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The 1991 Nobel Prize Winners—from Patch Clamps (Neher and Sakmann) to Spaghetti Theory (de Gennes), Social Costs (Coase), and NMR (Ernst)—Were All Citation Superstars

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ABSTRACT

Each year, we review the citation records for the current group of Nobel Prize winners. This series of essays began over a decade ago. In 1991, unlike the previous year, all of the winners proved to be citation superstars. We've listed their most-cited papers, discussed the impact of their work, and reviewed *Citation Classic®* commentaries, written by the winners or their collaborators. These provide a unique perspective on the research that led to the Nobel Prize.

As I said nearly 30 years ago, it would be absurd to claim that a researcher deserves the Nobel Prize simply because he or she is a citation superstar.[1] Our essay on the 1990 Nobel Prizes[2] noted that several of the science prize-winners, although well cited, had received relatively fewer citations when compared with most Nobelists. This would be especially true in fields where the work was done many years ago. However, scientific work of Nobel class, unaccompanied by high citation impact, deserves some explanation, such as delayed recognition or whatever. It is the exception rather than the rule. In 1991, the rule prevailed, and all recipients are citation superstars.

Physiology or Medicine

This year's prize for physiology or medicine was awarded to Erwin Neher, director of the Membrane Biophysics Department, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany, and Bert Sakmann, physiologist, Max Planck Institute for Medical Research, Heidelberg, Germany, for their work, first published in 1976,[3] in determining the mechanism by which cells regulate the voltage across their membranes. Called the patch-clamp method, this technique allows researchers to measure individual ion channels in the cell membrane, to the level of picoamperes (10^{-12} amperes), by eliminating the membrane's electrical noise. Neher and Sakmann accomplished this by touching a cell membrane with a glass micropipette containing a saline solution and creating a seal to a small patch of the membrane by applying suction. This isolated a tiny section from the rest of the membrane, allowing measurement over precise areas.

From a citationist perspective, Neher and Sakmann would be considered prime Nobel candidates. Their most-cited paper, "Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," has received more than 4,000 citations to date, with more than 700 in 1990 alone.[4] In our 1990 essay on the most-cited papers of all time, it ranked as number 252.[5] By now, it is easily within the top 100. This paper elaborates on a meeting abstract by Neher published just a few months earlier.[6] The paper's citations continue to rise, with more than 800 in 1991.

These authors have numerous other publications with substantial citation records. Papers on which Neher was first author or coauthor were cited nearly 9,000 times. Sakmann's work has been cited more than 7,300 times. Naturally, there is a great deal of overlap in these estimates since they were coauthors on so many papers. We've indicated the counts for their top 10 papers in Table 1. These citation records simply reflect the widespread impact of their work.

Erwin Neher

Bert Sakmann

Both laureates are ranked by ISI®, according to data from the *Science Citation Index®* (*SCI®*), as among the top 300 scientists most cited in the 1980s, with 6,256 for Neher and 5,934 for Sakmann.[7]

In addition to substantial citation counts, Nobel-class researchers may be identified by having previously received "predictor" awards,[8] which are other prestigious prizes that recognize Nobel-class work. Here also, these laureates stand out. As with one of the 1990 winners in physiology or medicine, E. Donnall Thomas, Neher and Sakmann received the 1989 Gairdner Foundation award. In addition, among the many awards they have won individually, they are corecipients of the Leibniz Award of the Deutsche Forschungsgemeinschaft in 1986, the Louisa Gross-Horwitz Prize in 1986, and the Hellmut Vits-Preis in 1990. As Harriet Zuckerman notes in her book, *Scientific Elite*, "Nobel prizes do not go to unknowns."[9]

The techniques that they developed have given rise to a whole generation of research. By proving that cell membranes have individual ion channels through which minuscule currents can pass, scientists can now understand the processes by which nerve impulses travel, the fertilization process of eggs, and the regulation of the heartbeat. In addition, using their techniques, scientists are now beginning to understand the mechanisms of diseases such as cystic fibrosis (CF), in which the CF gene has been linked to chloride channels, and diabetes, in which researchers have used the technique to show how certain drugs can stimulate the beta cells to produce more insulin.[10]

Chemistry

New Zealand physicist Ernest Rutherford once said: "All of science is either physics or stamp collecting." When he won the 1908 Nobel Prize for chemistry, for "his investigations into the disintegration of the elements, and the chemistry of radioactive substances," he commented at the banquet that he "had dealt with many different transformations with various time-periods, but the quickest he had met was his own transformation from a physicist to a chemist."[11]

While Richard R. Ernst is a chemist, currently with the Eidgenössische Technische Hochschule (Swiss Federal Institute of Technology), Zürich, the primary efforts for which he was recognized with this award

Table 1. Ten most-cited papers by E. Neher and B. Sakmann. (A=citations 1945-1990; B=1991 citations, January-September; C=bibliographic reference.)

A	B	C
3,400	568	**Hamill O P, Marty A, Neher E, Sakmann B & Sigworth F J.** Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Arch.—Eur. J. Physiol.* 391:85-100, 1981.
472	43	**Fenwick E M, Marty A & Neher E.** Sodium and calcium channels in bovine chromaffin cells. *J. Physiol.—London* 331:599-635, 1982.
422	25	**Colquhoun D, Neher E, Reuter H & Stevens C F.** Inward current channels activated by intracellular Ca in cultured cardiac-cells. *Nature* 294:752, 1981.
411	34	**Neher E & Steinbach J H.** Local-anesthetics transiently block currents through single acetocholine-receptor channels. *J. Physiol.—London* 277:153, 1978.
408	13	**Neher E & Sakmann B.** Single-channel currents recorded from membrane of denervated frog muscle fibers. *Nature* 260:799-802, 1976.
300	15	**Neher E.** 2 fast transient current components during voltage clamp on snail neurons. *J. Gen. Physiol.* 58:36, 1971.
293	5	**Neher E & Stevens C F.** Conductance fluctuations and ionic pores in membranes. *Annu. Rev. Biophys. Biophys. Chem.* 6:345-81, 1977.
278	36	**Fenwick E M, Marty A & Neher E.** A patch clamp study of bovine chromaffin cells and their sensitivity to acetycholine. *J. Physiol.—London* 331:577-97, 1982.
275	14	**Sakmann B, Patlak J & Neher E.** Single acetocholine-activated channels show burst-kinetics in presence of desensitizing concentrations of agonist. *Nature* 286:71-3, 1980.
236	2	**Lux H D & Neher E.** Equilibration time course of [K+]O in cat cortex. *Exp. Brain Res.* 17:190-205, 1973.

were advances in Fourier-transformation nuclear magnetic resonance (FT-NMR) and two-dimensional NMR (2D-NMR)—as close to physics as a chemist might come. This work laid the foundation for the NMR imaging used today in medicine (as magnetic resonance imaging, or MRI), physics, biology, and, of course, chemistry.

Though Ernst did not invent NMR, he spent the 1960s and 1970s refining the technique, making it practical for real world applications. The technique was actually invented by two groups in the 1940s,[12,13] for which the principals, Felix Bloch, Stanford University, and Edward Purcell, Harvard University, won the Nobel Prize for physics in 1952. As noted in a *Citation Classic* commentary by N. Bloembergen,[14] about a paper on which he was a coauthor with Purcell:

> This work was stimulated by discussions of a group of physicists active in World War II radar development at the M.I.T. Radiation Laboratory. F. Bloch and W.W. Hansen, who were involved with radar work in other groups, independently and nearly simultaneously carried out a similar experiment, which they, together with M.C. Packard, called nuclear induction....

However, while the technology held great promise, the sensitivity of NMR in comparison to other spectroscopies worried researchers. Here, Ernst, with W.A. Anderson, produced the first of two developments that made NMR faster and more accurate, and for which the Nobel committee recognized him. The breakthrough came in 1966,[15] at Varian Associates, in Palo Alto, California, using single, high-energy pulses of radio waves containing all frequencies that would make atoms "flip," instead of a gradual sweep with a spectrum of radio waves that was in use previously.[16] As Ernst noted in his *Citation Classic*[17] on this benchmark paper:

> In 1964, we certainly did not foresee that this simple concept could revolutionize NMR. Initially, we did not have an online computer available. The free induction decays were acquired in a time averaging computer and punched on paper tape. The paper tape had to be carried from Palo Alto to IBM in San Jose to transfer the data to a bunch of cards. With the cards we went to

Table 2. Five most-cited papers by R.R. Ernst. (A=citations through 1990; B=1991 citations, January-September; C=bibliographic reference.)

A	B	C
1,408	97	**Aue W P, Bartholdi E & Ernst R R.** Two-dimensional spectroscopy. Application to nuclear magnetic resonance. *J. Chem. Phys.* 64:2229-46, 1976.
820	109	**Jeener J, Meier B H, Bachmann P & Ernst R R.** Investigation of exchange process by 2-dimensional NMR-spectroscopy. *J. Chem. Phys.* 71:4546-53, 1979.
424	44	**Macura S & Ernst R R.** Elucidation of cross relaxation in liquids by two-dimensional NMR-spectroscopy. *Molec. Phys.* 41:95-117, 1980.
400	16	**Nagayama K, Kumar A, Wuthrich K & Ernst R R.** Experimental techniques of two-dimensional correlated spectroscopy. *J. Magn. Res.* 40:321-34, 1980.
367	11	**Kumar A, Welti D & Ernst R R.** NMR Fourier zeugmatography. *J. Magn. Res.* 18:69-83, 1975.

Table 3. The five papers on which R.R. Ernst was a coauthor that have been ranked as among the most-cited papers from the years in which they were published. (A=category; B=citations through 1990; C=1991 citations, January-September; D=bibliographic reference.)

A	B	C	D
Chemistry	290	24	**Macura S, Huang Y, Suter D & Ernst R R.** Two-dimensional chemical exchange and cross-relaxation spectroscopy of coupled nuclear spins. *J. Magn. Resonance* 43:259-81, 1981.
Chemistry	182	19	**Braunschweiler L, Bodenhausen G & Ernst R R.** Analysis of networks of coupled spins by multiple quantum N.M.R. *Mol. Phys.* 48:535, 1983.
Chemistry	271	44	**Sorensen O W, Eich G W, Levitt M H, Bodenhausen G & Ernst R R.** Product operator formalism for the description of NMR pulse experiments. *Prog. Nucl. Magn. Reson. Spectros.* 16:163-92, 1983.
Physical Sciences	115	4	**Sorensen O W & Ernst R R.** Elimination of spectral distortion in polarization transfer experiments. Improvements and comparison of techniques. *J. Magn. Resonance* 51:477-89, 1983.
Physical Sciences	240	11	**Wider G, Macura S, Kumar A, Ernst R R & Wuthrich K.** Homonuclear two-dimensional ^{1}H NMR of proteins. Experimental procedures. *J. Magn. Resonance* 56:207, 1984.

the Palo Alto Computer Service Center where the Fourier transformation and the plotting were done. The entire process took about 48 hours in comparison with a normal spectrum being run in just ten minutes! Nevertheless, we claimed in our paper a substantial time saving—and the readers believed it!

Ernst's second important development was 2-dimensional NMR, on which he and his coauthors published in 1976.[18] As he noted in a *Citation Classic*[19] commentary on this paper:

> Since the appearance of the paper, the field has experienced (after a slow start) an explosive development. Indeed, a new dimension of spectroscopy has become accessible, and an almost unaccountable number of useful techniques has emerged. Perhaps the most useful application of 2D spectroscopy is for determining the structure of biological macromolecules in solutions. The initial steps and much of the development were done in a fruitful collaboration with Kurt Wüthrich that started in 1976 and that continues today.

One of the 300 most-cited scientists from 1981 through 1990[7] (5,844 cites), Ernst, as with all of the 1991 winners, is certainly a citation superstar. His four most-cited papers together have been cited more than 1,200 times. In all, he has authored or coauthored papers that have received a total of more than 11,300 cites. Table 2 presents the citation records of his five most-cited papers. And, as an indication of the importance of his continuing research, Table 3 lists five papers published in the 1980s that have made our lists of most-cited papers. Note that he has papers in both chemistry

Ronald H. Coase

and physical sciences listings. These are very high numbers for chemical science.

And, while the Nobel is likely the highest honor, he also has been awarded the Wolf Foundation Prize, shared in 1991 with Alex Pines, author of a recent *Citation Classic*.[20] And, he was notified of his Nobel award while inflight to receive the Louisa Gross-Horwitz Prize.

Physics

Pierre-Gilles de Gennes, the director of the Ecole de Physique et Chimie, College de France, Paris, received the 1991 Nobel Prize for physics. A theoretician, his prodigious body of work now spans more than 30 years. The breadth of his work runs from polymers (his "spaghetti" theory of polymer flow), to superconductivity, liquid crystals, and, recently, to ultra-divided matter (important in the real world for such things as food, cosmetics, and toothpastes).[21] In announcing his prize, the awards committee called de Gennes "the Isaac Newton of our time," because of his success in applying mathematics to generalized explanations of many different phenomena.[22]

Of the 1991 Nobelists, de Gennes's citation record is first among superstars. As a first author, he has 34 papers and four books, published between 1958 and 1985, cited more than 100 times each through 1990. These papers alone account for more than 13,000 cites, with his total citation record for all publications exceeding 15,800 cites. We noted one of his papers[23] in our essay on the most-cited chemistry papers of 1982.[24] In the 1980s, publications by de Gennes received 2,160 citations. Table 4 lists his 10 most-cited publications.

As with Ernst, de Gennes's work is cross-disciplinary and based in intricate mathematics—especially rewarding as there is no Nobel Prize for mathematics. According to Patricia E. Cladis, AT&T Bell Laboratories, Murray Hill, New Jersey, one of de Gennes's great gifts was in making his subtle mathematical ideas accessible to all physicists. She states in *The New York Times*, "De Gennes is as heavily armed with math as any theorist, but he wears these arms lightly and gracefully."[22]

Economics

In awarding Ronald H. Coase the 1991 Nobel Memorial Prize in economic sciences, the academy cited two works, "The nature of the firm," 1937,[25] where Coase revived the stagnant field of industrial organizations, and "The problem of social cost," 1960,[26] where he forced economists and lawyers to rethink what it takes to allow markets to work efficiently.

Recognizing quality over quantity, the Nobel committee chose an economist who, in six decades, has published just a dozen research papers of significance. According to Robert Cooter, Boalt School of Law, University of California, "Most economists maximize the amount they write. Coase maximized the amount others wrote about his work."[27] This was verified in the 1989 *Current Contents* ® essays on the core journals in economics.[28] In Part 2 of that essay, Arthur M. Diamond, Jr., calls Coase "the citation superstar" of the most-cited papers from the core journals in economics. One of his two publications on the list, "The problem of social cost," is the most-cited article on the list—and by no small mar-

Table 4. Ten most-cited publications by P.-G. de Gennes. (A=citations through 1990; B=1991 citations, January-September; C=bibliographic reference.)

A	B	C
2,105	302	**de Gennes P-G.** *Scaling concepts in polymer physics.* Ithaca, NY: Cornell University Press, 1979.
1,984	155	**de Gennes P-G.** *Physics of liquid crystals.* Oxford, England: Oxford University Press, 1974.
853	66	**de Gennes P-G.** Reptation of a polymer chain in presence of fixed obstacles. *J. Chem. Phys.* 55:572, 1971.
770	59	**de Gennes P-G.** *Superconductivity of metals and alloys.* New York: Benjamin, 1966. 274 p.
530	13	**de Gennes P-G.** Exponents for excluded volume problem as derived by Wilson method. *Phys. Lett. A* 38:339, 1972.
422	30	**de Gennes P-G.** Boundary effects in superconductors. *Rev. Mod. Phys.* 36:225, 1964.
413	30	**de Gennes P-G.** Dynamics of entangled polymer-solutions. 1. Rouse model. *Macromolecules* 9:587-93, 1976.
359	13	**de Gennes P-G.** Short-range order effects in isotropic phase of nematics and cholesterics. *Mol. Cryst. Liquid Cryst.* 12:193, 1971.
298	3	**de Gennes P-G & Friedel J.** Anomalies de resistivite dans certains metux magnetiques. *J. Phys. Chem. Solids* 4:71-7, 1958.
291*	44	**de Gennes P-G & Taupin C.** Microemulsions and the flexibility of oil/water interfaces. *J. Phys. Chem.* 86:2294-304, 1982.

*Listed in: **Garfield E.** The 1982 chemistry articles most cited, 1982-1984. *Essays of an information scientist: ghostwriting and other essays.* Philadelphia: ISI Press, 1986. Vol. 8. p. 497-511.

gin. It had received 1,005 cites through 1986, while the second most-cited paper on the list had received 671. And, for a further comparison, the most-cited paper from noncore journals had received 868 cites. That paper was written by W.F. Sharpe,[29] winner of the 1990 Nobel Prize in economics. Here, we should note that, in general, economics papers receive relatively fewer citations than other fields, such as biology and chemistry, making his record even more impressive.

Also in that essay, Diamond discussed why the work of Coase was so unique.

> Coase's work is unusual because it contains almost no mathematics or sophisticated statistical analysis. This may explain why economists seldom mention Coase as a candidate for the Nobel Prize when they speculate on future winners.

Obviously, they have to speculate no longer. In 1990, we discussed how we might forecast Nobel Prize winners in economics.[30] In that essay, Coase was the 28th most-cited economist of all time, based on citations from 1966 to 1986 (1,950 citations). At the same time, Peter Passell of *The New York Times* informally polled a dozen economists. Coase was listed among the top six choices.[31] In updating his citation record, we find that his work has now been cited more than 2,400 times.

Conclusion

In closing, we note that these researchers have not only risen to the top of their fields, they actually created the fields for which they were recognized. Their citation records bear out the importance of their work, and, as is usually the case with the Nobel Prize, their work reflects both a commitment over many years and a quality of unique vision.

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