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MULTILAYER KNOCKOFF FILTER: CONTROLLED VARIABLE SELECTION AT MULTIPLE RESOLUTIONS

BY EUGENE KATSEVICH[1] AND CHIARA SABATTI[2]

Stanford University

We tackle the problem of selecting from among a large number of variables those that are "important" for an outcome. We consider situations where groups of variables are also of interest. For example, each variable might be a genetic polymorphism, and we might want to study how a trait depends on variability in genes, segments of DNA that typically contain multiple such polymorphisms. In this context, to discover that a variable is relevant for the outcome implies discovering that the larger entity it represents is also important. To guarantee meaningful results with high chance of replicability, we suggest controlling the rate of false discoveries for findings at the level of individual variables and at the level of groups. Building on the knockoff construction of Barber and Candès [*Ann. Statist.* **43** (2015) 2055–2085] and the multilayer testing framework of Barber and Ramdas [*J. Roy. Statist. Soc. Ser. B* **79** (2017) 1247–1268], we introduce the multilayer knockoff filter (MKF). We prove that MKF simultaneously controls the FDR at each resolution and use simulations to show that it incurs little power loss compared to methods that provide guarantees only for the discoveries of individual variables. We apply MKF to analyze a genetic dataset and find that it successfully reduces the number of false gene discoveries without a significant reduction in power.

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GROUND-LEVEL OZONE: EVIDENCE OF INCREASING SERIAL DEPENDENCE IN THE EXTREMES

BY DEBBIE J. DUPUIS[1] AND LUCA TRAPIN

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As exposure to successive episodes of high ground-level ozone concentrations can result in larger changes in respiratory function than occasional exposure buffered by lengthy recovery periods, the analysis of extreme values in a series of ozone concentrations requires careful consideration of not only the levels of the extremes but also of any dependence appearing in the extremes of the series. Increased dependence represents increased health risks and it is thus important to detect any changes in the temporal dependence of extreme values. In this paper we establish the first test for a change point in the extremal dependence of a stationary time series. The test is flexible, easy to use and can be extended along several lines. The asymptotic distributions of our estimators and our test are established. A large simulation study verifies the good finite sample properties. The test allows us to show that there has been a significant increase in the serial dependence of the extreme levels of ground-level ozone concentrations in Bloomsbury (UK) in recent years.

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GENOME-WIDE ANALYSES OF SPARSE MEDIATION EFFECTS UNDER COMPOSITE NULL HYPOTHESES

BY YEN-TSUNG HUANG[1]

Academia Sinica

A genome-wide mediation analysis is conducted to investigate whether epigenetic variations M mediate the effect of socioeconomic adversity S on adiposity Y. The mediation effect can be expressed as a product of two parameters, the S–M association and the M–Y association conditional on S. We show that the joint significance test examining the two parameters separately has smaller p-values than the normality-based or the normal product-based test for the product and is a size α test. However, under multiple tests with sparse signals, the conventional joint significance test has a conservative test size and low power within a study because of the sparsity in signals and not accounting for the composition of different null hypotheses. We develop a novel test assessing the product of two normally distributed test statistics under a composite null hypothesis, where either one parameter is zero or both are zero. We show that the null composition can be adjusted by variances of test statistics without directly estimating proportions of different nulls. Advantages of the new test are illustrated in simulation and the epigenomic study. The new test identifies four methylation loci mediating the socioeconomic effect on adiposity with the false discovery rate less than 20% while existing methods had none surviving this cut-off.

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COMMON AND INDIVIDUAL STRUCTURE OF BRAIN NETWORKS[1]

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This article focuses on the problem of studying shared- and individual-specific structure in replicated networks or graph-valued data. In particular, the observed data consist of n graphs, $G_i, i = 1, \ldots, n$, with each graph consisting of a collection of edges between V nodes. In brain connectomics, the graph for an individual corresponds to a set of interconnections among brain regions. Such data can be organized as a $V \times V$ binary adjacency matrix A_i for each i, with ones indicating an edge between a pair of nodes and zeros indicating no edge. When nodes have a shared meaning across replicates $i = 1, \ldots, n$, it becomes of substantial interest to study similarities and differences in the adjacency matrices. To address this problem, we propose a method to estimate a common structure and low-dimensional individual-specific deviations from replicated networks. The proposed Multiple GRAph Factorization (M-GRAF) model relies on a logistic regression mapping combined with a hierarchical eigenvalue decomposition. We develop an efficient algorithm for estimation and study basic properties of our approach. Simulation studies show excellent operating characteristics and we apply the method to human brain connectomics data.

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CLONALITY: POINT ESTIMATION[1]

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Assessments of biological complexity for populations that are of mixed species are central in many biological contexts, including microbiomes, tumor cell population structure, and immune cell populations. Here we address the problem of quantifying the population diversity in experiments where high throughput DNA sequencing is used to distinguish a large number of cell subpopulations. Our model assumes a list of clonal species and their observed frequencies in each of several replicate sequencing libraries. Though the underlying distribution of frequencies cannot be estimated well from data coming from only a small fraction of the total cell population, one can estimate well the population-level *clonality*, defined as the sum of squared underlying fractions of the respective clones, the complement of the Gini–Simpson index. Specifically, we proposed to adaptively combine multiple unbiased estimators of *clonality* derived from pairs of replicates to construct a single estimator without relying on the commonly used but restrictive multinomial assumption. The new estimator performs particularly well for replicates of unequal size. We further illustrate the proposed methods with extensive simulations and a small real data example.

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PREDICTION MODELS FOR NETWORK-LINKED DATA[1]

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Prediction algorithms typically assume the training data are independent samples, but in many modern applications samples come from individuals connected by a network. For example, in adolescent health studies of risk-taking behaviors, information on the subjects' social network is often available and plays an important role through network cohesion, the empirically observed phenomenon of friends behaving similarly. Taking cohesion into account in prediction models should allow us to improve their performance. Here we propose a network-based penalty on individual node effects to encourage similarity between predictions for linked nodes, and show that incorporating it into prediction leads to improvement over traditional models both theoretically and empirically when network cohesion is present. The penalty can be used with many loss-based prediction methods, such as regression, generalized linear models, and Cox's proportional hazard model. Applications to predicting levels of recreational activity and marijuana usage among teenagers from the AddHealth study based on both demographic covariates and friendship networks are discussed in detail and show that our approach to taking friendships into account can significantly improve predictions of behavior while providing interpretable estimates of covariate effects.

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NONSTATIONARY SPATIAL PREDICTION OF SOIL ORGANIC CARBON: IMPLICATIONS FOR STOCK ASSESSMENT DECISION MAKING[1]

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The Rapid Carbon Assessment (RaCA) project was conducted by the US Department of Agriculture's National Resources Conservation Service between 2010–2012 in order to provide contemporaneous measurements of soil organic carbon (SOC) across the US. Despite the broad extent of the RaCA data collection effort, direct observations of SOC are not available at the high spatial resolution needed for studying carbon storage in soil and its implications for important problems in climate science and agriculture. As a result, there is a need for predicting SOC at spatial locations not included as part of the RaCA project. In this paper, we compare spatial prediction of SOC using a subset of the RaCA data for a variety of statistical methods. We investigate the performance of methods with off-the-shelf software available (both stationary and nonstationary) as well as a novel nonstationary approach based on partitioning relevant spatially-varying covariate processes. Our new method addresses open questions regarding (1) how to partition the spatial domain for segmentation-based nonstationary methods, (2) incorporating partially observed covariates into a spatial model, and (3) accounting for uncertainty in the partitioning. In applying the various statistical methods we find that there are minimal differences in out-of-sample criteria for this particular data set, however, there are major differences in maps of uncertainty in SOC predictions. We argue that the spatially-varying measures of prediction uncertainty produced by our new approach are valuable to decision makers, as they can be used to better benchmark mechanistic models, identify target areas for soil restoration projects, and inform carbon sequestration projects.

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AN ALGORITHM FOR REMOVING SENSITIVE INFORMATION: APPLICATION TO RACE-INDEPENDENT RECIDIVISM PREDICTION[1]

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Predictive modeling is increasingly being employed to assist human decision-makers. One purported advantage of replacing or augmenting human judgment with computer models in high stakes settings—such as sentencing, hiring, policing, college admissions, and parole decisions—is the perceived "neutrality" of computers. It is argued that because computer models do not hold personal prejudice, the predictions they produce will be equally free from prejudice. There is growing recognition that employing algorithms does not remove the potential for bias, and can even amplify it if the training data were generated by a process that is itself biased. In this paper, we provide a probabilistic notion of algorithmic bias. We propose a method to eliminate bias from predictive models by removing all information regarding protected variables from the data to which the models will ultimately be trained. Unlike previous work in this area, our procedure accommodates data on any measurement scale. Motivated by models currently in use in the criminal justice system that inform decisions on pre-trial release and parole, we apply our proposed method to a dataset on the criminal histories of individuals at the time of sentencing to produce "race-neutral" predictions of re-arrest. In the process, we demonstrate that a common approach to creating "race-neutral" models—omitting race as a covariate—still results in racially disparate predictions. We then demonstrate that the application of our proposed method to these data removes racial disparities from predictions with minimal impact on predictive accuracy.

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BAYESIAN SEMIPARAMETRIC JOINT REGRESSION ANALYSIS OF RECURRENT ADVERSE EVENTS AND SURVIVAL IN ESOPHAGEAL CANCER PATIENTS

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We propose a Bayesian semiparametric joint regression model for a recurrent event process and survival time. Assuming independent latent subject frailties, we define marginal models for the recurrent event process intensity and survival distribution as functions of the subject's frailty and baseline covariates. A robust Bayesian model, called Joint-DP, is obtained by assuming a Dirichlet process for the frailty distribution. We present a simulation study that compares posterior estimates under the Joint-DP model to a Bayesian joint model with lognormal frailties, a frequentist joint model, and marginal models for either the recurrent event process or survival time. The simulations show that the Joint-DP model does a good job of correcting for treatment assignment bias, and has favorable estimation reliability and accuracy compared with the alternative models. The Joint-DP model is applied to analyze an observational dataset from esophageal cancer patients treated with chemoradiation, including the times of recurrent effusions of fluid to the heart or lungs, survival time, prognostic covariates, and radiation therapy modality.

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A PENALIZED REGRESSION MODEL FOR THE JOINT ESTIMATION OF EQTL ASSOCIATIONS AND GENE NETWORK STRUCTURE[1]

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In this work, we present a new approach for jointly performing eQTL mapping and gene network inference while encouraging a transfer of information between the two tasks. We address this problem by formulating it as a multiple-output regression task in which we aim to learn the regression coefficients while simultaneously estimating the conditional independence relationships among the set of response variables. The approach we develop uses structured sparsity penalties to encourage the sharing of information between the regression coefficients and the output network in a mutually beneficial way. Our model, *inverse-covariance-fused lasso*, is formulated as a biconvex optimization problem that we solve via alternating minimization. We derive new, efficient optimization routines to solve each convex sub-problem that are based on extensions of state-of-the-art methods. Experiments on both simulated data and a yeast eQTL dataset demonstrate that our approach outperforms a large number of existing methods on the recovery of the true sparse structure of both the eQTL associations and the gene network. We also apply our method to a human Alzheimer's disease dataset and highlight some results that support previous discoveries about the disease.

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A BAYESIAN RACE MODEL FOR RESPONSE TIMES UNDER CYCLIC STIMULUS DISCRIMINABILITY[1]

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Response time (RT) data from psychology experiments are often used to validate theories of how the brain processes information and how long it takes a person to make a decision. When an RT results from a task involving two or more possible responses, the cognitive process that determines the RT may be modeled as the first-passage time of underlying competing (racing) processes with each process describing accumulation of information in favor of one of the responses. In one popular model the racers are assumed to be Gaussian diffusions. Their first-passage times are inverse Gaussian random variables and the resulting RT has a min-inverse Gaussian distribution. The RT data analyzed in this paper were collected in an experiment requiring people to perform a two-choice task in response to a regularly repeating sequence of stimuli. Starting from a min-inverse Gaussian likelihood for the RTs we build a Bayesian hierarchy for the rates and thresholds of the racing diffusions. The analysis allows us to characterize patterns in a person's sequence of responses on the basis of features of the person's diffusion rates (the "footprint" of the stimuli) and a person's gradual changes in speed as trends in the diffusion thresholds. Last, we propose that a small fraction of RTs arise from distinct, noncognitive processes that are included as components of a mixture model. In the absence of sharp prior information, the inclusion of these mixture components is accomplished via a two-stage, empirical Bayes approach. The resulting framework may be generalized readily to RTs collected under a variety of experimental designs.

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BAYESIAN ANALYSIS OF INFANT'S GROWTH DYNAMICS WITH *IN UTERO* EXPOSURE TO ENVIRONMENTAL TOXICANTS[1]

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Early infancy from at-birth to 3 years is critical for cognitive, emotional and social development of infants. During this period, infant's developmental tempo and outcomes are potentially impacted by *in utero* exposure to endocrine disrupting compounds (EDCs), such as bisphenol A (BPA) and phthalates. We investigate effects of ten ubiquitous EDCs on the infant growth dynamics of body mass index (BMI) in a birth cohort study. Modeling growth acceleration is proposed to understand the "force of growth" through a class of semiparametric stochastic velocity models. The great flexibility of such a dynamic model enables us to capture subject-specific dynamics of growth trajectories and to assess effects of the EDCs on potential delay of growth. We adopted a Bayesian method with the Ornstein–Uhlenbeck process as the prior for the growth rate function, in which the World Health Organization global infant's growth curves were integrated into our analysis. We found that BPA and most of phthalates exposed during the first trimester of pregnancy were inversely associated with BMI growth acceleration, resulting in a delayed achievement of infant BMI peak. Such early growth deficiency has been reported as a profound impact on health outcomes in puberty (e.g., timing of sexual maturation) and adulthood.

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JOINT MEAN AND COVARIANCE MODELING OF MULTIPLE HEALTH OUTCOME MEASURES

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Health exams determine a patient's health status by comparing the patient's measurement with a population reference range, a 95% interval derived from a homogeneous reference population. Similarly, most of the established relation among health problems are assumed to hold for the entire population. We use data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) on four major health problems in the U.S. and apply a joint mean and covariance model to study how the reference ranges and associations of those health outcomes could vary among subpopulations. We discuss guidelines for model selection and evaluation, using standard criteria such as AIC in conjunction with posterior predictive checks. The results from the proposed model can help identify subpopulations in which more data need to be collected to refine the reference range and to study the specific associations among those health problems.

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BAYESIAN LATENT HIERARCHICAL MODEL FOR TRANSCRIPTOMIC META-ANALYSIS TO DETECT BIOMARKERS WITH CLUSTERED META-PATTERNS OF DIFFERENTIAL EXPRESSION SIGNALS

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Due to the rapid development of high-throughput experimental techniques and fast-dropping prices, many transcriptomic datasets have been generated and accumulated in the public domain. Meta-analysis combining multiple transcriptomic studies can increase the statistical power to detect disease-related biomarkers. In this paper we introduce a Bayesian latent hierarchical model to perform transcriptomic meta-analysis. This method is capable of detecting genes that are differentially expressed (DE) in only a subset of the combined studies, and the latent variables help quantify homogeneous and heterogeneous differential expression signals across studies. A tight clustering algorithm is applied to detected biomarkers to capture differential meta-patterns that are informative to guide further biological investigation. Simulations and three examples, including a microarray dataset from metabolism-related knockout mice, an RNA-seq dataset from HIV transgenic rats and cross-platform datasets from human breast cancer are used to demonstrate the performance of the proposed method.

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MODELING WITHIN-HOUSEHOLD ASSOCIATIONS IN HOUSEHOLD PANEL STUDIES

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Household panel data provide valuable information about the extent of similarity in coresidents' attitudes and behaviours. However, existing analysis approaches do not allow for the complex association structures that arise due to changes in household composition over time. We propose a flexible marginal modeling approach where the changing correlation structure between individuals is modeled directly and the parameters estimated using second-order generalized estimating equations (GEE2). A key component of our correlation model specification is the "superhousehold", a form of social network in which pairs of observations from different individuals are connected (directly or indirectly) by coresidence. These superhouseholds partition observations into clusters with nonstandard and highly variable correlation structures. We thus conduct a simulation study to evaluate the accuracy and stability of GEE2 for these models. Our approach is then applied in an analysis of individuals' attitudes towards gender roles using British Household Panel Survey data. We find strong evidence of between-individual correlation before, during and after coresidence, with large differences among spouses, parent–child, other family, and unrelated pairs. Our results suggest that these dependencies are due to a combination of nonrandom sorting and causal effects of coresidence.

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FRÉCHET ESTIMATION OF TIME-VARYING COVARIANCE MATRICES FROM SPARSE DATA, WITH APPLICATION TO THE REGIONAL CO-EVOLUTION OF MYELINATION IN THE DEVELOPING BRAIN

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Assessing brain development for small infants is important for determining how the human brain grows during the early period of life when the rate of brain growth is at its peak. The development of MRI techniques has enabled the quantification of brain development. A key quantity that can be extracted from MRI measurements is the level of myelination, where myelin acts as an insulator around nerve fibers and its deployment makes nerve pulse propagation more efficient. The co-variation of myelin deployment across different brain regions provides insights into the co-development of brain regions and can be assessed as correlation matrix that varies with age. Typically, available data for each child are very sparse, due to the cost and logistic difficulties of arranging MRI brain scans for infants. We showcase here a method where data per subject are limited to measurements taken at only one random age, so that one has cross-sectional data available, while aiming at the time-varying dynamics. This situation is encountered more generally in cross-sectional studies where one observes p-dimensional vectors at one random time point per subject and is interested in the $p \times p$ correlation matrix function over the time domain. The challenge is that at each observation time one observes only a p-vector of measurements but not a covariance or correlation matrix. For such very sparse data, we develop a Fréchet estimation method. Given a metric on the space of covariance matrices, the proposed method generates a matrix function where at each time the matrix is a nonnegative definite covariance matrix, for which we demonstrate consistency properties. We discuss how this approach can be applied to myelin data in the developing brain and what insights can be gained.

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THE ROLE OF MASTERY LEARNING IN AN INTELLIGENT TUTORING SYSTEM: PRINCIPAL STRATIFICATION ON A LATENT VARIABLE[1]

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Students in Algebra I classrooms typically learn at different rates and struggle at different points in the curriculum—a common challenge for math teachers. Cognitive Tutor Algebra I (CTA1), an educational computer program, addresses such student heterogeneity via what they term "mastery learning," where students progress from one section of the curriculum to the next by demonstrating appropriate "mastery" at each stage. However, when students are unable to master a section's skills even after trying many problems, they are automatically promoted to the next section anyway. Does promotion without mastery impair the program's effectiveness?

At least in certain domains, CTA1 was recently shown to improve student learning on average in a randomized effectiveness study. This paper uses student log data from that study in a continuous principal stratification model to estimate the relationship between students' potential mastery and the CTA1 treatment effect. In contrast to extant principal stratification applications, a student's propensity to master worked sections here is never directly observed. Consequently we embed an item-response model, which measures students' potential mastery, within the larger principal stratification model. We find that the tutor may, in fact, be *more* effective for students who are more frequently promoted (despite unsuccessfully completing sections of the material). However, since these students are distinctive in their educational strength (as well as in other respects), it remains unclear whether this enhanced effectiveness can be directly attributed to aspects of the mastery learning program.

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CAPTURING HETEROGENEITY OF COVARIATE EFFECTS IN HIDDEN SUBPOPULATIONS IN THE PRESENCE OF CENSORING AND LARGE NUMBER OF COVARIATES

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The advent of modern technology has led to a surge of high-dimensional data in biology and health sciences such as genomics, epigenomics and medicine. The high-grade serous ovarian cancer (HGS-OvCa) data reported by The Cancer Genome Atlas (TCGA) Research Network is one example. The TCGA and other research groups have analyzed several aspects of these data. Here we study the relationship between Disease Free Time (DFT) after surgery among ovarian cancer patients and their DNA methylation profiles of genomic features. Such studies pose additional challenges beyond the typical big data problem due to population substructure and censoring. Despite the availability of several methods for analyzing time-to-event data with a large number of covariates but a small sample size, there is no method available to date that accommodates the additional feature of heterogeneity. To this end, we propose a regularized framework based on the finite mixture of accelerated failure time model to capture intangible heterogeneity due to population substructure and to account for censoring simultaneously. We study the properties of the proposed framework both theoretically and numerically. Our data analysis indicates the existence of heterogeneity in the HGS-OvCa data, with one component of the mixture capturing a more aggressive form of the disease, and the second component capturing a less aggressive form. In particular, the second component portrays a significant positive relationship between methylation and DFT for BRCA1. By further unearthing the negative relationship between expression and methylation for this gene, one may provide a biologically reasonable explanation that sheds light on the relationship between DNA methylation, gene expression and mutation.

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DEVELOPMENT OF A COMMON PATIENT ASSESSMENT SCALE ACROSS THE CONTINUUM OF CARE: A NESTED MULTIPLE IMPUTATION APPROACH[1]

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Evaluating and tracking patients' functional status through the post-acute care continuum requires a common instrument. However, different post-acute service providers such as nursing homes, inpatient rehabilitation facilities and home health agencies rely on different instruments to evaluate patients' functional status. These instruments assess similar functional status domains, but they comprise different activities, rating scales and scoring instructions. These differences hinder the comparison of patients' assessments across health care settings. We propose a two-step procedure that combines nested multiple imputation with the multivariate ordinal probit (MVOP) model to obtain a common patient assessment scale across the post-acute care continuum. Our procedure imputes the unmeasured assessments at multiple assessment dates and enables evaluation and comparison of the rates of functional improvement experienced by patients treated in different health care settings using a common measure. To generate multiple imputations of the unmeasured assessments using the MVOP model, a likelihood-based approach that combines the EM algorithm and the bootstrap method as well as a fully Bayesian approach using the data augmentation algorithm are developed. Using a dataset on patients who suffered a stroke, we simulate missing assessments and compare the MVOP model to existing methods for imputing incomplete multivariate ordinal variables. We show that, for all of the estimands considered, and in most of the experimental conditions that were examined, the MVOP model appears to be superior. The proposed procedure is then applied to patients who suffered a stroke and were released from rehabilitation facilities either to skilled nursing facilities or to their homes.

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A BAYESIAN MALLOWS APPROACH TO NONTRANSITIVE PAIR COMPARISON DATA: HOW HUMAN ARE SOUNDS?

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We are interested in learning how listeners perceive sounds as having human origins. An experiment was performed with a series of electronically synthesized sounds, and listeners were asked to compare them in pairs. We propose a Bayesian probabilistic method to learn individual preferences from nontransitive pairwise comparison data, as happens when one (or more) individual preferences in the data contradicts what is implied by the others. We build a Bayesian Mallows model in order to handle nontransitive data, with a latent layer of uncertainty which captures the generation of preference misreporting. We then develop a mixture extension of the Mallows model, able to learn individual preferences in a heterogeneous population. The results of our analysis of the musicology experiment are of interest to electroacoustic composers and sound designers, and to the audio industry in general, whose aim is to understand how computer generated sounds can be produced in order to sound more human.

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CAUSAL INFERENCE IN THE CONTEXT OF AN ERROR PRONE EXPOSURE: AIR POLLUTION AND MORTALITY[1]

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We propose a new approach for estimating causal effects when the exposure is measured with error and confounding adjustment is performed via a generalized propensity score (GPS). Using validation data, we propose a regression calibration (RC)-based adjustment for a continuous error-prone exposure combined with GPS to adjust for confounding (RC-GPS). The outcome analysis is conducted after transforming the corrected continuous exposure into a categorical exposure. We consider confounding adjustment in the context of GPS subclassification, inverse probability treatment weighting (IPTW) and matching. In simulations with varying degrees of exposure error and confounding bias, RC-GPS eliminates bias from exposure error and confounding compared to standard approaches that rely on the error-prone exposure. We applied RC-GPS to a rich data platform to estimate the causal effect of long-term exposure to fine particles ($PM_{2.5}$) on mortality in New England for the period from 2000 to 2012. The main study consists of 2202 zip codes covered by 217,660 1 km $\times$ 1 km grid cells with yearly mortality rates, yearly $PM_{2.5}$ averages estimated from a spatio-temporal model (error-prone exposure) and several potential confounders. The internal validation study includes a subset of 83 1 km $\times$ 1 km grid cells within 75 zip codes from the main study with error-free yearly $PM_{2.5}$ exposures obtained from monitor stations. Under assumptions of noninterference and weak unconfoundedness, using matching we found that exposure to moderate levels of $PM_{2.5}$ ($8 < PM_{2.5} \leq 10\ \mu g/m^3$) causes a 2.8% (95% CI: 0.6%, 3.6%) increase in all-cause mortality compared to low exposure ($PM_{2.5} \leq 8\ \mu g/m^3$).

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MODELING BIOMARKER RATIOS WITH GAMMA DISTRIBUTED COMPONENTS[1]

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We propose a regression model termed "extended GB2 model", which is designed to analyze ratios of biomarkers in epidemiological and medical research. Typical examples of biomarker ratios are given by the LDL/HDL cholesterol ratio in cardiovascular research and the amyloid-β 42/40 ratio in dementia research. Unlike regression modeling with a log-transformed response, which is often used to describe ratio outcomes in observational studies, the extended GB2 model directly links the expectation of the untransformed biomarker ratio to a set of covariates. This strategy allows for a simple interpretation of the predictor-response relationships in terms of multiplicative increases/decreases of the expected outcome, similar to Poisson and Cox regression. In the theoretical part of the paper, we derive the log-likelihood of the proposed model, analyze its properties, and provide details on confidence intervals and hypothesis testing. We will also present the results of a simulation study demonstrating the robustness of the proposed modeling approach against model misspecification. The usefulness of the method is demonstrated by two applications on the aforementioned LDL/HDL cholesterol and amyloid-β 42/40 ratios. For this, we analyze data from a cohort study on kidney disease and from a large observational database on neurodegenerative diseases.

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DYNAMICS OF HOMELESSNESS IN URBAN AMERICA[1]

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The relationship between housing costs and homelessness has important implications for the way that city and county governments respond to increasing homeless populations. Though many analyses in the public policy literature have examined inter-community variation in homelessness *rates* to identify causal mechanisms of homelessness [*J. Urban Aff.* **35** (2013) 607–625; *J. Urban Aff.* **25** (2003) 335–356; *Am. J. Publ. Health* **103** (2013) S340–S347], few studies have examined time-varying homeless *counts* within the same community [*J. Mod. Appl. Stat. Methods* **15** (2016) 15]. To examine trends in homeless population counts in the 25 largest U.S. metropolitan areas, we develop a dynamic Bayesian hierarchical model for time-varying homeless count data. Particular care is given to modeling uncertainty in the homeless count generating and measurement processes, and a critical distinction is made between the counted number of homeless and the true size of the homeless population. For each metro under study, we investigate the relationship between increases in the Zillow Rent Index and increases in the homeless population. Sensitivity of inference to potential improvements in the accuracy of point-in-time counts is explored, and evidence is presented that the inferred increase in the rate of homelessness from 2011–2016 depends on prior beliefs about the accuracy of homeless counts. A main finding of the study is that the relationship between homelessness and rental costs is strongest in New York, Los Angeles, Washington, D.C., and Seattle.

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BAYESIAN HIDDEN MARKOV TREE MODELS FOR CLUSTERING GENES WITH SHARED EVOLUTIONARY HISTORY[1]

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Determination of functions for poorly characterized genes is crucial for understanding biological processes and studying human diseases. Functionally associated genes are often gained and lost together through evolution. Therefore identifying co-evolution of genes can predict functional gene-gene associations. We describe here the full statistical model and computational strategies underlying the original algorithm *CLustering by Inferred Models of Evolution* (CLIME 1.0) recently reported by us (*Cell* **158** (2014) 213–225). CLIME 1.0 employs a mixture of tree-structured hidden Markov models for gene evolution process, and a Bayesian model-based clustering algorithm to detect gene modules with shared evolutionary histories (termed evolutionary conserved modules, or ECMs). A Dirichlet process prior was adopted for estimating the number of gene clusters and a Gibbs sampler was developed for posterior sampling. We further developed an extended version, CLIME 1.1, to incorporate the uncertainty on the evolutionary tree structure. By simulation studies and benchmarks on real data sets, we show that CLIME 1.0 and CLIME 1.1 outperform traditional methods that use simple metrics (e.g., the Hamming distance or Pearson correlation) to measure co-evolution between pairs of genes.

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SEQUENTIAL DIRICHLET PROCESS MIXTURES OF MULTIVARIATE SKEW *t*-DISTRIBUTIONS FOR MODEL-BASED CLUSTERING OF FLOW CYTOMETRY DATA[1]

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Flow cytometry is a high-throughput technology used to quantify multiple surface and intracellular markers at the level of a single cell. This enables us to identify cell subtypes and to determine their relative proportions. Improvements of this technology allow us to describe millions of individual cells from a blood sample using multiple markers. This results in high-dimensional datasets, whose manual analysis is highly time-consuming and poorly reproducible. While several methods have been developed to perform automatic recognition of cell populations most of them treat and analyze each sample independently. However, in practice individual samples are rarely independent, especially in longitudinal studies. Here we analyze new longitudinal flow-cytometry data from the DALIA-1 trial, which evaluates a therapeutic vaccine against HIV, by proposing a new Bayesian nonparametric approach with Dirichlet process mixture (DPM) of multivariate skew *t*-distributions to perform model based clustering of flow-cytometry data. DPM models directly estimate the number of cell populations from the data, avoiding model selection issues, and skew *t*-distributions provides robustness to outliers and nonelliptical shape of cell populations. To accommodate repeated measurements, we propose a sequential strategy relying on a parametric approximation of the posterior. We illustrate the good performance of our method on simulated data and on an experimental benchmark dataset. This sequential strategy outperforms all other methods evaluated on the benchmark dataset and leads to improved performance on the DALIA-1 data.

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COMPOSITIONAL MEDIATION ANALYSIS FOR MICROBIOME STUDIES[1]

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Motivated by recent advances in causal mediation analysis and problems in the analysis of microbiome data, we consider the setting where the effect of a treatment on an outcome is transmitted through perturbing the microbial communities or compositional mediators. The compositional and high-dimensional nature of such mediators makes the standard mediation analysis not directly applicable to our setting. We propose a sparse compositional mediation model that can be used to estimate the causal direct and indirect (or mediation) effects utilizing the algebra for compositional data in the simplex space. We also propose tests of total and component-wise mediation effects. We conduct extensive simulation studies to assess the performance of the proposed method and apply the method to a real microbiome dataset to investigate an effect of fat intake on body mass index mediated through the gut microbiome.

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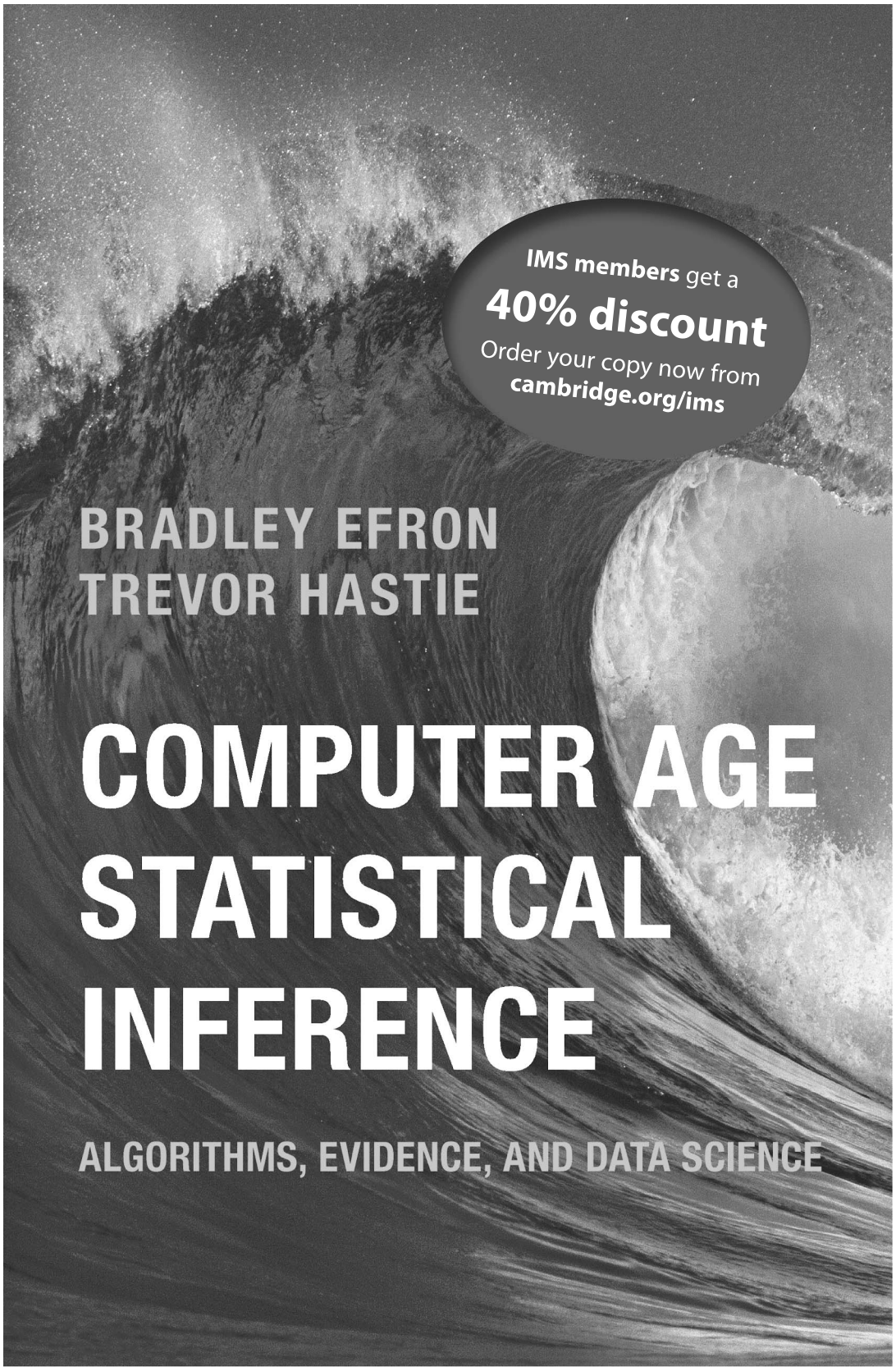
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