Memory and Archive – a Retrospective on a Career in Science

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Memory and Archive – a Retrospective on a Career in Science

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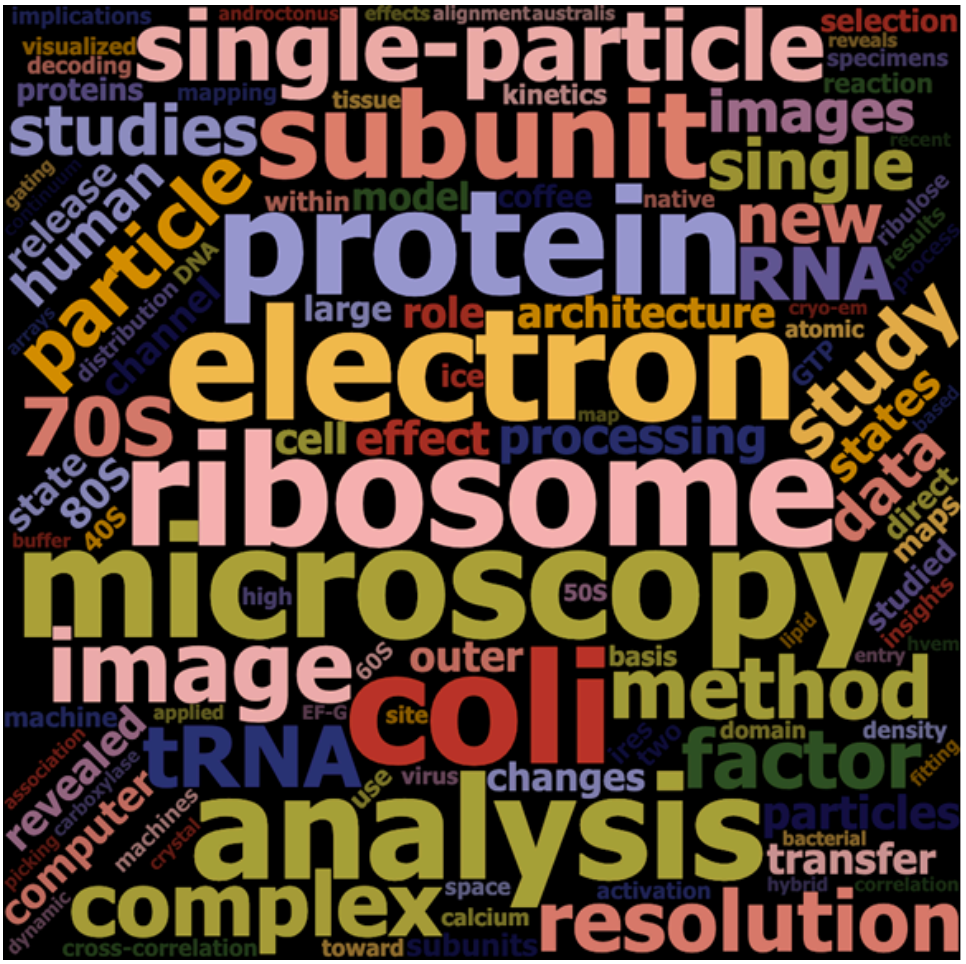

Scholar-Googler compilation of words appearing in titles of articles authored and co-authored by Joachim Frank from 1965 to 2024

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1. Introduction – Joachim Frank

I first met Jonas Piduhn, a German student of International Affairs at Columbia University's School of International and Public Affairs, in November 2022, and this meeting started a remarkable collaboration. In the following I will give a brief account on how this came about, partly from my own recollection, and partly from what I learned by talking to him.

In the fall of 2022 Jonas had started working toward his Master of International Affairs degree, focusing on Energy and Environment and International Conflict Resolution. Before that, he had already completed an undergraduate and a graduate degree in Economics at the Humboldt University in Berlin.

After I received the Order of Merit of the Federal Republic of Germany, with a ceremony in the residence of the General Consul David Gill, Jonas saw a photo of the event online. Having learned previously about my research and having read my novel "Aan Zee", he contacted me and asked for an opportunity to meet. Our first meeting took place on November 9th, 2022.

Later that year, as he looked for a 2023 summer internship as part of his graduate program, he asked me whether he could support my work – or in fact my literary activity – in some way. This gave me an idea: I told him that I'm in the process of cataloging a large amount of material (scientific manuscripts, drafts, correspondence, photographs, etc.) accumulated over the period of my career, since the 1960s, in preparation for archiving it in the special collection of the Butler Library of Columbia. Jonas immediately agreed to work on this project, pending a go-ahead from his advisor, which materialized without delay. My idea was motivated by the realization that I needed someone who was highly sophisticated and German-English bilingual, since much of the earlier part of the archive was populated with correspondence in German.

In July of 2023, we started working together on the cataloging of 51 boxes of material ranging from 1965 to now. Since then, Jonas has cataloged and summarized hundreds of documents – the present count stands at 3000. As he worked on it, the project became for me an amazing journey back in time. As I looked at the abstracts he accumulated, I uncovered many scientific exchanges that were forgotten, among these administrative memos and documentation of events that might have been turning points in my career. And the archive bristles with documented facts that seem quite outlandish today, such as months-long journeys

of manuscripts by postal mail, or the claim for a refund for a $4.- taxi ride from Penn Station to the Columbia Medical Center.

Our collaboration inspired us to write this paper, which centers around two subjects: the factors influencing innovation – Jonas' specialty – and the discrepancy between memory and documented facts, which I became aware of as I revisited my archive with his help. And Jonas surprised me with his use of an equation quantifying innovation that apparently has some currency in economics but, to our knowledge, has never been applied in the analysis of an individual's career.

Our paper is structured in the following way: First, Jonas will analyze the findings from his work on my archive, using terminology of commercial innovation taught in his Master classes in Economics. Following that, I will give examples for events that were either totally missing or incorrectly placed in my recollection**.** Third, we will offer concluding remarks on what we have learned from this dive into the past. A link is provided there to a video documenting an interview where we talk about the experience of our collaboration.

References to published literature are supplied throughout, whereas references to items in the cataloged archive will be added later in a revised version of this article, once the archive is deposited and curated.

2. What are the Factors Driving Innovation? - Jonas Piduhn

While going through every document in Frank's scientific archive, I have been able to see the development of ideas leading up to Frank's method for analyzing and merging blurry two-dimensional images of single molecules in the electron microscope into a sharp three-dimensional image, the method for which he was awarded the 2017 Nobel Prize in Chemistry.

I am in the process of reading and cataloging documents that range from scholarship motivation letters to the first bibliography of publications, from shipments of individual reprints across the world to travel arrangements for the 1974 International Congress on Electron Microscopy in Canberra, from housing arrangements in Cambridge to academic debates on the merits of research proposals. I believe that knowing the everyday steps of Frank's research over the course of six decades will provide valuable insights into the process of scientific innovation. The earliest documents in the archive I analyzed so far date back to 1957, when he was still in high school. In this article, we are focusing on the time period from 1957 to 1984.

As Frank stated in a 1975 seminar in Albany, “when the electron microscope was being developed, the question of any biological application was regarded with great skepticism. According to one then authoritative view, biological material would just burn away, leaving no clue as to the original structure”. Clearly, this view has evolved over time as technology evolved, and so has the view on the possibility of gaining meaningful three-dimensional images from cryo-electron microscopy.

Coming from an economics background, I immediately thought of a formula broadly derived from Paul Romer’s endogenous technical change contribution to understand how innovation processes happen over time:[1] [2]

$$\Delta A_t = \pi L_{A,t}^{\lambda} A_t^{\varphi}$$

ΔA_t being the number of new ideas *A* generated in period t, π being a productivity parameter, $L_{A,t}$ being the number of researchers in period t, λ measuring how much peers inspire each other, and φ measuring how much ancestors inspire the younger generation.

While these economic factors are meant to be used to analyze macroeconomic innovation activity, I believe the underlying ideas of gauging the innovation process can be applied to every single scientist. In the following, I will use this formula as a way to suggest categories for the analysis rather than apply it in an empirical economic way. I will introduce a snapshot of Frank’s innovation development with a focus on his early academic career using the categories of Romer’s formula. My analysis will focus on the years up to the mid-1980s of Frank’s career, the time Frank described as the “Eureka!” stage in his Life in Science lecture.[3]

[1] Romer, P. M. (1990). Endogenous Technological Change. Journal of Political Economy, 98(5), pp. 71-102. http://www.jstor.org/stable/2937632

[2] Jones, C. I. (2019). Paul Romer: Ideas, nonrivalry, and endogenous growth. The Scandinavian Journal of Economics, 121(3), 859-883.

[3] Frank, J. (2022).Speech by Joachim Frank. Journal of Science, Humanities and Arts (JOSHA) 9, Issue 5 -10. September 4 2022. doi:10.17160/josha.9.5.850

The Four Stages of Frank's Career

In his speech on the occasion of his 82nd birthday at Columbia University in 2022 (actually a Covid-19-delayed celebration of his 80th), Frank stated that when looking back at his life in science, he can see four stages. First, the stage he calls "Crucible of Ideas" in which he explored various ideas, directions and approaches without seeing a clear path. Second, the "Eureka!" stage of his science life happened when Frank conceived the idea of structure determination from a collection of single molecules in solution, which was to become his main research interest. Insights into this stage will be provided in the following sections. Third, Joachim Frank entered the "Ribosome-as-Guinea-Pig" stage in which he further developed his idea with the aid of the ribosome and turned into a structural biologist in the process. Finally, the "Apotheosis" stage, starting with his 2017 Chemistry Nobel Prize,[4] is still going on as Frank sees his technique flourish at the forefront of life science around the world.

Number of Researchers

Frank started working on projects related to electron microscopy as a Research Assistant at Max-Planck-Institut für Eiweiss- und Lederforschung (later part of the MPI for Biochemistry in Martinsried) in 1967. Over the course of his early years in academia, up to 1984, Frank exchanged letters with more than 350 researchers and institutions. Among the scientists he exchanged most letters with were Benjamin Siegel, Wolfgang Haenicke, Robert Glaeser, Peter Zingsheim, Harold Erickson, Peter Hawkes, and Walter Hoppe.

Cross-inspiration among Researchers of the Same Generation

An important driver of innovation is cross-inspiration among researchers of the same generation. Going by the volume of letters and eliminating senior investigators, the most influential same-generation researchers were: Harold Erickson and Bob Glaeser in the United States, Peter Hawkes in the United Kingdom and Wolfgang Haenicke and Peter Zingsheim in Germany.

First, Harold Erickson and Bob Glaeser influenced Frank's work particularly during his postdoctoral stay in the USA. Frank had been awarded the Harkness Fellowship, which allowed him to do postdoctoral research in the US, get acquainted with the

[4] Frank, J. (2022).Speech by Joachim Frank. Journal of Science, Humanities and Arts (JOSHA) 9, Issue 5 -10. September 4 2022. doi:10.17160/josha.9.5.850

culture first-hand and get to meet Erickson and Glaeser. As further detailed below, he spent two years starting in the fall of 1970 visiting three renowned research labs. The Harkness Fellowship also provided extra money that had to be spent traveling around in the USA. Frank and his wife decided to buy a used Plymouth Valiant convertible and spent the remaining funds to pay for traveling and accommodation during several trips. This created opportunities for Frank to make the personal acquaintance of several researchers at different stages of their career.

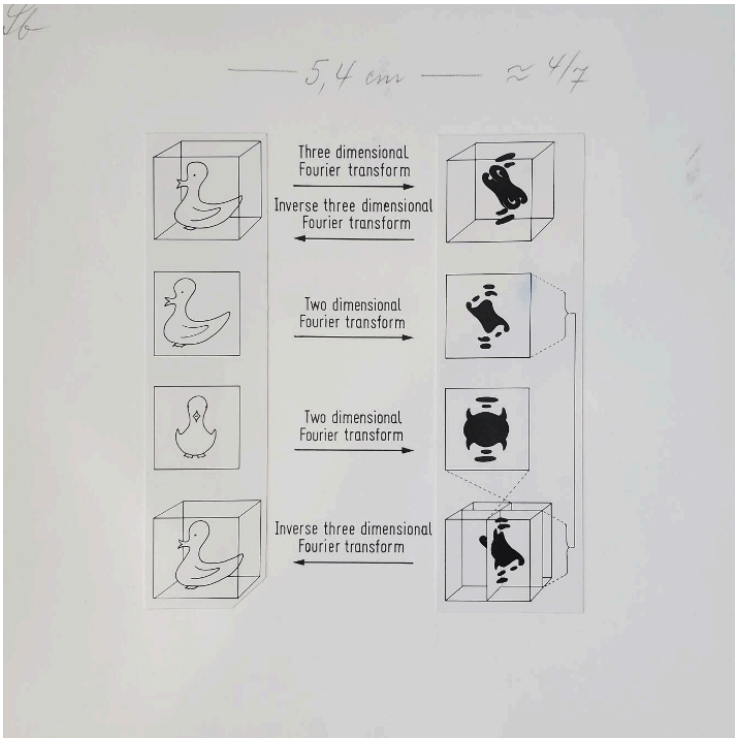
Frank first met Harold Erickson from Duke University at the Hirschegg Symposium in 1970. During their exchanges, Erickson provided suggestions on setting up an optical diffractometer to search the plates for the area with best diffraction pattern and they exchanged views on the VICAR image processing software of the Jet Propulsion Lab, which enabled the processing of very large images and later became a model for Frank's development of SPIDER.

Erickson invited Frank "to come for a seminar when passing the East Coast" in 1970. Frank was "glad to do so next summer, probably July or August. At this time we (me and my wife) will spend our two months traveling sponsored by my Fellowship". When visiting Duke University in 1971, Frank gave a lecture on his work. On that occasion he and his wife stayed with the Erickson family.

During Frank's time at the University of California, Berkeley, he worked in the group of Robert Glaeser. Born in 1937, Glaeser was just slightly older than Frank but already a tenure-track assistant professor at the time. Glaeser worked on radiation damage of molecules exposed to the electron beam and its effect on image resolution. Starting with this early research collaboration, the two have stayed in contact until now.

For instance, when later (1974) receiving the offer by Donald Parsons to start as a Senior Research Scientist at the Division of Laboratories and Research of the New York State Health Department, he consulted with Glaeser about this path to "being carried into the olymp so quickly, without a struggle for tenure" before accepting this offer. The risk, of course, was that a position without academic affiliation might prove to become a later obstacle to a successful academic career. Second, Peter Hawkes at the Cavendish Laboratory in Cambridge, UK, was an early correspondent who was drawn to Frank's work by a common interest. The exchanges with Hawkes, who was also just a few years older than Frank, were highly influential on Frank's development of ideas. In their exchange of letters in 1970, Hawkes expressed interest in the work Frank had been doing "on

computer-filtering of electron micrographs and on the use of autocorrelation techniques to test the significance of details seen in the electron image close to the 'limit of resolution'". This contact proved instrumental for Frank's later choice of the Cavendish lab as his first stage of professional career after his time as a postdoc, in 1973.



Sample from the archive: illustration of the Fourier slice theorem, attributed to James Lake, sized for submission to the publisher of the book edited by J.K. Koehler.

In 1970 Hawkes asked Frank whether he could borrow a copy of his thesis. Frank sent a copy to Hawkes from his parent's home Hüttental.[5] When sending the copy back to Frank, Hawkes reaffirmed his appreciation of Frank's work. He was "extremely impressed by the extent of your work, which answers a great many of the questions about image processing that had been bothering me". Based on this assessment, Hawkes recommended Frank as contributor of a chapter on electron image processing to James Koehler's planned book entitled "Advanced Techniques in Biological Electron Microscopy (J. Koehler, ed.)".[6] When the book came out, three

[5]Hüttetal was an interim name of a larger municipality including former Weidenau, until it became part of the city of Siegen.

[6] Frank, J. (1973). Computer processing of electron micrographs. In Advanced Techniques in Biological Electron Microscopy, J.K. Koehler, ed. (Heidelberg, Springer Verlag), pp. 215 - 274.

years later, this chapter would prove to establish Frank's scholarship in this new area of digital image processing and would lead to the job offer by the New York State Department of Health in Albany.

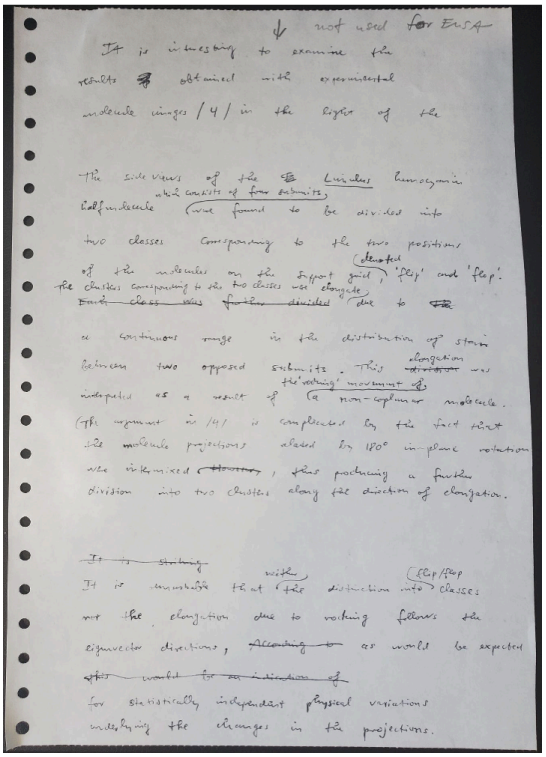
Hawkes' expertise in electron optics was a major asset Frank could draw on. In the winter of 1972/1973, while still working as a visiting scientist in Walter Hoppe's lab, Frank asked Hawkes for feedback on his paper "dealing with properties of partially coherent transfer functions" before submitting it for publication in the journal Optik, where it appeared in 1973. In this work, Frank showed that the influence of partial coherence on the contrast transfer function could be approximated as a simple product with an envelope function. With Hawkes' recommendation, Frank's letter to Vernon Ellis Cosslett in 1972 (see below) inquiring about a position was well received. After he joined Cosslett's lab as a group leader, his professional interaction and friendship with Hawkes became a major support.

Third, a collaboration with Wolfgang Haenicke and Peter Zingsheim between the late 1970s and early 1980s was a major influence on Frank's work. Zingsheim and Haenicke both worked at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. The project addressed the structure of the acetylcholine receptor using the single-particle averaging approach, resulting in three papers. Their paper "Statistical significance of molecule projections by single particle averaging" was the result of their final collaborative project, which was published in the Journal of Microscopy in 1984.

As Haenicke was a postdoctoral student in Zingsheim's group, it was a collaboration between Frank and Zingsheim, with Haenicke and Frank going into the details of the projects in their correspondence. Both exchanged more than 30 letters, covering the discussions and formulations of the three papers, including all logistics of publication, starting with the choice of journals. Frank also exchanged letters with Zingsheim in 1978 regarding Frank's first proof of concept paper on the two-dimensional averaging of low-dose images of glutamine synthetase.

When analyzing the cross-inspirations among researchers of the same generation, Frank's contacts with his later co-Nobel Laureates Jacques Dubochet and Richard Henderson are essential to mention. His first letters with Dubochet were exchanged in 1978. Dubochet had invited Frank to hold a seminar at the EMBL. In these letters Frank and Dubochet discussed the design of their image processing systems and the compatibility of their software.

Henderson and Frank both attended the 1968 Protein Workshop co-organized by Walter Hoppe and Max Perutz in Hirschegg. Henderson was one of the presenters and Frank was a participant of the workshop.[7] Frank, Dubochet, and Henderson all presented lectures at the 1979 workshop on "Regular 2D arrays of biomacromolecules: structure determination and assembly" in Burg Gemen, Germany, and in a course organized by the European Molecular Biology Organization in Heidelberg, Germany in 1982.



Sample from the archive: a page from a draft of a paper on the use of multivariate statistical analysis in sorting of molecule images.

Cross-generational Inspiration

Walter Hoppe, **Benjamin Siegel** and **Vernon Cosslett** were Frank's most-contacted cross-generational inspirations during his early career and contributed to the "standing on the shoulders of giants" effect. These three professors, in this order, were Frank's mentors in his early career years.[8]

[7] Frank, J. (2022). Walter Hoppe - X-ray crystallographer and visionary pioneer in electron microscopy. In Advances in Imaging and Electron Physics (Elsevier).

[8] Image credits: Archiv der Max-Planck-Gesellschaft, Berlin-Dahlem (n.d.); Microscopy Society of America. (n.d.). https://microscopy.org/search?q=benjamin+siegel; Honorary membership | Gesellschaft Deutscher


Walter Hoppe


Benjamin Siegel


Vernon Ellis Cosslett

First, Walter Hoppe (1917-1987) was Joachim Frank's Ph.D. thesis supervisor and a pioneer in electron microscopy.[9] During Frank's initial period of working with Hoppe from 1967 to his Ph.D. in 1970, he very much shaped Frank's early career. Frank now describes Hoppe's impact as follows: "He introduced me to the concepts of X-ray crystallography as well as image formation in electron microscopy, mainly by pointing to seminal publications in both fields. His role as co-organizer (with Max Perutz) of meetings on protein crystallography and electron microscopy in Hirschegg and Alpbach was instrumental for my early exposure to several exponents in these fields, as well as for the opportunity to meet students from other groups with similar interests."

As Hoppe's student, Frank was able to critically analyze his mentor's approach to 3D reconstruction of biological molecules using the electron microscope. This first-row seat allowed Frank to see the flaws of the experimental design, particularly in regard to radiation damage. The ensuing vigorous debates with his mentor shaped Frank's ideas for his own "single-particle" approach, which he developed later based on his thesis work. Returning to Hoppe's lab (which had meanwhile moved to the new site in Martinsried) for a brief time after his Harkness-sponsored stay in the USA, Frank focused on theoretical work, on partial coherence.[10] This

Chemiker e.V., Vernon Ellis Cosslett (n.d.). https://en.gdch.de/gdch/prizes-and-awards/honorary-membership.html

[9] Frank, J. (2022). Walter Hoppe - X-ray crystallographer and visionary pioneer in electron microscopy. In Advances in Imaging and Electron Physics (Elsevier).

[10] Frank, J. (1973). The envelope of electron microscopic transfer functions for partially coherent illumination. Optik 38, pp. 519-539.

work did not require collaboration with Hoppe's group, except for some interactions with Dieter Typke, then senior postdoctoral student under Hoppe.

The second cross-generational influence was Benjamin Siegel (1916-1990). Siegel's laboratory at Cornell University was the place for Frank's third and last research stay during the Harkness Fellowship after the Jet Propulsion Lab/Caltech and UC Berkeley. Siegel, 34 years older than Frank, had joined Cornell in 1949 to be the head of Cornell's newly founded electron microscopy laboratory.[11] Under his leadership an experimental 600-kV intermediate voltage electron microscope was built. Hoppe and Langer had invited Siegel to the 1970 Hirschegg Symposium. Leading up to this meeting, Frank and Siegel had started exchanging letters about plans for Frank's visit to Cornell University. Both discussed the final arrangements for this stay during the Hischegg Symposium. During his time at Cornell, in 1972, Frank continued to work on problems related to computer processing of electron microscope images.

Based on an evaluation of Frank's work at Cornell University, Siegel sent a letter of recommendation for Frank to the German Research Foundation (DFG) in the summer of 1972, supporting the funding application for Frank's position in Hoppe's institute later that year. He described Frank as an "extremely able and knowledgeable research worker who has proceeded to develop the problem in an original and independent manner" and who has done previous work on "problems related to computer processing of electron microscope images". Siegel and Frank stayed in touch for a number of years following Frank's departure from Cornell. However, their main correspondence occurred between 1969 to 1975.

Third, Vernon Ellis Cosslett (1908-1990) was Frank's host at the Cavendish Laboratory between June 1973 and the fall of 1975. Cosslett was the founder of the Electron Microscopy Section of the Cavendish Laboratory at the University of Cambridge.[12] While there is little evidence in the archive for direct communication between Frank and Cosslett during the time he worked there, Frank states that a number of undocumented personal exchanges were influential for his direction of research.

[11] The New York Times. (1990, March 27). Benjamin Siegel, 73, Scientist and Educator. The New York Times. https://www.nytimes.com/1990/03/27/obituaries/benjamin-siegel-73-scientist-and-educator.html

[12] Mulvey, T., & Hirsch, P. B. (1994). Vernon Ellis Cosslett, 16 June 1908 - 21 November 1990. Biographical Memoirs of Fellows of the Royal Society, 40, 61–84. https://doi.org/10.1098/rsbm.1994.0029

In his letter to Cosslett from December 1971 inquiring about a position in his lab, Frank mentioned Hoppe, Nathan and Glaeser as his references and stated that he had already been in contact with Hawkes at the Cavendish Laboratory. Cosslett acknowledged this letter in January 1972, and stated that "we would indeed be glad to have you join the team which we are forming to work on problems of high-resolution electron microscopy." During Frank's time in Cambridge, he was having monthly meetings with Cosslett on the progress of his research and the mentoring of two of his students. In 1979, Frank contributed a paper on "Image analysis in electron microscopy" to the Journal of Microscopy's "Special Issue - The Cosslett Festschrift" on the occasion of Cosslett's 70th birthday.

Career Choices

One aspect that is not covered in the innovation formula is the impact of career choices. Going through Joachim Frank's archive has strengthened my understanding of a scientific career as a dynamic process with potential twists and turns. Three aspects stood out to me in this latter aspect.

First, already during his high school years, Frank showed a particular interest in physics, and to a lesser degree in chemistry. He was a member of the chemistry and physics working groups. In his Certificate of Maturity [Abiturzeugnis], it was noted that he had completed them "with lively interest and praiseworthy success" and "with great interest and outstanding success," respectively.

Second, during his undergraduate time studying physics, Frank showed strong interests in other areas, as well. At one time he thought of "abandoning physics and instead wanting to construct kinetical objects using all kinds of optical, mechanical, and acoustic effects". Later, he got interested in computer graphics, graphical communication patterns and linguistic possibilities. In his Harkness Fellowship application, he highlighted an interdisciplinary interest in linguistics. He wrote that "a language carrying historical standards of thinking and behavior seems to be inadequate to reduce aggression between men and to initiate a rational organization of society; perhaps one day mankind will be able to overcome aggression using non-verbal communication media." The interest in language and literature has always been a passion throughout the decades of his academic career.

Third, Frank's career might well have taken a different turn in 1974. In a letter to Dr. Maurice Strong, the Executive Director of the United Nations Environmental Programme (UNEP) on March 5th, 1974, he applied for an image processing

position at UNEP after reading about the 'Earthwatch' project in the London TIMES. Frank stapled the September 6, 1973, TIMES article “Wellsian setting for ‘Earthwatch’” to his copy of the letter to Dr. Strong. The Earthwatch Programme had been designed to follow through on recommendations made at the United Nations Stockholm Conference on the Environment in 1972.

In his letter he asked “if under the UNEP programme a position equivalent to my background would be available for a person who is able to develop methods of image analysis, apply ideas proven useful in other fields, and help develop a program system for processing of images obtained from satellites.” Frank was considering “pollution control and environmental protection as a more useful application of his skills.” While a notice showing that the application was received was sent to Frank, asking him to fill out the UNEP Personal History Form, there was no follow up on a suitable vacancy in line with his professional background.

This snapshot of Joachim Frank’s innovation journey focusing on his early academic career shows that all three factors outlined in the innovation formula played an important role: the number of researchers in the field, inspiration among researchers of the same generation, and cross-generational inspiration. In addition, his academic trajectory reflects his notion of paying attention to “peripheral vision” in finding solutions for problems he encountered in his research. Frank’s interdisciplinary commitment and openness to new approaches is also exemplified in his decision to give me – an International Affairs student with prior degrees in economics but no background in natural sciences – the opportunity to conduct this challenging archive cataloging project.

3. The Curious Mismatch between Memory and Archive - Joachim Frank

My scientific archive is finite yet vast. It contains documents with facts both relevant and irrelevant, with a border in between whose placement very much depends on the eye of the beholder. As intangible, digital media have largely replaced paper, bunches of pages stapled or clipped together, with rust marks where the paperclip sat for years, will appear nothing but exotic, particularly to the eyes of the new generation. But it is the medium that has survived in readable form for hundreds of years, which cannot be said of the ephemeral contents of digital archives as they change format and physical medium almost every decade.

This makes me think of another archiving project, albeit much larger in scale: Ben Porter's "Collection of Contemporary Letters/Repository of Unpublished Materials" in Colby College's Special Collections, in Maine. On the website we read "Colby alumnus and Maine native Bernard Harden Porter (1911–2004) was an artist, writer, philosopher, and scientist. [*He participated in the Manhattan project and, after Hiroshima and Nagasaki, left science in favor of the arts* –JF]. A pioneer in the arts, he is known for his landmark work as an author and publisher. As an artist he produced mail art, found- and performance poetry, typography, sculpture, photography, artists' books, and collage. Housed in Colby College Libraries' Special Collections, Bern Porter's Collection of Contemporary Letters is an eclectic mix of published and unpublished materials that reflects the complexity, creativity and humor of Porter himself."[13]

Embedded somewhere in the 70 linear feet of uncatalogued material are manuscripts I sent Porter after I met him in Albany where he did a performance in my backyard to an audience of the former artist collective WORKSPACE.[14] Porter recognized early the importance of preserving every step of the creative process in arts and science, particularly at the time when word-processing took over from drafting *manu*scripts by hand – incidentally the original meaning of the word.

I would hesitate to call my archive a Pandora's Box, but it is true that a lot of surprising and at times uncomfortable truths are hidden in there. Without reviewing Jonas' systematic abstracting and cataloging in each of its installments, I would not

[13] The Bern Porter Collection at Colby College Libraries | Colby College Research | Digital Commons @ Colby. (n.d.). https://digitalcommons.colby.edu/porter_collection/

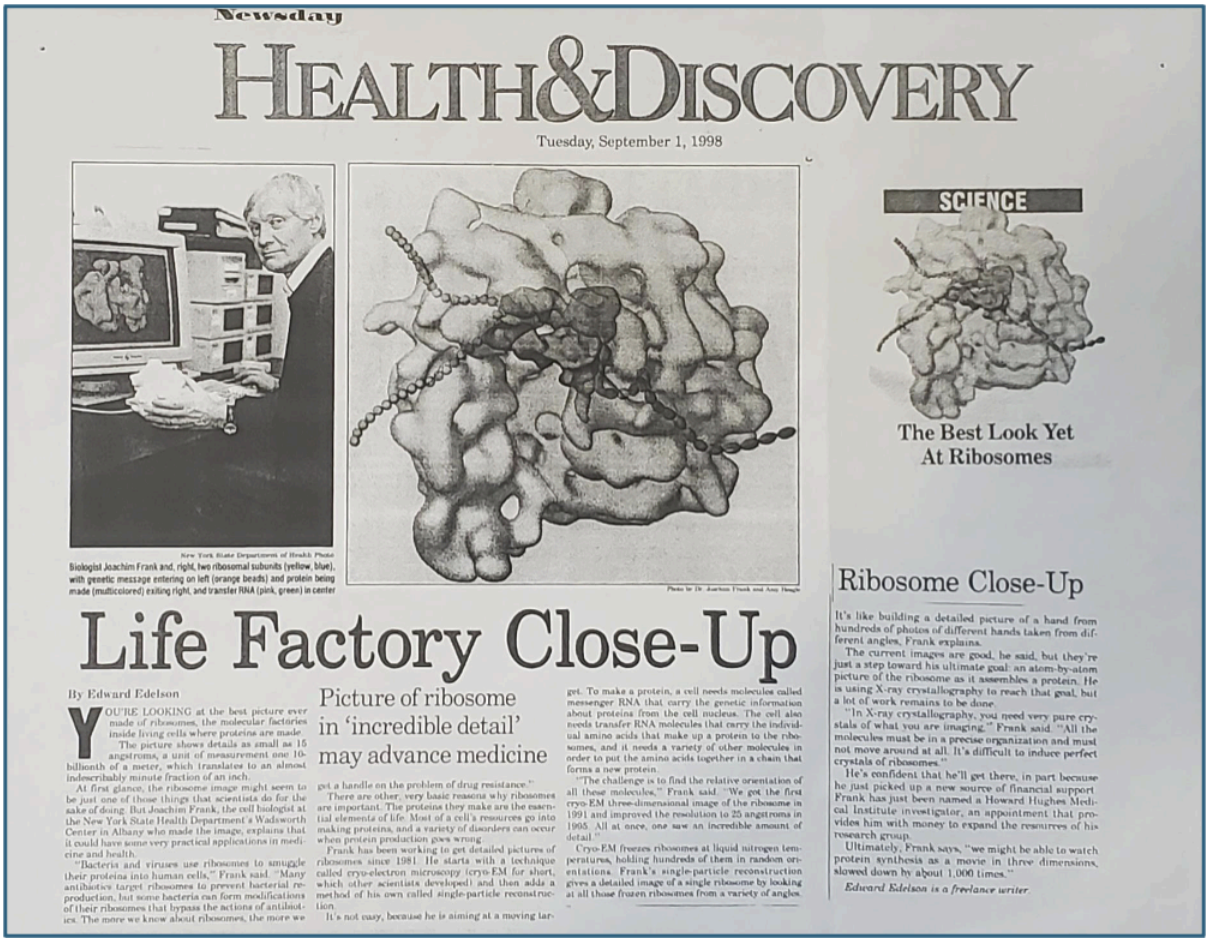
[14] Franx Fiction. (2023, December 14). WORKSPACE Archive donated to SUNY Albany - Franx Fiction - Joachim Frank. Franx Fiction - Joachim Frank. https://franxfiction.com/workspace-archive-donated-to-suny-albany/

have been confronted with documented facts that are plainly contradicted by my memory. Or it might be better to say that my memory is in some parts contradicted by documented facts. Among the discrepancies I found were reversals of cause and effect, incorrect timelines, confusions about who did what and why, misattributions of quotes, and – of course – events totally forgotten.

Implicit in an account of the past are the possibilities of multiple bifurcations, and different resulting trajectories my life might have taken. When I went through the little abstracts Jonas produced as he worked along the timeline, I was astonished by the number of times I had considered switching fields, and putting my efforts into a completely different area: of environmental sciences. The fact that I had forgotten most of these attempts is a testament to the selectiveness of memory, but it also says something about an active subconscious process of claiming agency and ownership over the pruned trajectory actually taken.

Most surprising for me was the discovery of my interview by Columbia University in the spring of 1979, an invitation by Barbara Low (1920-2019), then faculty member in the department I belong to today. A recruitment had been set in motion for the newly created biophysics program, and I duly presented my lecture on May 31, 1979 at 4 pm after meeting with seven members of the faculty. However, despite expressed enthusiasm about my presentation, the faculty decided to postpone investment into electron microscopy for a year. But no further invitations followed.

So here is the alternative branch of the trajectory, a branch my memory suppressed for a reason: a different faculty vote, or less hesitancy to invest in new technology, might have brought me to Columbia as a tenure-track assistant professor with a significant amount of teaching load and the responsibility to set up an EM facility from scratch. It is a sure bet that the development of the single-particle concepts and programs would have been delayed, compared to the peace and quiet at the Wadsworth Center, so the Nobel Prize might no longer be in the future. What is worse, I would never have met my present wife, and would face the specter of losing much of what is now so dear to me: my daughter along with her family, including two granddaughters.



Newsday

HEALTH&DISCOVERY

Tuesday, September 1, 1998

SCIENCE

The Best Look Yet At Ribosomes

Biologist Joachim Frank and, right, two ribosomal subunits (yellow, blue), with genetic message entering on left (orange beads) and protein being made (multicolored) exiting right, and transfer RNA (pink, green) in center

Life Factory Close-Up

By Edward Edelson

Picture of ribosome in 'incredible detail' may advance medicine

YOU'RE LOOKING at the best picture ever made of ribosomes, the molecular factories inside living cells where proteins are made.

The picture shows details as small as 15 angstroms, a unit of measurement one 10-billionth of a meter, which translates to an almost indescribably minute fraction of an inch.

At first glance, the ribosome image might seem to be just one of those things that scientists do for the sake of doing. But Joachim Frank, the cell biologist at the New York State Health Department's Wadsworth Center in Albany who made the image, explains that it could have some very practical applications in medicine and health.

"Bacteria and viruses use ribosomes to smuggle their proteins into human cells," Frank said. "Many antibiotics target ribosomes to prevent bacterial reproduction, but some bacteria can form modifications of their ribosomes that bypass the actions of antibiotics. The more we know about ribosomes, the more we get a handle on the problem of drug resistance."

There are other, very basic reasons why ribosomes are important. The proteins they make are the essential elements of life. Most of a cell's resources go into making proteins, and a variety of disorders can occur when protein production goes wrong.

Frank has been working to get detailed pictures of ribosomes since 1981. He starts with a technique called cryo-electron microscopy (cryo-EM for short, which other scientists developed) and then adds a method of his own called single-particle reconstruction.

It's not easy, because he is aiming at a moving target. To make a protein, a cell needs molecules called messenger RNA that carry the genetic information about proteins from the cell nucleus. The cell also needs transfer RNA molecules that carry the individual amino acids that make up a protein to the ribosomes, and it needs a variety of other molecules in order to put the amino acids together in a chain that forms a new protein.

"The challenge is to find the relative orientation of all these molecules," Frank said. "We got the first cryo-EM three-dimensional image of the ribosome in 1991 and improved the resolution to 25 angstroms in 1995. All at once, one saw an incredible amount of detail."

Cryo-EM freezes ribosomes at liquid nitrogen temperatures, holding hundreds of them in random orientations. Frank's single-particle reconstruction gives a detailed image of a single ribosome by looking at all those frozen ribosomes from a variety of angles.

Ribosome Close-Up

It's like building a detailed picture of a hand from hundreds of photos of different hands taken from different angles, Frank explains.

The current images are good, he said, but they're just a step toward his ultimate goal: an atom-by-atom picture of the ribosome as it assembles a protein. He is using X-ray crystallography to reach that goal, but a lot of work remains to be done.

"In X-ray crystallography, you need very pure crystals of what you are imaging," Frank said. "All the molecules must be in a precise organization and must not move around at all. It's difficult to induce perfect crystals of ribosomes."

He's confident that he'll get there, in part because he just picked up a new source of financial support. Frank has just been named a Howard Hughes Medical Institute investigator, an appointment that provides him with money to expand the resources of his research group.

Ultimately, Frank says, "we might be able to watch protein synthesis as a movie in three dimensions, slowed down by about 1,000 times."

Edward Edelson is a freelance writer.

Sample from the archive: in its newsletter, the New York State Department of Health celebrates the advances in cryo-EM visualization of the ribosome.

4. Conclusion - Jonas Piduhn and Joachim Frank

The dive into the archive, which was made possible by this once-in-a-lifetime collaboration, has been an eye-opener for both of us. Seeing innovation analyzed from the perspective of an economist has been quite surprising for the scientist in our team. And seeing a life's work unfold in meticulously kept documents has been a unique experience for a student who is just embarking on his own journey.

Our experience is further documented in a video interview, published by JOSHA, which can be accessed via the following YouTube link: ▶ Memory and Archive -- a Retrospective on a Career in Science.

The interview was conducted by Anita Eisakhani and filmed by Jonas Piduhn.

About the Authors

Jonas Piduhn is a 2024 Master of International Affairs graduate from Columbia University's School of International and Public Affairs. Previously, he completed his undergraduate and graduate degrees in economics at Humboldt University Berlin. He has published articles among others with the Council on Foreign Relations, Columbia University, Konrad-Adenauer-Foundation and Frankfurter Allgemeine Zeitung. He focuses on interdisciplinary research. His publications include papers on innovation, big ocean states, the European Union and the global fight against climate change.

Joachim Frank is a Professor of the Department of Biochemistry and Molecular Biophysics, and the Department of Biological Sciences at Columbia University. He studied Physics at the University of Freiburg and received his Ph.D. from the Technical University in Munich. In 1975 he joined the Wadsworth Center in Albany as a Senior Research Scientist. In 1985, he joined the faculty of the Department of Biomedical Sciences of SUNY Albany. In 2008 he moved to New York to assume his current position. Dr. Frank's lab has developed techniques of single-particle reconstruction of biological macromolecules using the electron microscope, specializing in mathematical and computational approaches. He has applied these techniques of visualization to explore the structure and dynamics of the ribosome during the process of protein synthesis. They are now widely used to study the structure of the COVID-19 virus and other pathogens and biomolecules implicated in human diseases.

Dr. Frank is a member of the National Academy of Sciences and of the American Academy of Microbiology. He is also a fellow of the American Academy of Arts and Sciences and of the American Association for the Advancement of Science. In 2014 he was honored with the Franklin Medal for Life Science. In 2017 he shared the Wiley Prize in Biomedical Sciences with Richard Henderson and Marin van Heel. He was awarded the 2017 Nobel Prize in Chemistry together with Jacques Dubochet and Richard Henderson.