretic mobility.[32]

Subsequently, throughout the mid-1950s, Grabar and Williams wrote three extensive articles in the *Journal of Immunology* that discussed the various applications of the this new experimental design to the immunological study of serum proteins: the first described the general applications of the immuno-electrophoretic method to the study of human serum fractions; the second discussed the immuno-electrophoretic study of antiserum types and the distribution of their constituent antibodies; and the last focused on the employment of this instrumentation for understanding the nature of human γ-globulin.[33]

Yet, given its indubitable value, this powerful technique developed by Grabar and Williams represents nothing but a derivative, however creative it may be, of the various experimental attempts that came before it. First and foremost, as implied by the title of their short 1953 report, this method was a unification of gel electrophoresis and immunodiffusion analysis: the procedure, to rephrase the above quotation, comprised a primary step of electrophoresing the selected antigens on a gel medium, followed by a secondary step of introducing an immune serum or antiserum (monoclonal antibody) lateral to the direction of electrophoretic migration. The resulting visualized arcs reflected the precipitation of specific antibody-antigen binding complexes if present. Even Grabar and Williams stated themselves that their ''novel'' approach to the immunological study of serum components was just ''an analytic method combining zone electrophoresis in gelified

[31] Grabar and Williams, 1953.

[32] Grabar and Williams, 1955, p. 74.

[33] Williams and Grabar, 1955a, b, c.

media, described by Gordon et al., with immunochemical analysis in gels by a modification of [an earlier] method.''[34]

As such, bracketing for the moment the historical development of immunodiffusion analysis, which is outside the scope of this paper, the gel electrophoretic aspect of their ''immuno-electrophoretic method'' more specifically points to the considerable degree to which Grabar and Williams had relied on formerly established laboratory practices. On top of their regular citation and explicit borrowing of the agar electrophoretic system first developed by Gordon and his research associates, Grabar and Williams noted that ''the essential elements of the apparatus employed for immunoelectrophoretic analysis are the same as those used for ordinary paper electrophoresis.''[35] This statement does not merely imply that they were well aware of other contemporary scientists' use of filter paper strips as electrophoretic support; the statement more directly suggests that Grabar and Williams had correctly understood the similar underlying principle behind agar gel and filter paper electrophoreses. To put in more concrete terms, after recognizing the instrumental constraints of the early Tiselius apparatus, scientists had proceeded in many different ways to improve electrophoretic instrumentation in general, but these varying paths all shared one common goal: to achieve successful zonal separation with an appropriate solid support. Therefore, Grabar and Williams' reference to the ''ordinary paper electrophoresis'' strip when describing their own gelified apparatus astutely captures the ways in which different trajectories of molecular biomedical science intersected on the level of material epistemology in the 1950s.

The immuno-electrophoretic method depended on existing experimental systems and the conceptual tools associated with them, as one would expect, but the technology also inspired new ideas. For his part at least, Grabar quickly noted that the use of agar gels had one major disadvantage: ''the samples are usually introduced in the gel, mixed with melted agar, thus being heated to 40–45°C. Thus there is a constant danger of denaturing certain more sensitive protein components. A possible interaction of agar with some of the substances analysed cannot be excluded.''[36] Because of this defect, in a report that he co-authored with two other scientists working at the Medical Branch of the University of Texas, Wiktor W. Nowinski and Bruce D. Genereaux, they claimed that ''pectin seems to present certain advantages over agar'' as

[34] Williams and Grabar, 1955a, p. 158.

[35] Williams and Grabar, 1955a, p. 158.

[36] Grabar et al., 1956.

the main supporting medium for gel electrophoresis.[37] They found that "the use of pectin," for example, "has the advantage that the gel is prepared at room temperature and that the gelification can be more easily controlled."[38] The shift from using agar jelly to pectin jelly demonstrates the ways in which the development of the original immuno-electrophoretic method played a determinant role in motivating Grabar to consider other potential solid supporting media for zone electrophoresis.

In 1957, familiar with the early filter paper electrophoresis, Joachim Kohn, a pathologist at Queen Mary's Hospital in London, proposed an alternative supporting material for the electrophoresis of serum proteins – cellulose acetate. Using 20-cm long by 5-cm wide cellulose acetate microbiology filter strips, Kohn separated five serum protein fractions plus a pre-albumin (transthyretin) band in half the time required for regular filter paper electrophoresis. According to Kohn, the practical advantages of using this type of bacteriological membrane filter to prevent convection in zonal electrophoresis were mainly its "chemical purity, minimal absorption and hence absence of tailing; very neat separation and complete transparency both to visible and U.V. light, when cleared by immersion in a suitable fluid."[39]

In the same year that he proposed the idea of using cellulose acetate as an inert stabilizing material for zone electrophoresis, Kohn introduced the potential application of this bacteriological membrane filter to Grabar and Williams' immuno-electrophoretic method.[40] In the following year, 1958, Kohn presented a paper that discussed this new analytic procedure at the Sixth Colloquium on Protides of the Biological Fluids.[41] From the late 1950s throughout the early 1970s, Kohn published extensively on his newly invented technique by which Grabar and Williams' immuno-electrophoretic method was carried out on cellulose acetate membranes.[42] Kohn's development of cellulose acetate electrophoresis for immunological studies, much like Grabar's earlier shift from agar to pectin and Gordon's switch from silica jelly to agar jelly before that, illustrates the gradual historical process by which both the material practice of molecular science and the articulated ideas of molecular separation reciprocally transformed one another over time.

[37] Grabar et al., 1956, p. 430.

[38] Grabar et al., 1956, p. 430.

[39] Kohn, 1957a, p. 302. See also Kohn, 1958a.

[40] Kohn, 1957b.

[41] Kohn, 1959. See also Kohn, 1958b.

[42] Kohn, 1960a, b, 1967, 1968a, b, 1969, 1970, 1971; Consden and Kohn 1959.

Today, medical scientists more frequently use ''immunoglobulin electrophoresis,'' or maybe ''immuno-electrophoretic analysis,'' to refer to Grabar and Williams' method. However, its earliest designation ''immuno-electrophoretic *method*,'' first adopted in the mid-1950s, is worth keeping in mind in its own right, because the term squarely conveys its initial historical affiliations with the technological bases of molecular biomedical science. It was the specific merging of the then popular analytic method of immunochemistry with gel electrophoresis – characterized by zonal as opposed to moving boundary separation – that gave birth to immuno-electrophoresis, a laboratory routine in biomedicine today primarily used to detect the blood levels of three major immunoglobulins: Immunoglobulin M (IgM), G (IgG), and A (IgA).

The Conceptualization of Molecular-Sieve Electrophoresis

From the early free solution apparatus to the filter paper technique, Tiselius had contributed to the gradual dissemination of electrophoresis in both European and North American laboratories of diverse scientific disciplines in many crucial ways. The development and refinement of the ''immuno-electrophoretic method'' by scientists whose work touched on various aspects of immunology and protein studies, especially in the 1950s, was only one example of a trajectory of biomedical applications that it continues to have up to the present day. Around the same time when the possibility of immuno-electrophoresis was first conceived, both the term ''zone electrophoresis'' and its twin laboratory technique – filter paper electrophoresis – were already popular vocabulary and practice among those physical chemists, biochemists, and other biomedical scientists interested in the preparative and analytical studies of biomolecules.

There is no doubt that the effort and prestige of the Uppsala School of separation science played a decisive role in the popularization of both the concept of zone electrophoresis and the method of filter paper electrophoresis.[43] At the same time, the magnitude of influence of zone and filter paper electrophoreses in molecular biochemical studies rose sharply not only because they offered other scientists a new and useful perspective, but also because they allowed other scientists to come up with new biomolecular ideas and practices that appeared as their direct

[43] See, for example, Arne Tiselius, ''Introduction,'' in Bier, 1959, pp. xv–xx; Kekwick and Pedersen, 1974; Hjertén, 1988, 2002, 2003; Vesterberg, 1989, 1993; Putnam,1993.

descendents. Interestingly, the shift in attention from moving boundary to zone electrophoresis in the early 1950s, accompanied by the increasing acceptance of the filter paper approach to macromolecular electrophoresis, soon gave rise to an episode in the history of gel electrophoresis in which notable advancements in electrophoresis were made in North America, but less so in Europe. This period, spanning roughly from 1952 to 1962, began with Tiselius' studies on filter paper electrophoresis and ended in a full circle, however ironically, with the coinage of the term "molecular-sieve" electrophoresis by his student Stellan Hjertén at Uppsala; although the term was formally coined by someone from the Uppsala School, scientists working in North America, without question, contributed most significantly to its laboratory development.[44]

After Henry G. Kunkel, an immunologist at the Rockefeller Institute for Medical Research, returned to New York in the early 1950s from his visit to Uppsala where he had helped Tiselius to improve the filter paper technique, he immediately worked with his colleague Robert J. Slater to experiment with different types of supporting media for zone electrophoresis. They tried filter paper, potato starch, sea sand, ground glass, soft glass beads, and agar. For each substance, they determined the relative mobility of electroosmotic flow, a higher measure of which indicates that the buffer solution flows to the cathode with a speed *closer* to the speed by which the protein of interest migrates towards the anode under the influence of an electric field, thus making the protein more likely to remain stationary in the system and, accordingly, rendering the supporting medium less desirable for electrophoresis. They found that only potato starch had the low degree of electroosmotic flow comparable to that of filter paper. At the same time, Kunkel and Slater observed that "no significant adsorption was observed with the starch for any of a large group of proteins and peptides that were tested."[45] Because of its low adsorption of molecules in aqueous buffers, the starch system was found to have a major advantage over the filter paper apparatus. To be sure, Kunkel and Slater did acknowledge the main benefit that the filter paper method could offer but the starch method could not: "The filter paper system possessed the advantage of the extreme sensitivity and simplicity of the protein staining technic with

[44] Although I adopt the term "Uppsala School" in this paper, I am fully aware of the historiographic problems associated with the idea of "research schools" noted by historians of science. See, for example, the essays collected in Geison et al. 1992. One qualification for my usage of the term "Uppsala School" comes from it being an actor's category: see Hjertén, 2002.

[45] Kunkel and Slater, 1952, p. 42.

bromphenol blue. No success was achieved in adapting this to the starch.''[46] But they never took a step further and reconciled the different advantages (and disadvantages) associated with each medium.

It was not long before another scientist, with formal training in biochemistry, picked up where Kunkel and Slater had left off and consequently developed a gel electrophoretic system that had the additional ability to separate molecules based on size. This person was Oliver Smithies, then a researcher in the Connaught Medical Research Laboratory at the University of Toronto.[47] In the manner most of the earlier modifications of gel electrophoresis were first reported, Smithies initially submitted a short article to *Nature* on 8 December 1954 that briefly introduced ''a method of zone electrophoresis using starch *gel* as the supporting medium.''[48] The word ''gel'' is important because, as he explained later in his (more formal and lengthier) famous 1955 article, the procedure that he had developed simply merged the filter paper technique first described by Tiselius and Kunkel with the starch *grain* technique proposed by Kunkel and Slater. Adjusting for the shortcomings of each technique, Smithies defined his method of starch gel zone electrophoresis as one that ''combine[s] the advantages of the low adsorption characteristic of the starch-grain method with the convenience of protein detection by staining characteristic of the filter-paper method.''[49]

Smithies explained how he had arrived at the starch gel method and how it differed from Kunkel and Slater's starch grain system as follows:

> [Kunkel and Slater's] method used starch *grains* as a support for the electrophoresis. It was rather like carrying out electrophoresis in a wet bed of sand, with migration occurring through the buffer in the spaces *between* the grains. I noted with envy that the starch grains were gloriously free from absorption problems, and I thought that for this reason starch might solve my problems with insulin [separation following the filter paper procedure]. Unfortunately, in order to detect the protein zones after starch grain electrophoresis, it was necessary to carry out Folin chemical assays for protein on about 40 transverse slices of the moist starch bed. This I could not manage to do, for I had no technical help of any type, not even a dishwasher. Fortunately, however, my childhood

[46] Kunkel and Slater, 1952, p. 44.

[47] Smithies first commented on the impractical applications of the moving boundary method for macromolecular purification in Smithies, 1954.

[48] Smithies, 1955a, p. 307 (emphasis added).

[49] Smithies, 1955b, p. 629 (emphasis original).

> memories are strong, and I recalled one day when I was about 12 years old helping my mother with the laundry and observing that the starch she used for my father's shirts was liquid when hot but turned to a jelly when cold. Remembering this, I thought that if I cooked the starch and allowed it to cool, then the proteins could migrate *through* the resulting jelly, and could subsequently be detected by staining, in the way that worked with filter paper electrophoresis.[50]

That is, because in Kunkel and Slater's experiment the proteins migrated in the buffer *between* the sand-like starch grains, they had suggested a non-molecular sieving electrophoretic method in which the supporting medium did not have the ability to retard the flow of molecules in terms of size. By contrast, the proteins migrated *through* the starch jelly in Smithies' study, so the electrophoretic system that he came up with had unique molecular sieving properties, according to which larger molecules would migrate towards the anode (if the target of analysis is negatively charged) slower than the smaller molecules.[51]

Using starch gel, Smithies confirmed that previous immunological studies of human serum proteins, most of which applied Tiselius' earlier filter paper method, had correctly identified albumin and γ-globulin. His visualized results, however, revealed a number of heretofore unidentified serum components in the region between the positions of alpha- and beta-globulins.[52] With this finding, Smithies' method became widely appreciated and endorsed throughout the second half of the 1950s, both in Europe and North America, and Smithies himself published extensively to promote his starch gel system.[53]

By confronting the limitations of the two different objects used by earlier scientists – filter paper and starch grain, and in utilizing what the two objects *could* do for zone electrophoresis, Smithies had welded together an experimental system that exemplifies what Hans-Jörg Rheinberger calls a "conjuncture" in the history of science where unforeseen directions are enabled by previous experimental processes.[54]

[50] Smithies, 1995, pp. 1–2.

[51] I want to thank Oliver Smithies (Department of Pathology and Laboratory Medicine, University of Northern Carolina at Chapel Hill) and Robert F. Baker (Department of Biological Sciences, University of Southern California) for clarifying the concept of molecular sieving gel electrophoresis over our e-mail correspondences in November 2006.

[52] Smithies, 1955a, p. 307; Smithies, 1955b, pp. 633–641.

[53] See e.g. Smithies, 1959.

[54] Rheinberger, 1997, p. 133.

Accordingly, Smithies' starch gel brought new epistemic objects, namely previously unacknowledged serum components, into view.[55] Smithies' observation of these serum components, in other words, was a proof of both a step forward in biomolecular knowledge specifically *and* how such a step forward was enabled by the practical dimension of scientific instrumentation more generally.

Apart from the substantive results of his study, Smithies' starch gel method opened up unforeseen directions in concrete material practice. In 1959, two groups of scientists proposed an even more desirable supporting medium, the synthetically cross-linked polyacrylamide gels, which also had strong molecular sieving features.[56] Leonard Ornstein, working with his partner Baruch J. Davis at the Cell Research Laboratory of the Mount Sinai Hospital in New York, credited Smithies for demonstrating the molecular sieving property of starch gel: ''Remarkable resolution has been achieved when advantage is taken of the frictional properties of gels to aid separation by sieving at the molecular level (see Smithies).'' Immediately in the next sentence, Ornstein pointed out quite succinctly the power of his newly proposed electrophoretic method using polyacrylamide gels in lieu of starch gels: it ''takes advantage of the adjustability of the pore size of a synthetic gel.''[57] As explained by another group of scientists at the University of Pennsylvania in the same year, polyacrylamide gels are normally prepared by a ''polymerization-cross-linking reaction,'' i.e., the polyermization of acrylamide (the activated monomer) and metholenebisacrylamide (the cross-linker).[58] The formation of this more chemically inert medium would allow scientists, based on their research interest, to control the pore size of the polyacrylamide gel by adjusting the concentrations of its activated monomer and the cross-linker. Having control over the gel concentrations, a possibility that emerged only after Smithies had constructed his starch gel molecular sieving apparatus, researchers were now equipped with a stronger electrophoretic system for both preparative and analytic studies of biological molecules.

In 1962, one of Tiselius' students at Uppsala, Stellan Hjertén, claimed that he had also been investigating the potential molecular

[55] For the gel electrophoresis of human serum components, according to Rheinberger's working definitions, technically speaking, the serum proteins are the ''epistemic things'' and the various stabilizing media, including Smithies' starch gel in this example, represent the ''technical objects.'' See Rheinberger, 1997, pp. 28–31.

[56] Raymond and Weintraub, 1959; Davis et al. 1959. Davis and Ornstein refined their paper and later published it as two separate parts: Ornstein, 1964; Davis, 1964.

[57] Ornstein, 1964, p. 321.

[58] Raymond and Weintraub, 1959.

sieving capacity of polyacrylamide gels around the same time that the two groups of scientists in New York and Pennsylvania published their findings respectively in 1959. According to Hjertén, because both groups' studies had already been presented to the public, he decided not to publish his own results in any scientific journal at that point.[59] Still, Hjertén did eventually present his experimental findings in the *Journal of Chromatography*, after realizing "that the potentialities of molecular sieving…, which the flexibility of the polyacrylamide gel offers, have not been more extensively pointed out and utilized."[60] In the title of his article, Hjertén chose the term "molecular-sieve electrophoresis" to convey more directly the sieving advantages associated with cross-linked polyacrylamide gels when used for electrophoresis. It was the first time that the term appeared in a scientific journal, and other scientists quickly adopted it in their own writings.

Throughout the 1960s, the concept of "molecular-sieve electrophoresis" gradually became embedded within the term "gel electrophoresis" itself, even though non-molecular sieving gel electrophoresis, of course, still existed. When scientists referred to successful trials of "gel electrophoresis," they readily assumed from the outset the value of its molecular sieving effect. Meanwhile, Harry Svensson (who later changed his name to Harry Rilbe), originally also affiliated with Uppsala but later in Stockholm, propounded by 1962 a basic theory of isoelectric focusing (molecular separation based on the chemical property of charge, as opposed to the physical property of size).[61] At the time, however, Svensson had trouble coming up with favorable buffer carrier ampholytes for this procedure. Two years later, his student, Olof Vesterberg, found a way to obtain ampholytes with many protolytic groups that had suitable pK values and isoelectric points: by boiling a mixture of carboxylic acids and polyvalent amines.[62] Building on Svensson and Vesterberg's work, two separate groups of scientists in 1969 sketched out in detail the method of "two-dimensional electrophoresis," in which proteins are first separated according to charge

[59] Hjertén, 1963. See also Hjertén, 1988, pp. 7–8.

[60] Hjertén, 1963, p. 66.

[61] Svensson, 1961, 1962. The history of isoelectric focusing, of course, deserves explication in its own right, but falls outside the scope of this paper. It can be traced back to the work of Alexander Kolin at the University of Chicago in 1954. See Kolin, 1954a, b.

[62] Vesterberg, 1989, p. 12; Vesterberg, 1993, pp. 1246, 1248. For Vesterberg's first publication of this method, see Vesterberg and Svensson, 1966.

(isoelectric focusing) in the first dimension then separated according to size (polyacrylamide gel electrophoresis) in the second dimension.[63] By 1970, gel electrophoresis no longer simply meant zone electrophoresis; it also meant molecular-sieve electrophoresis.

Experimental Practice and the Material Epistemology of Biomolecular Science

The development of gel electrophoresis between the mid-1940s and the late 1960s brings into visibility the dynamics of experimental practice, in which new techniques and scientific knowledge developed in tandem – the ways in which the *material epistemology* of biomolecular science facilitated the concrete processes of scientific knowledge formation. First, researchers who worked to achieve a sharper discrete separation and visualization of biological molecules – amino acids, peptides, serum proteins, and other small and large molecules – all had taken steps to improve electrophoresis by relying on existing forms of instrumentation and their related conceptual tools. Working with different groups of research colleagues, Gordon, for instance, proposed agar gel electrophoresis when working in Prague based on his prior experience with performing ionophoresis on silica jelly in England. Putting together Gordon's contribution and the widely-used diffusion method in immunochemistry, Grabar and Williams developed their immunoelectrophoretic method in Paris around the mid-1950s. Similarly, a comprehensive description of two-dimensional electrophoresis appeared in 1969 that simply combined molecular-sieve gel electrophoresis and isoelectric focusing, both of which underwent a series of historical stages of development, with each stage emerging out of earlier experimental efforts.

Moreover, in relying on the existing interplay between practice and ideas, biomolecular scientists also offered new ways to conceptualize electrophoresis and the new vocabulary necessary for explaining these conceptualizations. In coining "zone electrophoresis," for example, Tiselius frequently associated this concept of discrete (macro)molecular separation with the filter paper method that he had refined with Kunkel, among others in his Uppsala lab. But, as I have suggested near

[63] Dale and Latner, 1969; Macko and Stegemann, 1969. Smithies and Poulik first proposed a two dimensional electrophoretic system using starch gel in 1956: see Smithies and Poulik, 1956.

the beginning of this paper, Gordon was already working with others in Prague and England in the second half of the 1940s to come up with ways of separating molecules into absolute zones. When Tiselius made the implicit reference to Gordon's work in his statement "Zone electrophoresis, particularly in gels, has also been called 'ionophoresis' as one of its first applications was with low molecular weight substances (amino acids, peptides)," he followed by an immediate self-validation of the term he was supposedly responsible for by simply dismissing Gordon's choice of word: "but as the zone methods now have found wide application also with protein and other large molecular weight material this term ["ionophoresis"] does not seem adequate as a name for migration experiments in supporting media." Apparently, the persuasiveness of Tiselius' statement had to do with what Gordon did and what he thought he did: namely, he separated amino acids and peptides electrophoretically knowing that he was separating small molecules and not some macromolecules. In other words, much the same way the notion of "molecular-sieve electrophoresis" was consolidated later by his student Hjertén, Tiselius' consolidation of "zone electrophoresis" epitomizes the significance of scientists' reliance on the already existing interaction between the material practice of molecular separation and its conceptual counterpart.

Finally, at the same time that old forms of instrumentation have the technological capacity to inspire new experimental systems, they also could bring researchers unforeseen problems, both practical and conceptual. Recall that when Gordon shifted from silica jelly ionophoresis to agar gel electrophoresis, he faced the problem of removing the agar jelly, itself mobile when subjected to an electromotive force, from the protein substances being analyzed. The difficulty with avoiding agar contamination, however, was not really a problem before he considered and indeed experimented with agar jelly for macromolecular separation. Smithies' development of starch gel electrophoresis provides another telling example when one considers how he confronted the limitations of Tiselius' filter paper technique after knowing about Kunkel and Slater's starch grain method. Molecular adsorption only became a defect of the filter paper technique when Kunkel and Slater demonstrated that starch grain had a distinctly low adsorption property, and Smithies was able to find a way to unify the two methods to overcome the problems originally associated with each procedure. The example of gel electrophoresis, henceforth, shows that the new problems, alongside the new potentials, generated by the rearrangement of old experimental systems into new modes of instrumentation had consistently served as a prominent driving

force behind the historical development of laboratory biomolecular science.

After the 1960s, genetic engineering would come to acquire the center stage in molecular biology. The purification, characterization, and commercialization of restriction enzymes provided the condition of possibility for the recombination of DNA molecules that brought new possibilities to biotechnology.[64] Recombinant DNA technology also required the separation and isolation of DNA fragments in order for effective ''vectors,'' phages or plasmids, to be developed. New ways of separating molecular fragments following cleavage were thus central to successful physical mappings of DNA molecules. Because the differentiation of DNA molecules into discrete bands constitutes such an important step in the overall apparatus of recombinant DNA preparation, the rapid replacement of centrifugation and other molecular separation techniques by gel electrophoresis indicates the pervasiveness of this technique in post-1960s molecular biology and biochemistry. Moreover, without the full development of gel electrophoresis, there could have been arguably no amino acid and nucleic acid sequence analyses. If the entire molecular biology industry is at issue in this regard, the specific novel concepts (such as ''zone electrophoresis'') associated with the gel electrophoretic apparatus must had played a critical role in the shaping of the history of not just DNA sequencing itself, but the trajectory by which the DNA structural model consolidated its historical significance by the late 1960s and early 1970s.[65]

[64] For a *longue durée* study of how the emerging attempt in the 1970s to see genetic engineering as the prototypical ''modern'' biotechnology is essentially an act of forgetting biotechnology's own history, see Bud, 1993. In this paper, I have only focused on the epistemological layer of the history of biomolecular science. I am aware of the importance of the commercial aspect of the history of any scientific instrumentation, especially for developments in the post-WWII era, but the historical claims I make here concern more directly with epistemology. On the commercialization of molecular biology, see De Chadarevin 2002, pp. 356–362. See also the coverage in Wright, 1994.

[65] As Angela Creager and Gregory Morgan have recently shown, structural studies of viruses at least played an equally important role as the Watson-Crick DNA model in the history of biomolecular scientific research in the 1950s and early 1960s. See Creager and Morgan, 2008. Similarly, Soaray de Chadarevian stresses the less than self-evident status of the double helix model in the organization of certain ideas in and the direction of biological research around the time: ''The double helix found its place and importance in a complex web of experimental data and hypothesis, much of which was acquired quite independently and sometimes itself provided the very evidence for the proposed structure.'' De Chadarevin 2002, p. 194.

Historiographic Lessons from the History of Gel Electrophoresis

The history of gel electrophoresis that I have followed does not reflect a neat linear historical progression from the free solution Tiselius equipment of the 1930s to the polyacrylamide gel electrophoresis of the 1960s. At any given point, researchers in Europe and North America performed electrophoresis on a variety of different supporting media: while some might be using filter paper strips, others experimented with bacteriological cellulose acetate membranes. And at several notable (con)junctures, scientists combined a specific electrophoretic procedure with another type of instrumentation to yield laboratory techniques, such as the immuno-electrophoretic method, which may or may not have directly contributed to the overall advancement of gel electrophoresis.

By focusing on the experimental dimension of biomolecular science, I have attempted to trace a history of molecular biology without restricting myself to sources that made explicit reference to the term "molecular biology" itself. Taking molecular biology as a case study, my goal has been to bring into sharper focus the implicit contributions of the material epistemology of a particular branch of science to its disciplinary formation over time. A major nexus of debate in the historiography of molecular biology, for instance, revolves around the precise chronological origin of the field. While some like Robert Olby have suggested that molecular biology emerged in the 1930s, others like Pnina Abir-Am have argued for its birth in the post-WWII era.[66] Alternatively, according to my own analysis, I would support Soraya de Chadarevian's interpretation that the disciplinary formation of molecular biology really took shape only after the late 1950s.[67] That *none* of the scientists who made significant contributions to the development of gel electrophoresis self-identified as a "molecular biologist," and yet this experimental method gradually appeared in most molecular biology laboratories over the course of the 1960s and beyond, suggests that molecular biology proper really consolidated in the 1960s and not before.[68]

By tracing the historical changes in biomolecular instrumentation, my research also provides an alternative understanding of a topic of

[66] Olby, 1974a, b; Abir-Am, 1997.

[67] De Chadarevin 2002.

[68] On this point, see also de Chadarevian and Strasser, 2002. For example, Creager and Morgan's recent study of Rosalind Franklin's structural studies of the *Tobacco mosaic virus* takes this historiographical re-interpretation as its point of departure. See Creager and Morgan, 2008.

intense discussion among historians of biology: the impact of the Rockefeller Foundation and the physical sciences on the rise of molecular biology. A great portion of the early historiography argues for the prominent role played by the Rockefeller Foundation in the disciplinary establishment of molecular biology, stressing the generous financial support from the Foundation's Natural Sciences Division under the direction of Warren Weaver.[69] And this historiographical interpretation is often supported by the body of literature that emphasizes how the importation of cognitive and technical skills from the physical sciences oriented biology towards a reductionist molecular paradigm and agency.[70] As an example, recall Lily Kay's study of the early Tiselius apparatus, in which she argues that the development of the apparatus during the 1930s and 1940s largely depended on the financial resources offered by the Foundation, and its gradual reception in biological laboratories typified the broader institutional and intellectual trends of the life sciences at the time – characterized by the systematic applications of tools from the physical sciences.[71]

Yet, in assessing the influence of the Rockefeller Foundation and the physical sciences on the disciplinary formation of molecular biology, scholars have all too often overlooked a critical factor: the way science gets probed and transformed through its evolving material epistemology. This paper suggests that in order to trace the historical origins of molecular biology, one does not need to privilege the emergence of the term "molecular biology" or make large claims about funding patterns. Concentrating on how scientists negotiated the practices and ideas of gel electrophoresis, my study demonstrates that the Rockefeller Foundation did indeed play an important role in the history of molecular biology, but its impact was primarily indirect and became embedded within the laboratory tools themselves after the mid-1940s. In introducing, building, and promoting the huge Tiselius apparatus, the Foundation not only helped shape the explicit financial, institutional, and intellectual trends of the life sciences during the 1930s and 1940s, but it had also initiated, however indirectly, a series of experimental

[69] In addition to Kay's *Molecular Vision of Life* (1993) and other essays (1988 and 1989), see Weaver, 1970; Kohler, 1976, 1991. This historiographical interpretation is challenged by Abir-Am, 1982. Abir-Am's controversial article initiated a series of replies from several major historians of biology. See Bartels, 1984; Fuerst, 1984; Olby, 1984; and Yoxen, 1984. For Abir-Am's reply, see Abir-Am, 1984.

[70] See n. 6 and de Chadarevian, 2002. On these two points, I have also synthesized the vast historiography of biomolecular science for a more generalized and interdisciplinary audience in Chiang, 2007.

[71] Kay, 1988.

undertakings that would eventually lead to the conceptualization and successful instrumentation of discrete molecular separation, a central component of modern molecular biology research.

In this sense, Kay and others' approach to assessing the impact that the Rockefeller Foundation and the physical sciences had made on the life sciences on the level of historical epistemology is somewhat incomplete. Alternatively, in showing the complicated and overlapping historical processes by which the gel electrophoretic instrumentation unfolded over the course of roughly two decades, this study has explored the role of the Foundation and physical science in the development of molecular biology through a heretofore frequently neglected epistemological layer of biomolecular science. By taking advantage of my present awareness of the ubiquitous applications of gel electrophoresis across modern molecular biology laboratories, I have bring to shaper focus a historical story of molecular biology in the 1950s and 1960s that does not touch on the DNA structure, the genetic code, or the central dogma. This may seem like a reverse teleological approach, but it has allowed me to look into the thus far largely under-appreciated realm of material epistemology in the history of biological science. It is precisely with the benefit of hindsight that historians are able to raise questions about a topic that otherwise would have been inconceivable in its own historical context. The development of gel electrophoresis reveals not only how molecular separations improved over time, but, more importantly, how the scope of biology changed around the mid-twentieth century outside the world of Watson and Crick.

Acknowledgements

The author wishes to thank Michael S. Mahoney, Angela N. H. Creager, and the journal's three anonymous reviewers for their careful and insightful comments on earlier versions of this paper. The author alone is responsible for any remaining errors. The paper was first written for a graduate seminar on the material epistemology of science, ''Thinking Through Things and Thinking Things Through,'' under the supervision of Michael S. Mahoney in the Program in History of Science, Princeton University, and, accordingly, it is dedicated in memory of him. An earlier version of the paper was presented at the 42nd Meeting of the Joint Atlantic Seminar for the History of Biology, the 2007 Annual Meeting of the Canadian Society for the History and Philosophy of Science, and the 2007 Biennial

Meeting of the International Society for the History, Philosophy, and Social Study of Biology.

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