

PROCEEDINGS OF THE
FOURTH BERKELEY SYMPOSIUM

VOLUME IV

PROCEEDINGS *of the* FOURTH
BERKELEY SYMPOSIUM ON
MATHEMATICAL STATISTICS
AND PROBABILITY

*Held at the Statistical Laboratory
University of California
June 20–July 30, 1960,*

with the support of
University of California
National Science Foundation
Office of Naval Research
Office of Ordnance Research
Air Force Office of Research
National Institutes of Health

VOLUME IV

CONTRIBUTIONS TO BIOLOGY AND PROBLEMS OF MEDICINE

EDITED BY JERZY NEYMAN

UNIVERSITY OF CALIFORNIA PRESS
BERKELEY AND LOS ANGELES
1961

UNIVERSITY OF CALIFORNIA PRESS
BERKELEY AND LOS ANGELES
CALIFORNIA

CAMBRIDGE UNIVERSITY PRESS
LONDON, ENGLAND

© 1961 BY
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

The United States Government and its offices, agents, and employees, acting within the scope of their duties, may reproduce, publish, and use this material in whole or in part for governmental purposes without payment of royalties thereon or therefor. The publication or republication by the government either separately or in a public document of any material in which copyright subsists shall not be taken to cause any abridgment or annulment of the copyright or to authorize any use or appropriation of such copyright material without the consent of the copyright proprietor.

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 49-8189

PRINTED IN THE UNITED STATES OF AMERICA

CONTENTS OF PROCEEDINGS, VOLUMES I, II, AND III

Volume I—Theory of Statistics

F. J. ANSCOMBE, Examination of residuals. RICHARD BELLMAN, A mathematical formulation of variational processes of adaptive type. Z. W. BIRNBAUM, On the probabilistic theory of complex structures. DAVID BLACKWELL, Exponential error bounds for finite state channels. L. BREIMAN, Optimal gambling systems for favorable games. HERMAN CHERNOFF, Sequential tests for the mean of a normal distribution. Y. S. CHOW and HERBERT ROBBINS, A martingale system theorem and applications. D. R. COX, Tests of separate families of hypotheses. TORE DALENIUS, JAROSLAV HÁJEK, and STEFAN ZUBRZYCKI, On plane sampling and related geometrical problems. H. E. DANIELS, The asymptotic efficiency of a maximum likelihood estimator. GEORGE B. DANTZIG and ALBERT MADANSKY, On the solution of two-stage linear programs under uncertainty. F. N. DAVID and EVELYN FIX, Rank correlation and regression in a non-normal surface. BRUNO DE FINETTI, The Bayesian approach to the rejection of outliers. R. L. DOBRUSHIN, Mathematical problems in the Shannon theory of optimal coding of information. THOMAS S. FERGUSON, On the rejection of outliers. R. FORTET, Hypothesis testing and estimation for Laplacian functions. J. L. HODGES, Jr. and E. L. LEHMANN, Comparison of the normal scores and Wilcoxon tests. HAROLD HOTELLING, The behavior of some standard statistical tests under nonstandard conditions. W. JAMES and CHARLES STEIN, Estimation with quadratic loss. J. KIEFER, Optimum experimental designs V, with applications to systematic and rotatable designs. TOSIO KITAGAWA, Successive processes of statistical optimizing procedures. WILLIAM KRUSKAL, The coordinate-free approach to Gauss-Markov estimation, and its application to missing and extra observations. D. V. LINDLEY, The use of prior probability distributions in statistical inference and decisions. EMANUEL PARZEN, Regression analysis of continuous parameter time series. ROY RADNER, The evaluation of information in organizations. C. RADHAKRISHNA RAO, Asymptotic efficiency and limiting information. ALFRÉD RÉNYI, On measures of entropy and information. HERMAN RUBIN, The estimation of discontinuities in multivariate densities, and related problems in stochastic processes. LEONARD J. SAVAGE, The foundations of statistics reconsidered. L. SCHMETTERER, Stochastic approximation. CLAUDE E. SHANNON, Two-way communication channels. HERBERT SOLOMON, On the distribution of quadratic forms in normal variates. ANTONÍN ŠPACĚK, Statistical estimation of semantic provability. A. J. THOMASIAN, The metric structure of codes for the binary symmetric channel. JOHN W. TUKEY, Curves as parameters, and touch estimation. I. VINCZE, On two-sample tests based on order statistics. S. S. WILKS, A combinatorial test for the problem of two samples from continuous distributions. HERMAN O. A. WOLD, Unbiased predictors. J. WOLFOWITZ, A channel with infinite memory.

Volume II—Probability Theory

B. V. GNEDENKO, Alexander Iacovlevich Khinchin. J. L. DOOB, Appreciation of Khinchin. YU. K. BELAYEV, Continuity and Hölder's conditions for sample functions of stationary Gaussian Processes. K. L. CHUNG, Probabilistic methods in Markov chains. HARALD CRAMÉR, On some classes of nonstationary stochastic processes. J. H. CURTISS, A stochastic treatment of some classical interpolation problems. J. L. DOOB, Notes on martingale theory. A. DVORETZKY, P. ERDÖS, and S. KAKUTANI, Nonincrease every-

where of the Brownian motion process. E. B. DYNKIN, Transformations of Markov processes connected with additive functionals. MAREK FISZ, Characterization of sample functions of stochastic processes by some absolute probabilities. B. V. GNEDENKO, V. S. KOROLUK, and A. V. SKOROKHOD, Asymptotic expansions in probability theory. ULF GRENNANDER, Stochastic groups and related structures. OTTO HANŠ, Random operator equations. HENRY HELSON and DAVID LOWDENSLAGER, Vector-valued processes. WASSILY HOEFFDING, On sequences of sums of independent random vectors. KIYOSI ITÔ, Wiener integral and Feynman integral. SHIZUO KAKUTANI, Spectral analysis of stationary Gaussian processes. SAMUEL KARLIN and JAMES MCGREGOR, Occupation time laws for birth and death processes. PAUL LÉVY, An extension of the Lebesgue measure of linear sets. YU. V. LINNIK, On the probability of large deviations for the sums of independent variables. EUGENE LUKACS, Recent developments in the theory of characteristic functions. J. G. MAULDON, Asymmetric oriented percolation on a plane. JACQUES NEVEU, Lattice methods and submarkovian processes. E. J. G. PITMAN, Some theorems on characteristic functions of probability distributions. YU. V. PROHOROV, The method of characteristic functionals. G. E. H. REUTER, Competition processes. M. ROSENBLATT, Independence and dependence. YU. A. ROZANOV, An application of the central limit theorem. CZESŁAW RYLL-NARDZEWSKI, Remarks on processes of calls. WALTER L. SMITH, On some general renewal theorems for nonidentically distributed variables. FRANK SPITZER, Recurrent random walk and logarithmic potential. LAJOS TAKÁCS, The transient behavior of a single server queueing process with a Poisson input. K. URBANIK, Generalized stochastic processes with independent values. DAVID M. G. WISHART, An application of ergodic theorems in the theory of queues. A. M. YAGLOM, Second-order homogeneous random fields. KOSAKU YOSIDA, On a class of infinitesimal generators and the integration problems of evolution equations.

Volume III—Astronomy, Meteorology, and Physics

J. A. CRAWFORD, The motion of charged particles in a random magnetic field. W. B. FRETTER, Problems in the measurement of ionization in tracks in a cloud chamber. J. M. HAMMERSLEY, On the statistical loss of long-period comets from the solar system, II. J. M. HAMMERSLEY, On the dynamical disequilibrium of individual particles. DAVID G. KENDALL, The distribution of energy perturbations for Halley's and some other comets. DAVID G. KENDALL, Some problems in the theory of comets, I. DAVID G. KENDALL, Some problems in the theory of comets, II. R. H. KERR, Perturbations of cometary orbits. L. LE CAM, A stochastic description of precipitation. J. L. LOVASICH, N. U. MAYALL, J. NEYMAN, and E. L. SCOTT, The expansion of clusters of galaxies. R. A. LYTTLETON, On the statistical loss of long-period comets from the solar system, I. R. MINKOWSKI, The luminosity function of extragalactic radio sources. JERZY NEYMAN and ELIZABETH L. SCOTT, Field galaxies: luminosity, redshift, and abundance of types. Part I. Theory. THORNTON PAGE, Average masses of the double galaxies. LAURENT SCHWARTZ, Density of probability of presence of elementary particles. S. M. ULAM, On some statistical properties of dynamical systems. W. J. YOUNDEN, Statistical problems arising in the establishment of physical standards.

PREFACE

THE FOURTH BERKELEY SYMPOSIUM on Mathematical Statistics and Probability was organized by the personnel of the Statistical Laboratory and of the Department of Statistics, University of California, Berkeley, comprised of Professors E. W. Barankin, D. Blackwell, F. Cogburn, E. Fix, J. L. Hodges, Jr., L. Le Cam, E. L. Lehmann, M. Loève, J. Neyman, R. Radner, H. Scheffé, E. L. Scott, and A. J. Thomasian. The plan of the Symposium was drawn and the contributors selected with an active participation of two Advisory Committees. For advice regarding theory of probability and statistics and also regarding some applications, we are indebted to the Advisory Committee composed of delegates of the American Mathematical Society, Professor J. H. Curtiss, J. L. Doob, and William Feller, of delegates of the Institute of Mathematical Statistics, Professors Albert H. Bowker and H. E. Robbins, and of the Editor of the *Annals of Mathematical Statistics*, Professor W. H. Kruskal. The program on biology and on problems of health was arranged with the help of another Advisory Committee composed of representatives of the National Institutes of Health, Drs. M. Berman, R. Bryan, H. F. Dorn, S. Geisser, S. Greenhouse, J. Hearon, M. Shimkin, and J. L. Stephenson, and also Drs. A. Berger, J. Jacquez, H. B. Jones, and C. Tobias. This help is very gratefully acknowledged.

The purpose of the Berkeley Symposia is to stimulate research through the lectures of the carefully selected speakers and by providing opportunity for personal contacts extending over several weeks spent in Berkeley for scholars from different centers, and by publishing the *Proceedings*.

The *Proceedings* are intended to represent a comprehensive cross section of contemporary thinking on problems of probability and mathematical statistics. Although completeness is difficult to achieve, the Statistical Laboratory is gratified by the gradual increase in the number of intellectual centers throughout the world represented at the successive Symposia. In particular, the present *Proceedings* are much richer than those of the earlier Symposia because of the several contributions from members of the great Russian school of probability. These contributions were secured through the kind cooperation of the National Academy of Sciences in Washington, D. C. and of the Academy of Sciences of the U.S.S.R. in Moscow, and hearty thanks are due to both institutions.

Volume I of the *Proceedings* is given to the theory of statistics. Volume II contains papers on probability. As a preliminary section this volume contains the record of a special meeting of the Symposium dedicated to the memory of the recently deceased remarkable probabilist A. I. Khinchin. It is a pleasure to thank Professor B. V. Gnedenko for providing us with a photograph of the late Professor Khinchin. It appears as the frontispiece of Volume II.

Although a comprehensive representation of theoretical developments is difficult to achieve, the field of application of the theory of probability and of statistics is currently so broad and contains so many different domains that any significant approach to completeness of coverage is simply impossible, even in a meeting extending over six weeks. Particular domains of application require separate symposia. The several domains that were actually discussed at the Fourth Symposium were selected partly on the basis of personal preference of certain scholars invited to the Symposium for the excellence of their work in a number of fields and partly because of the related research conducted at the Statistical Laboratory.

Applications to physical sciences are published in Volume III of the *Proceedings*. They include astronomy, meteorology, and physics.

Volume IV of the *Proceedings* is given to biology and problems of medicine. Here, with reference to one particular subject, namely theory of carcinogenesis, substantial effort was expended to collect not only a comprehensive representation of the current theoretical statistical and probabilistic work but also papers characterizing various relevant empirical findings. Thus, the fourth volume of these *Proceedings* includes papers outlining the important biological studies relevant to the theory of carcinogenesis, from experiments on cellular phenomena, through studies of viruses, to large-scale surveys on the possible effects of low level radiation, one of the most dreaded carcinogens.

A realistic and precise theory of carcinogenesis seems to belong to the category of those problems in which the solution depends on a close cooperation and mutual understanding of experimenters on the one hand and of statisticians on the other. It is hoped that Volume IV of these *Proceedings* will contribute to the establishment of such understanding and cooperation.

The sources of financial support of the Fourth Symposium are listed on the title page of each volume of these *Proceedings* and this support is here very gratefully acknowledged. First and foremost, hearty thanks are due to Professor Clark Kerr, President of the University of California, for his generous grant made several years before the Symposium. This initial grant insured the organization of the Symposium. However, without the subsequent generous financial support of the National Science Foundation, followed by those of the Air Force Office of Research and Development, of the Office of Naval Research, and of the Office of Ordnance Research, the meeting could not have been held on the scale that actually was achieved. A special grant and also considerable moral support of the National Institutes of Health helped to organize a series of sessions on biology and medicine.

In addition to direct grants of funds, the organization of the Symposium obtained a most valuable indirect support kindly provided by the U. S. Air Force Office of Scientific Research and, to an even greater extent, by the Office of Naval Research. This indirect support consisted in the air transportation for a number of foreign guests over the oceans, both the Atlantic and the Pacific.

Without this form of help, foreign participation in the Fourth Symposium would have been greatly reduced.

The growth of the Symposia is naturally accompanied by the corresponding growth of the *Proceedings*, from about 500 pages for the First Symposium of 1945/46 to about 2000 printed pages for the Fourth. Speedy publication of this amount of scientific material naturally presents a number of problems. This is particularly true when a substantial part of the material is originally written in foreign languages and requires translation into English. This is even more particularly true when it is desired to produce books at a relatively low price which will make them accessible to young scholars.

In the above connection I am greatly indebted to a number of colleagues and friends for their work on the translation of manuscripts and for their help to simplify some of the formulas so as to make them less expensive to set in type. In particular my thanks are due to Professor Evelyn Fix, to Professor Lucien Le Cam, to Dr. Emma Lehmer, to Professor and Mrs. J. G. Mauldon, and to Professor Elizabeth L. Scott. Further thanks for help in translations are also due to Drs. I. J. Abrams, A. R. Kraiman, and L. Neustadt of the Space Technology Laboratories.

For work on the preparation of some of the manuscripts for the printers my thanks go to several Research Assistants in the Statistical Laboratory, S. Bhuchongkul, N. L. Cook, M. Darland, J. Denny, J. Fabius, S. S. Jogdeo, J. Karush, W. Klonecki, J. Kraft, W. Lawton, J. L. Lovasich, P. Mikulski, L. Regelson, and G. D. Woodard. Before being sent to the printers, many manuscripts had to be retyped. This was excellently done by Mrs. Sharlee Guise and Mrs. Julia Rubalcava.

Special thanks are due W. H. Newkirk who, as copy editor of the *Proceedings*, took care of the many complexities of publishing with uncommon care and unceasing patience.

Financial difficulties connected with the publication were overcome with the effective help of the Editorial Committee of the University of California, due to the generous subvention of the IBM Company and to additional grants from the RAND Corporation and from the Space Technology Research Laboratories. All this help is gratefully acknowledged.

Funds and adequate personnel are, of course, indispensable in any substantial enterprise. However, in addition to these most necessary elements, for an organization to run smoothly it is necessary that it include someone whose continuous care, initiative, foresight, and good common sense would make the organization "click." For this role in the organization of the Symposium it is a pleasure to thank my colleague and friend, Professor Elizabeth L. Scott.

Mr. August Frugé, the Director of the University of California Press, was most cooperative and helpful in organizing the publication of the *Proceedings*. The speed with which the *Proceedings* are published is very essential, and one year taken to produce about 2000 pages in print is an excellent record. However,

the actual speed in manufacturing the books is even better than it looks, for, to this editor's deep shame and regret, the manuscripts of which he himself is a co-author were the last to be delivered to the Press. In fact, they were delivered in the last days of June 1961, and my thanks to Mr. Frugé are accompanied by sincere apologies.

JERZY NEYMAN
Director, Statistical Laboratory

CONTENTS

NIELS ARLEY—Theoretical Analysis of Carcinogenesis	1
P. ARMITAGE and R. DOLL—Stochastic Models for Carcinogenesis	19
M. S. BARTLETT—Monte Carlo Studies in Ecology and Epidemiology	39
R. E. BELLMAN, J. A. JACQUEZ, and R. KALABA—Mathematical Models of Chemotherapy	57
AGNES BERGER and RUTH Z. GOLD—On Comparing Survival Times	67
JOSEPH BERKSON and J. L. HODGES, JR.—A Minimax Estimator for the Logistic Function	77
MONES BERMAN—Application of Differential Equations to the Study of the Thyroid System	87
HAROLD F. BLUM—Comparable Models for Carcinogenesis by Ultraviolet Light and by Chemical Agents.	101
W. RAY BRYAN—Virus Carcinogenesis	123
D. G. CHAPMAN—Statistical Problems in Dynamics of Exploited Fisheries Populations	153
CHIN LONG CHIANG—On the Probability of Death from Specific Causes in the Presence of Competing Risks	169
GEORGE B. DANTZIG, JAMES C. DEHAVEN, and CRAWFORD F. SAMS—A Mathematical Model of the Chemistry of the External Respiratory System	181
W. J. DIXON—Some Statistical Uses of Large Computers	197
JOHN E. DUNN, JR.—Relation of Carcinoma in Situ to Invasive Carcinoma of the Cervix Uteri	211
MURRAY EDEN—A Two-Dimensional Growth Process	223
SEYMOUR GEISSER—The Latin Square as a Repeated Measurements Design	241
JOHN T. GENTRY and ELIZABETH PARKHURST—Low Level Radiation Effects.	251

SAMUEL W. GREENHOUSE—A Stochastic Process Arising in the Study of Muscular Contraction	257
HARDIN B. JONES—Mechanism of Aging Suggested from Study of Altered Death Risks	267
NATHAN MANTEL—Principles of Chemotherapeutic Screening	293
L. MARTIN—Stochastic Processes in Physiology	307
G. RASCH—On General Laws and the Meaning of Measurement in Psychology	321
JOHN L. STEPHENSON—Integral Equation Description of Transport Phenomena in Biological Systems	335
WILLIAM F. TAYLOR—On the Methodology of Studying Aging in Humans	347
CORNELIUS A. TOBIAS—Quantitative Approaches to the Cell Division Process	369
HOWARD G. TUCKER—A Stochastic Model for a Two-Stage Theory of Carcinogenesis	387
W. A. O'N. WAUGH—Age-Dependence in a Stochastic Model of Carcinogenesis	405