Proc. Hiroshima Univ. RIRBM, 44, 2003

Division of Bio-Medical Informatics
Department of Environmetrics and Biometrics

Professor	Megu OHTAKI, Ph.D.
Assistant Professor	Kenichi SATOH, Ph.D.
Research Associate	Tetsuji TONDA, M.S.
Postgraduate Student	I Made ARCANA, M.S.
Postgraduate Student	Takeshi SHIMAMOTO, M.S.
Postgraduate Student	Mohd. Muzibur RAHMAN, M.S.
Postgraduate Student	Noriyuki KAWANO, M.A.
Research Fellow	Yasuto SATOU, M.S.
Research Fellow	Chie MURAKI ASANO, Ph.D.
Visiting Joint Researcher	Keiko OTANI, Ph.D.

The purpose of this department is to develop theories and their applications for analyses of medical, biological and E nvironmental data. The main research projects carried out in 2001 and in the process of making plan in this department are summarized as follows:

1. Study of mathematical models for radiation carcinogenesis.
2. Study of exploratory methods for nonlinear structures in multi-dimensional regression data.
3. Study of genomic variety for cancer patients.
4. Study of geographical distribution of cancer mortality in Japan using municipality-specific SMR data.
5. EPMC estimation in discriminant analysis when the dimension and sample sizes are large.
6. Study of body burdens for environmental contaminants such as Dioxin compounds in human.
7. Monte Carlo Method for Testing Number of Components for Normal Mixture Model.

We developed computer algorithms/software for these studies and to apply the methodologies for analyses of the real data. We also cooperated with many other researchers in the environmental or biomedical fields and give their studies all aspects of support in theoretical and technological methodologies, such as biometrics, mathematical science, information science and computer science.

Some academic meetings were organized by our department in this fiscal year. One was the symposium on "Mathematical Modeling and Statistical Analysis in Biomedical Research", which was held on January 30, 31 and February 1, 2003, at Ondo (Kure city), and was covered by Basic Study(A)of Grant-in-Aid, Scientific Research, Ministry of Education and Science, Japan. Professor Murray Clayton (Wisconcin University, U.S.), Professor Ker-Chau Li (UCLA, U.S.), Professor Jeffrey L. Thorne, Dr. Stephane Aris-Brosou (North Carolina Univerisity)and Professor W. K. Fung (Hong Kong Univeristy)were invited as guest speakers. One more mini-symposium was held on December 14, 2002, where Dr. Hidetoshi Shimodaira (Tokyo Technical Institute)gave a lecture on Bootstrap method.

As for personal affairs, Professor Megu Ohtaki attended SSC2002, which was held at MacMaster University in Hamilton (Canada) on 24-27 May 2003, as an invited speaker. Professor Megu Ohtaki, Dr. Kenichi Satoh and Dr. Keiko Otani attended the international workshop on SIR, which was held at La Trobe University in Bundoora (Australlia) on 2-4 October 2003, and gave talks. Mr. Tetsuji Tonda joined our department as a research associate, Mr. Mohd. Muzibur Rahman and Mr. Tokuyuki Kawano also did as Postgraduate students, and so did Dr. Chie Asano as a Research Fellow.

1. Study of mathematical models for radiation carcinogenesis.

Ohtaki, M., Imade Arcana, Kai, R.[*1], Niwa, O.[*2], Izumi, S.[*3], Satoh, K., (*1Oita Univ. of Nurse Sci., *2Kyoto Univ., *3RERF)

Purpose: To develop mathematical models of radiation carcinogenesis and cell death.
Method and Results: We extended the classical multi-target model to those models having heterogeneity target size. The simplest model consists of a geometric series of target size. If the common rate is large, the survival curve asymptotically approximates to that of the single target model with the minimum size of target regardless of the number of targets. We also developed multi-target models of cell death with taking effect of recovery from damage into consideration. As for Armitage-Doll type of multistage models for carcinogenesis, some Monte Carlo simulations on the relationship between the number of stages and mutation rate were done, then we found that the relation depends not only on cell division, cell death but speed of differentiation, and that it should be hard to estimate the number of stages using ordinary epidemiologic or animal experimental observations.

2. Study of exploratory methods for nonlinear structures in multi-dimensional regression data.

Ohtaki, M., Satoh, K., Rahaman, M. M., Zhu, L.[*1], Goto, M.[*2], Fujikoshi, Y.[*3] (*1Hong Kong Univ., *2Osaka Univ., *3Graduate School of Science)

Purpose: To develop statistical methods for exploring nonlinear structure in multi-dimensional regression data.
Methods and Results: We studied the performance of SIR, pHd, SAVE and SIR-SAVE, which is a linear combination of SIR and SVAE, using computer simulation method. We found that SIR-SAVE works better than else algorithms and that the choice of the slice number should be paid attention. We also studied on "SSIR", which is the special algorithm of SIR with two slices, to explore an EDR vector on the single index model, in which the step of principle component analysis for the original SIR can be avoided by using two sample mean vectors in two slices of response variable and those difference vector.

3. Study of genomic variety for cancer patients

Ohtaki, M., Otani, K.[*1], Satoh, K., Tonda, T., Nishiyama, M.[*2], Matsuura, M.[*3], Miki, Y.[*3], Noda, T.[*3], Ando, M.[*4], Saito, A.[*4] (*1JBIC, *2Translational Cancer Res., *3JFCR, *4NEC)

Purpose: To explore important genes which are related to degree of cancer risk or sensitivity side-effect of anti-tumor drug.
Methods and Results: We developed a mathematical model for cDNA microarray gene expression data to separate crude observations into true signals and experimental errors and proposed an efficient algorithm for normalization of cDNA microarray data. We applied our methods to the cDNA microarray measurements using two different fluorescent dyes to identify differently expressed genes between a query and a reference sample.

4．Study of geographical distribution of cancer mortality in Japan using municipality-specific SMR data.

Ohtaki, M., Satoh, K., Kawasaki, H.*1, Nakayama, T.*2, Yanagihara, H.*3, Yamaguchi, N.*4（*1School of Medicine, *2Oita University of Nurse Sciences, *3Inst. Stat. Math., *4Tokyo Women's Medical Univ.）

Purpose: To explore the spatial-time distribution of cancer mortality in Japan.
Methods and Results: We developed a statistical system for visualization of spatial-time distribution of cancer SMR in Japan using spatial-time nonparametric smoothing with Poisson-gamma model. Using this system, we developed animated SMR maps of major cancers in Japan for the period from 1975 to 1994.

5．EPMC estimation in discriminant analysis when the dimension and sample sizes are large

Tonda, T., Wakaki, H.* and Fujikoshi, Y.*（*Graduate School of Science）

Purpose: To construct an estimator of error-rates when the dimension and sample sizes are large.
Method and Results: We obtain a higher order asymptotic unbiased estimator for the expected probability of misclassification (EPMC) of the linear discriminant function when the dimension and the sample sizes are large. We also study a numerical comparison for the performance of our estimator with other estimator. It is shown that the bias and MSE of our estimator are less than the other estimators.

6．Study of body burdens for environmental contaminants such as Dioxin compounds in human.

Fujioka, T.*1, Otani, K.*2, Ohtaki, M.（*1Graduate School of Science, *2JBIC）

Purpose: To estimate half -lives for Dioxin compounds in human blood.
Methods and Results: We devised the statistical model proposed at the study for fiscal 2000 to estimate the half-lives for dioxins in human. This model based on the pharmacokinetic theory takes into consideration individual differences in dioxin intake and elimination. We analyzed a set of data for longitudinal measurements of dioxin concentration in blood of workers who had engaged in dismantling the municipal waste incinerators.

7．Monte Carlo Method for testing number of components for normal mixture model.

Shimamoto, T., Muraki, C., Satoh, K., Ohtaki, M.

Purpose: A statistical test about the number of the component in the mixture normal distribution that has two at most components.
Methods and Results: One method based on the Monte Carlo method for the statistical official approval about the number of the component in the mixed normal distribution that has at most two components was devised. The pseudo random number under the normal distribution was made to occur, and the significance of the likelihood ratio that the experience distribution of the likelihood ratio test statistics was seek by using the mixture ratio estimated from the data and observed was evaluated.

8．Database of witnesses by Hibakusha and its content analysis

Kawano, N., Hoshi, M*1., Matsuo, M.*2, Satoh, K., Ohtaki, M.（*1Int. Radiat. Inform. Cent., *1Institute for Peace Science）

Purpose: Deeper understanding of Hiroshima and Nagasaki A-bombs and preserving *Hibakusha's* witnesses

Methods and Results: We attempt at making database of witnesses by *hibakusha*. These *hibakusha's* witnesses have been collected by International Radiation Information Center and Institute for Peace Science, Hiroshima University. We input full text of new five witnesses into a computer in 2002. We will try to open the database to the public, but we consider the issues of *hibakusha's* privacy and the copyright on a book. This is a joint research project with Institute for Peace Science, Hiroshima University. We also attempt to clarify the realities of atomic bomb dropped on Hiroshima in 1945. For this purpose, we analyze the content of witnesses of *hibakusha*. First, we try to answer a question, "who wrote the witnesses of *hibakusha* and what were they watching and writing?" Second, we choose the words or terms in the witnesses of hibakusha that are often used. We clarify the realities of atomic bomb in terms of analyzing the terms or words.

List of Contributions

A. Original Papers

1. Shiraishi, K.[*1], Shimura, T.[*1], Taga, M.[*1], Uematsu, N.[*1], Gondo, Y.[*1], Ohtaki, M., Kominami, R.[*2] and Niwa, O.[*1] ([*1]Kyoto University, [*2]Niigata University): Persistent induction of somatic reversions of the pink-eyed unstable mutation in Fl mice Born to fathers irradiated at the spermatozoa stage, Radiat. Res., 157, 661-667, 2002.

2. Otani, K.[*1], Ohtaki, M., Watanabe, S.[*2] ([*1]JBIC, [*2]Tokyo Univ. of Agri. Sci.): A random effects nonlinear regression model for analysis of environmental contamination data, Environmetrics, 14, 149-157, 2003.

3. Takeuchi, Y.[*1], Satoh, K., Ohtaki, M. Hayakawa, T.[*2], Tanaka, H.[*3] and Kimura, A.[*3] ([*1]Hiroshima Red Cross Blood Center, [*2]Dept. Epidemiology, [*3]Hematology and Oncology): Increased risk of myelodysplastic syndrome (MDS) in atomic bomb survivors, Hiroshima Igaku, 55, 214-215, 2002. (C)

4. Yamaguchi, T.[*1], Okada, T.[*2], Takeuchi, K.[*3], Tonda, T., Ohtaki, M., Shinoda, S.[*1], Masuzawa, T.[*1], Ozawa, K.[*2] and Inaba, T.[*4] ([*1]Surgical Neurology, [*2]Jichi Medical School, [*3]Anatomy, [*4]Molecular Oncology): Enhancement of thymidine kinase-mediated killing of malignant glioma by BimS, a BH3-only cell death activator, Gene Therapy, 10(5), 375-385, 2003.

5. Yanagihara, H.[*] and Tonda, T. ([*]Inst. Stat. Math.): Adjustment on an asymptotic expansion of the distribution function with chi-squared approximation, Hiroshima Math. J., 33(1), 15-25, 2003.

6. Tonda, T. and Wakaki, H.[*] ([*]Graduate School of Science): Asymptotic expansion of the null distribution of the likelihood ratio statistic for testing the equality of variances in a nonnormal one-way ANOVA model, Hiroshima Math. J., 33(1), 113-126, 2003.

B. Meeting Presentations

1. Ohtaki, M., Kawasaki, H.[*1], Satoh, K., Nakayama, T.[*2], Yanagihara, H.[*3] and Yamaguchi, N.[*4] ([*1]School of Medicine, [*2]Oita University of Nurse Sciences, [*3]Inst. Stat. Math., [*4]Tokyo Women's Medical Univ.): Visualization of time and geographical distribution of cancer mortality in Japan, Annual Meeting of Statistical Society of Canada 2002, Hamilton (Canada), 2002.

2. Ohtaki, M., Kawasaki, H.[*1], Satoh, K., Nakayama, T.[*2], Yanagihara, H.[*3] and Yamaguchi, N.[*4] ([*1]Hiroshima Univ., [*2]Japan Atomic Energy Research Institute, [*3]The Institute of Statistical Mathematics, [*4]National Cancer Center Research Institute): Visualization of time-spatial distribution of cancer mortality in Japan using municipality-specific demographic data, The

2002 Taipei International Statistical Symposium and Bernoulli Society EAPR Conference, Taipei（Taiwan）, 2002.

3．Ohtaki, M., Kawasaki, H.*1, Satoh, K., Nakayama, T.*2, Yanagihara, H.*3 and Yamaguchi, N.*4（*1Hiroshima Univ., *2Oita Univ. of Nursing and Health Sciences, *3The Institute of Statistical Mathematics, *4Tokyo Women's Medical Univ.）: Visualization of time-spatial distribution of cancer mortality in Japan using municipality-specific demographic data, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

4．Satoh, K., Ohtaki, M.: Multiple regression for single index model, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

5．Tonda, T. and Wakaki, H*1（*1Graduate School of Science）: EPMC estimation in discriminant analysis when the dimension and sample sizes are large, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

6．I Made Arcana, Ohtaki, M.: A frailty model for cell death based on the multi-target hypothesis and its application to analysis of annimal irradiation data, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

7．Shimamoto, T., Muraki, C., Satoh, K., Ohtaki, M.: Monte Carlo Method for Testing Number of Components for Normal Mixture Model, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

8．Otani, K.*1, Ohtaki. M., Satoh, K. and Nishiyama, M.*2（*1JBIC, *2Translational Cancer Res.）: Analysis of cDNA microarray gene expression data, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

9．Muraki, C., Asano, A.* and Ohtaki, M.（*Faculty of Integrated Arts and Sciences）: The applying method of logistic discriminant analysis and a neural network in object identification, The 70th Annual Meeting of the Japan Statistical Society, Tokyo, 2002.

10．Ohtaki, M. and Zhu, L.*（*Hong Kong Univ.）: A note of the extension of Sliced Inverse Regression, Symposium on Recent Developments in Sliced Inverse Regression, Bundoora（Australia）, 2002.

11．Satoh, K., Otani, K.*1 and Ohtaki, M., Nishiyama, M.*2（*1JBIC, *2Translational Cancer Res.）: Multiple regression for single index model & its application to exploration of effective genes on anticancer drugs, Symposium on Recent Developments in Sliced Inverse Regression, Bundoora（Australia）, 2002.

12．Otani, K.*1, Ohtaki. M., Satoh, K. and Nishiyama, M.*2（*1JBIC, *2Translational Cancer Res.）: Normalization of cDNA microarray gene expression data, The 16th Symposium of the JSCS, Nagasaki, 2002.

13．Satoh, K. and Ohtaki, M.: Multiple regression for single index model, The 16th Symposium of the Journal of the Japanese Society of Computational Statistics, Nagasaki, 2002.

14．Fujioka, T.*1, Otani, K.*2 and Ohtaki, M.（*1Graduate School of Science, *2JBIC）: Estimation of Half -lives for Dioxin Compounds in Human Blood, Symposium on “Theory and application of environmental data analysis”, Tokyo, 2002.

15．Ohtaki, M. and Zhu, L.*（*Hong Kong Univ.）: A Monte Carlo simulation study on dimension reduction methods related to SIR, Symposium on Mathematical Foundation for Biostatistics, Tokyo, 2002.

16. Motegi, H.[*1], Toki, H.[*1], Ohtaki, M., Satoh, K., Masuya, H.[*2], Suzuki, T.[*2], Inoue, M.[*2], Kobayashi, K.[*2], Wakana, S.[*1], Gondo, Y.[*1], Minowa, O.[*1], Shiroishi, T.[*1] and Noda, T.[*1] ([*1]Mouse Functional Genomics Research Group, RIKEN GSC,[*2]Population and Quantitative Genomics Team, RIKEN GSC): Blood screening for a large scale mouse mutagenesis project in RIKEN GSC, 25th Annual Meeting of the Molecular Biology Society of Japan, Yokohama, 2002.

17. I Made Arcana and Ohtaki, M.: Heterogeneous Multi-target model for Irradiation Experimental Data Analysis, Symposium of Statistical Base of High Dimensional Information Processing, Hiroshima, 2003.

18. Fujioka, T.[*1], Otani, K.[*2] and Ohtaki, M. ([*1]Graduate School of Science, [*2]JBIC): Estimation of Half -lives for Dioxin Compounds in Human Blood, Symposium of Statistical Base of High Dimensional Information Processing, Hiroshima, 2003.

19. Shimamoto, T. and Muraki, C.: Monte Carlo Method for Testing Number of Components for Normal Mixture Model, Symposium of Statistical Base of High Dimensional Information Processing, Hiroshima, 2003.

20. Mohd. Muzibur Rahman: An extension of correlation coefficient for measuring non linear trend, Symposium of Statistical Base of High Dimensional Information Processing, Hiroshima, 2003.

21. Ohtaki, M., Otani, K.[*1], Satoh, K. and Nishiyama, M.[*2] ([*1]JBIC, [*2]Translational Cancer Res.): Mathematical model for cDNA microarray data, Symposium on Mathematical Modeling and Statistical Analysis in Biomedical Research, Ondo (Hiroshima), 2003.

22. Ohtaki, M., Kawasaki, H.[*1], Satoh, K., Nakayama, T.[*2], Yanagihara, H.[*3] and Yamaguchi, N.[*4] ([*1]School of Medicine, [*2]Oita University of Nurse Sciences, [*3]Inst. Stat. Math., [*4]Tokyo Women's Medical Univ.): Visualization of spatial-time distribution of cancer mortality risk, Symposium on Mathematical Modeling and Statistical Analysis in Biomedical Research, Ondo (Hiroshima), 2003.