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MULTISCALE POISSON PROCESS APPROACHES FOR DETECTING AND ESTIMATING DIFFERENCES FROM HIGH-THROUGHPUT SEQUENCING ASSAYS

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Estimating and testing for differences in molecular phenotypes (e.g., gene expression, chromatin accessibility, transcription factor binding) across conditions is an important part of understanding the molecular basis of gene regulation. These phenotypes are commonly measured using high-throughput sequencing assays (e.g., RNA-seq, ATAC-seq, ChIP-seq), which provide high-resolution count data that reflect how the phenotypes vary along the genome. Multiple methods have been proposed to help exploit these high-resolution measurements for differential expression analysis. However, they ignore the count nature of the data, instead using normal distributions that work well only for data with large sample sizes or high counts. Here we develop count-based methods to address this problem. We model the data for each sample using an inhomogeneous Poisson process with spatially structured underlying intensity function and then, building on multiscale models for the Poisson process, estimate and test for differences in the underlying intensity function across samples (or groups of samples). Using both simulation and real ATAC-seq data, we show that our method outperforms previous normal-based methods, especially in situations with small sample sizes or low counts.

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DYNAMIC MODELING AND ONLINE MONITORING OF TENSOR DATA STREAMS WITH APPLICATION TO PASSENGER FLOW SURVEILLANCE

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Passenger flow surveillance in urban transport systems has emerged as a major global issue for smart city management. Governments are taking proper measures to monitor passenger flow in order to maintain social stability and to prevent unexpected group events. It is critical to develop a passenger flow surveillance system that continuously monitors the passenger flow over time and triggers a signal as soon as the passenger flow begins to deteriorate so that timely government intervention can be implemented. In this paper passenger flow surveillance is novelly formulated as dynamic modeling and online monitoring of tensor data streams. Existing tensor monitoring methods either rely heavily on the assumption that the tensor coefficients exhibit a low-rank structure or are inapplicable to general-order tensors. We propose a unified monitoring framework based on the tensor normal distribution to overcome these challenges. We begin by developing a tensor model selection procedure that ensures that the chosen tensor structure strikes a balance between model complexity and estimation accuracy. Then we propose an online estimation procedure to dynamically estimate the tensor parameters on which sequential change-detection procedures, using the generalized likelihood ratio test, are proposed. Extensive simulations and an analysis of real passenger flow data in Hong Kong demonstrate the efficacy of our approach.

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Key words and phrases. Passenger flow surveillance, online monitoring, tensor data streams, tensor normal distribution, model selection, control chart.

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CONTINUOUS AND ATLAS-FREE ANALYSIS OF BRAIN STRUCTURAL CONNECTIVITY

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Brain structural networks are often represented as discrete adjacency matrices with elements summarizing the connectivity between pairs of regions of interest (ROIs). These ROIs are typically determined a priori using a brain atlas. The choice of atlas is often arbitrary and can lead to a loss of important connectivity information at the sub-ROI level. This work introduces an atlas-free framework that overcomes these issues by modeling brain connectivity using smooth random functions. In particular, we assume that the observed pattern of white matter fiber tract endpoints is driven by a latent random function defined over a product manifold domain. To facilitate statistical analysis of these high-dimensional functional data objects, we develop a novel algorithm to construct a data-driven reduced-rank function space that offers a desirable trade-off between computational complexity and flexibility. Using real data from the Human Connectome Project, we show that our method outperforms state-of-the-art approaches that use the traditional atlas-based structural connectivity representation on a variety of connectivity analysis tasks. We further demonstrate how our method can be used to detect localized regions and connectivity patterns associated with group differences.

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A BOOTSTRAP MODEL COMPARISON TEST FOR IDENTIFYING GENES WITH CONTEXT-SPECIFIC PATTERNS OF GENETIC REGULATION

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Understanding how genetic variation affects gene expression is essential for a complete picture of the functional pathways that give rise to complex traits. Although numerous studies have established that many genes are differentially expressed in distinct human tissues and cell types, no tools exist for identifying the genes whose expression is differentially regulated. Here we introduce DRAB (differential regulation analysis by bootstrapping), a gene-based method for testing whether patterns of genetic regulation are significantly different between tissues or other biological contexts. DRAB first leverages the elastic net to learn context-specific models of local genetic regulation and then applies a novel bootstrap-based model comparison test to check their equivalency. Unlike previous model comparison tests, our proposed approach can determine whether population-level models have equal predictive performance by accounting for the variability of feature selection and model training. We validated DRAB on mRNA expression data from a variety of human tissues in the Genotype-Tissue Expression (GTEx) Project. DRAB yielded biologically reasonable results and had sufficient power to detect genes with tissue-specific regulatory profiles while effectively controlling false positives. By providing a framework that facilitates the prioritization of differentially regulated genes, our study enables future discoveries on the genetic architecture of molecular phenotypes.

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PATIENT RECRUITMENT USING ELECTRONIC HEALTH RECORDS UNDER SELECTION BIAS: A TWO-PHASE SAMPLING FRAMEWORK

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Electronic health records (EHRs) are increasingly recognized as a cost-effective resource for patient recruitment in clinical research. However, how to optimally select a cohort from millions of individuals to answer a scientific question of interest remains unclear. Consider a study to estimate the mean or mean difference of an expensive outcome. Inexpensive auxiliary covariates predictive of the outcome may often be available in patients' health records, presenting an opportunity to recruit patients selectively, which may improve efficiency in downstream analyses. In this paper we propose a two-phase sampling design that leverages available information on auxiliary covariates in EHR data. A key challenge in using EHR data for multiphase sampling is the potential selection bias, because EHR data are not necessarily representative of the target population. Extending existing literature on two-phase sampling design, we derive an optimal two-phase sampling method that improves efficiency over random sampling while accounting for the potential selection bias in EHR data. We demonstrate the efficiency gain from our sampling design via simulation studies and an application evaluating the prevalence of hypertension among U.S. adults leveraging data from the Michigan Genomics Initiative, a longitudinal biorepository in Michigan Medicine.

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A NOVEL BAYESIAN MODEL FOR ASSESSING INTRATUMOR HETEROGENEITY OF TUMOR INFILTRATING LEUKOCYTES WITH MULTIREGION GENE EXPRESSION SEQUENCING

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Intratumor heterogeneity (ITH) of tumor-infiltrated leukocytes (TILs) is an important phenomenon of cancer biology with potentially profound clinical impacts. Multiregion gene expression sequencing data provide a promising opportunity that allows for explorations of TILs and their intratumor heterogeneity for each subject. Although several existing methods are available to infer the proportions of TILs, considerable methodological gaps exist for evaluating intratumor heterogeneity of TILs with multiregion gene expression data. Here we develop ICeITH, immune cell estimation reveals intratumor heterogeneity, a Bayesian hierarchical model that borrows cell-type profiles as prior knowledge to decompose mixed bulk data while accounting for the within-subject correlations among tumor samples. ICeITH quantifies intratumor heterogeneity by the variability of targeted cellular compositions. Through extensive simulation studies, we demonstrate that ICeITH is more accurate in measuring relative cellular abundance and evaluating intratumor heterogeneity compared with existing methods. We also assess the ability of ICeITH to stratify patients by their intratumor heterogeneity score and associate the estimations with the survival outcomes. Finally, we apply ICeITH to two multiregion gene expression datasets from lung cancer studies to classify patients into different risk groups according to the ITH estimations of targeted TILs that shape either pro- or antitumor processes. In conclusion, ICeITH is a useful tool to evaluate intratumor heterogeneity of TILs from multiregion gene expression data.

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SCALABLE MULTIPLE NETWORK INFERENCE WITH THE JOINT GRAPHICAL HORSESHOE

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Network models are useful tools for modelling complex associations. In statistical omics such models are increasingly popular for identifying and assessing functional relationships and pathways. If a Gaussian graphical model is assumed, conditional independence is determined by the nonzero entries of the inverse covariance (precision) matrix of the data. The Bayesian graphical horseshoe estimator provides a robust and flexible framework for precision matrix inference, as it introduces local, edge-specific parameters which prevent over-shrinkage of nonzero off-diagonal elements. However, its applicability is currently limited in statistical omics settings, which often involve high-dimensional data from multiple conditions that might share common structures. We propose: (i) a scalable expectation conditional maximisation (ECM) algorithm for the original graphical horseshoe and (ii) a novel joint graphical horseshoe estimator, which borrows information across multiple related networks to improve estimation. We show numerically that our single-network ECM approach is more scalable than the existing graphical horseshoe Gibbs implementation, while achieving the same level of accuracy. We also show that our joint-network proposal successfully leverages shared edge-specific information between networks while still retaining differences, outperforming state-of-the-art methods at any level of network similarity. Finally, we leverage our approach to clarify gene regulation activity within and across immune stimulation conditions in monocytes, and formulate hypotheses on the pathogenesis of immune-mediated diseases.

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JOINT MIXED MEMBERSHIP MODELING OF MULTIVARIATE LONGITUDINAL AND SURVIVAL DATA FOR LEARNING THE INDIVIDUALIZED DISEASE PROGRESSION

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Patients with Alzheimer's disease (AD) often exhibit substantial heterogeneity in disease progression due to multiple genetic causes for such a complex disease. Investigating diverse subtypes of neurodegeneration and individualized disease progression is essential for early diagnosis and precision medicine. In this article we present a novel joint mixed membership model for multivariate longitudinal AD-related biomarkers and time of AD diagnosis. Unlike conventional finite mixture models that assign each subject a single subgroup membership, the proposed model assigns partial membership across subgroups, allowing subjects to lie between two or more subgroups. This flexible structure enables individualized disease progression and facilitates the identification of clinically meaningful neurological statuses often elusive in current mixed effects models. We employ a spline-based trajectory model to characterize complex and possibly nonlinear patterns of multiple longitudinal clinical markers. A Cox model is then used to examine the effects of time-variant risk factors on the hazard of developing AD. We develop a Bayesian method coupled with efficient Markov chain Monte Carlo sampling schemes to perform statistical inference. The proposed approach is assessed through extensive simulation studies and an application to the Alzheimer's Disease Neuroimaging Initiative study, showing a better performance in AD diagnosis than existing joint models.

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OUTCOME-GUIDED DISEASE SUBTYPING BY GENERATIVE MODEL AND WEIGHTED JOINT LIKELIHOOD IN TRANSCRIPTOMIC APPLICATIONS

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With advances in high-throughput technology, molecular disease subtyping by high-dimensional omics data has been recognized as an effective approach for identifying subtypes of complex diseases with distinct disease mechanisms and prognoses. Conventional cluster analysis takes omics data as input and generates patient clusters with similar gene expression pattern. The omics data, however, usually contain multifaceted cluster structures that can be defined by different sets of genes. If the gene set associated with irrelevant clinical variables (e.g., sex or age) dominates the clustering process, the resulting clusters may not capture clinically meaningful disease subtypes. This motivates the development of a clustering framework with guidance from a prespecified disease outcome, such as lung function measurement or survival, in this paper. We propose two disease subtyping methods by omics data with outcome guidance using a generative model or a weighted joint likelihood. Both methods connect an outcome association model and a disease subtyping model by a latent variable of cluster labels. Compared to the generative model, weighted joint likelihood contains a data-driven weight parameter to balance the likelihood contributions from outcome association and gene cluster separation, which improves generalizability in independent validation but requires heavier computing. Extensive simulations and two real applications in lung disease and triple-negative breast cancer demonstrate superior disease subtyping performance of the outcome-guided clustering methods in terms of disease subtyping accuracy, gene selection and outcome association. Unlike existing clustering methods, the outcome-guided disease subtyping framework creates a new precision medicine paradigm to directly identify patient subgroups with clinical association.

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LEARNING AND FORECASTING OF AGE-SPECIFIC PERIOD MORTALITY VIA B-SPLINE PROCESSES WITH LOCALLY-ADAPTIVE DYNAMIC COEFFICIENTS

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Although the analysis of human mortality has a well-established history, the attempt to accurately forecast future death-rate patterns for different age groups and time horizons still attracts active research. Such a predictive focus has motivated an increasing shift toward more flexible representations of age-specific period mortality trajectories at the cost of reduced interpretability. Although this perspective has led to successful predictive strategies, the inclusion of interpretable structures in modeling of human mortality can be, in fact, beneficial for improving forecasts. We pursue this direction via a novel B-spline process with locally-adaptive dynamic coefficients. Such a process outperforms state-of-the-art forecasting strategies by explicitly incorporating the core structures of period mortality within an interpretable formulation which enables inference on age-specific mortality trends and the corresponding rates of change across time. This is obtained by modeling the age-specific death counts via a Poisson log-normal model parameterized through a linear combination of B-spline bases with dynamic coefficients that characterize time changes in mortality rates via suitably defined stochastic differential equations. While flexible, the resulting formulation can be accurately approximated by a Gaussian state-space model that facilitates closed-form Kalman filtering, smoothing and forecasting, for both the trends of the spline coefficients and the corresponding first derivatives, which measure rates of change in mortality for different age groups. As illustrated in applications to mortality data from different countries, the proposed model outperforms state-of-the-art methods, both in point forecasts and in calibration of predictive intervals. Moreover, it unveils substantial differences in mortality patterns across countries and ages, both in the past decades and during the COVID-19 pandemic.

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LATENT CONJUNCTIVE BAYESIAN NETWORK: UNIFY ATTRIBUTE HIERARCHY AND BAYESIAN NETWORK FOR COGNITIVE DIAGNOSIS

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Cognitive diagnostic assessment aims to measure specific knowledge structures in students. To model data arising from such assessments, cognitive diagnostic models with discrete latent variables have gained popularity in educational and behavioral sciences. In a learning context, the latent variables often denote sequentially acquired skill attributes, which is often modeled by the so-called attribute hierarchy method. One drawback of the traditional attribute hierarchy method is that its parameter complexity varies substantially with the hierarchy's graph structure, lacking statistical parsimony. Additionally, arrows among the attributes do not carry an interpretation of statistical dependence. Motivated by these, we propose a new family of *latent conjunctive Bayesian networks* (LCBNs), which rigorously unify the attribute hierarchy method for sequential skill mastery and the Bayesian network model in statistical machine learning. In an LCBN the latent graph not only retains the hard constraints on skill prerequisites as an attribute hierarchy but also encodes nice conditional independence interpretation as a Bayesian network. LCBNs are identifiable, interpretable, and parsimonious statistical tools to diagnose students' cognitive abilities from assessment data. We propose an efficient two-step EM algorithm for structure learning and parameter estimation in LCBNs and establish the consistency of this procedure. Application of our method to an international educational assessment dataset gives interpretable findings of cognitive diagnosis.

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QUANTILE REGRESSION DECOMPOSITION ANALYSIS OF DISPARITY RESEARCH USING COMPLEX SURVEY DATA: APPLICATION TO DISPARITIES IN BMI AND TELOMERE LENGTH BETWEEN U.S. MINORITY AND WHITE POPULATION GROUPS

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We develop a quantile regression decomposition (QRD) method for analyzing observed disparities (OD) between population groups in socioeconomic and health-related outcomes for complex survey data. The conventional decomposition approaches use the conditional mean regression to decompose the disparity into two parts, the part explained by the difference arising from the different distributions in the explanatory covariates and the remaining part, which is unexplained by the covariates. Many socioeconomic and health outcomes exhibit heteroscedastic distributions, where the magnitude of observed disparities varies across different quantiles of these outcomes. Thus, differences in the explanatory covariates may account for varying differences in the OD across the quantiles of the outcome. The QRD can identify where there are greater differences in the outcome distribution, for example, 90th quantile, and how important the covariates are in explaining those differences. Much socioeconomic and health research relies on complex surveys, such as the National Health and Nutrition Examination Survey (NHANES), that oversample individuals from disadvantaged/minority population groups in order to provide improved precision. QRD has not been extended to the complex survey setting. We improve the QRD approach proposed in Machado and Mata (2005) to yield more reliable estimates at the quantiles, where the data are sparse, and extend it to the complex survey setting. We also propose a perturbation-based variance estimation method. Simulation studies indicate that the estimates of the unexplained portions of the OD across quantiles are unbiased and the coverage of the confidence intervals are close to nominal value. This methodology is used to study disparities in body mass index (BMI) and telomere length between race/ethnic groups estimated from the NHANES data.

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BAYESIAN HIDDEN MARKOV MODELS FOR LATENT VARIABLE LABELING ASSIGNMENTS IN CONFLICT RESEARCH: APPLICATION TO THE ROLE CEASEFIRES PLAY IN CONFLICT DYNAMICS

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A crucial challenge for solving problems in conflict research is in leveraging the semisupervised nature of the data that arise. Observed response data, such as counts of battle deaths over time, indicate latent processes of interest, such as intensity and duration of conflicts, but defining and labeling instances of these unobserved processes requires nuance and imprecision. The availability of such labels, however, would make it possible to study the effect of intervention-related predictors—such as ceasefires—directly on conflict dynamics (e.g., latent intensity) rather than through an intermediate proxy, like observed counts of battle deaths. Motivated by this problem and the new availability of the ETH-PRIO Civil Conflict Ceasefires data set, we propose a Bayesian autoregressive (AR) hidden Markov model (HMM) framework as a sufficiently flexible machine learning approach for semisupervised regime labeling with uncertainty quantification. We motivate our approach by illustrating the way it can be used to study the role that ceasefires play in shaping conflict dynamics. This ceasefires data set is the first systematic and globally comprehensive data on ceasefires, and our work is the first to analyze this new data and to explore the effect of ceasefires on conflict dynamics in a comprehensive and cross-country manner.

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SEMIPARAMETRIC ESTIMATION FOR DYNAMIC NETWORKS WITH SHIFTED CONNECTING INTENSITIES

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Neural circuits are of paramount importance in the nervous system, as they are the essential infrastructure in guiding animal behavior. However, modeling the development of neural circuits poses significant challenges due to inherent properties of the development process. First, the neural circuit development process is transient, where the course of development can only be observed once. Second, despite potentially sharing similar underlying mechanisms for development, neural circuits from different subjects possess distinct sets of neurons, which limits the sharing of information across subjects. Third, neurons have diverse, unobserved activation times, which may obscure the analysis of neural activities. In light of these challenges, this study presents a novel approach aimed at clustering neurons based on their connecting behaviors while accommodating disparities at the neuron level. To this end, we propose a dynamic stochastic block model that accommodates unknown time shifts. We establish the conditions that guarantee the identifiability of cluster memberships of nodes and representative connecting intensities across clusters. Using methods for shape invariant models, we propose computationally efficient semiparametric estimation procedures to simultaneously estimate time shifts, cluster memberships, and connecting intensities. We illustrate the performance of the proposed procedures via extensive simulation experiments. We further apply the proposed method on a motor circuit development data from zebrafish to reveal distinct roles of neurons and identify representative connecting behaviors.

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A NONPARAMETRIC MIXED-EFFECTS MIXTURE MODEL FOR PATTERNS OF CLINICAL MEASUREMENTS ASSOCIATED WITH COVID-19

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Some patients with COVID-19 show changes in signs and symptoms, such as temperature and oxygen saturation days before being positively tested for SARS-CoV-2, while others remain asymptomatic. It is important to identify these subgroups and to understand what biological and clinical predictors are related to these subgroups. This information will provide insights into how the immune system may respond differently to infection and can further be used to identify infected individuals. We propose a flexible nonparametric mixed-effects mixture model that identifies risk factors and classifies patients with biological changes. We model the latent probability of biological changes using a logistic regression model and trajectories in the latent groups using smoothing splines. We developed an EM algorithm to maximize the penalized likelihood for estimating all parameters and mean functions. We evaluate our methods by simulations and apply the proposed model to investigate changes in temperature in a cohort of COVID-19-infected hemodialysis patients.

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BENEFITS AND COSTS OF MATCHING PRIOR TO A DIFFERENCE IN DIFFERENCES ANALYSIS WHEN PARALLEL TRENDS DOES NOT HOLD

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The consequence of a change in school leadership (e.g., principal turnover) on student achievement has important implications for education policy. The impact of such an event can be estimated via the popular difference in difference (DiD) estimator, where those schools with a turnover event are compared to a selected set of schools that did not have such an event. The strength of this comparison depends on the plausibility of the "parallel trends" assumption that the "treated group" of those schools which had leadership turnover, absent such turnover, would have changed "similarly" to those which did not. To bolster such a claim, one might generate a comparison group, via matching, that is similar to the treated group with respect to pretreatment outcomes and/or pretreatment covariates. Unfortunately, as has been previously pointed out, this intuitively appealing approach also has a cost in terms of bias. To assess the trade-offs of matching in our application, we first characterize the bias of matching prior to a DiD analysis under a linear structural model that allows for time-invariant observed and unobserved confounders with time-varying effects on the outcome. Given our framework, we verify that matching on baseline covariates generally reduces bias. We further show how additionally matching on pretreatment outcomes has both cost and benefit. First, matching on pretreatment outcomes partially balances unobserved confounders, which mitigates some bias. This reduction is proportional to the outcome's reliability, a measure of how coupled the outcomes are with the latent covariates. Offsetting these gains, matching also injects bias into the final estimate by undermining the second difference in the DiD via a regression-to-the-mean effect. Consequently, we provide heuristic guidelines for determining to what degree the bias reduction of matching is likely to outweigh the bias cost. We illustrate our guidelines by reanalyzing a principal turnover study that used matching prior to a DiD analysis and find that matching on both the pretreatment outcomes and observed covariates makes the estimated treatment effect more credible.

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A LATENT PROCESS MODEL FOR MONITORING PROGRESS TOWARD HARD-TO-MEASURE TARGETS WITH APPLICATIONS TO MENTAL HEALTH AND ONLINE EDUCATIONAL ASSESSMENTS

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The recent shift to remote learning and work has aggravated longstanding problems, such as the problem of monitoring the mental health of individuals and the progress of students toward learning targets. We introduce a novel latent process model with a view to monitoring the progress of individuals toward a hard-to-measure target of interest and measured by a set of variables. The latent process model is based on the idea of embedding both individuals and variables measuring progress toward the target of interest in a shared metric space, interpreted as an interaction map that captures interactions between individuals and variables. The fact that individuals are embedded in the same metric space as the target helps assess the progress of individuals toward the target. We demonstrate, with the help of simulations and applications, that the latent process model enables a novel look at mental health and online educational assessments in disadvantaged subpopulations.

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EXPOSURE EFFECTS ON COUNT OUTCOMES WITH OBSERVATIONAL DATA, WITH APPLICATION TO INCARCERATED WOMEN

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Causal inference methods can be applied to estimate the effect of a point exposure or treatment on an outcome of interest using data from observational studies. For example, in the Women's Interagency HIV Study, it is of interest to understand the effects of incarceration on the number of sexual partners and the number of cigarettes smoked after incarceration. In settings like this where the outcome is a count, the estimand is often the causal mean ratio, that is, the ratio of the counterfactual mean count under exposure to the counterfactual mean count under no exposure. This paper considers estimators of the causal mean ratio based on inverse probability of treatment weights, the parametric g-formula, and doubly robust estimation, each of which can account for overdispersion, zero-inflation, and heaping in the measured outcome. Methods are compared in simulations and are applied to data from the Women's Interagency HIV Study.

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SUPPORT VECTOR MACHINE FOR DYNAMIC SURVIVAL PREDICTION WITH TIME-DEPENDENT COVARIATES

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Predicting time-to-event outcomes using time-dependent covariates is a challenging problem. Many machine learning approaches, such as tree-based methods and support vector regression, predominantly utilize only baseline covariates. Only a few methods can incorporate time-dependent covariates, but they often lack theoretical justification. In this paper we present a new framework for event time prediction, leveraging the support vector machines to forecast the associated counting processes. Utilizing the kernel trick, we accommodate nonlinear functions in both time and covariate spaces. Subsequently, we use a chain algorithm to predict future events. Theoretical analysis proves that our method is equivalent to comparing time-varying hazard rates among at-risk subjects, and we obtain the convergence rate of the resulting prediction loss. Through simulation studies and a case study on Huntington's disease, we demonstrate the superior performance of our approach compared to alternative methods based on machine learning, deep learning, and statistical models.

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NONCONVEX SVM FOR CANCER DIAGNOSIS BASED ON MORPHOLOGIC FEATURES OF TUMOR MICROENVIRONMENT

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The surroundings of a cancerous tumor impact how it grows and develops in humans. New data from early breast cancer patients contains information on the collagen fibers surrounding the tumorous tissue—offering hope of finding additional biomarkers for diagnosis and prognosis—but poses two challenges for typical analysis. Each image section contains information on hundreds of fibers, and each tissue has multiple image sections contributing to a single prediction of tumor vs. nontumor. This nested relationship of fibers within image spots within tissue samples requires a specialized analysis approach.

We devise a novel support vector machine (SVM)-based predictive algorithm for this data structure. By treating the collection of fibers as a probability distribution, we can measure similarities between the collections through a flexible kernel approach. By assuming the relationship of tumor status between image sections and tissue samples, the constructed SVM problem is nonconvex, and traditional algorithms can not be applied. We propose two algorithms that exchange computational accuracy and efficiency to manage data of all sizes. The predictive performance of both algorithms is evaluated on the collagen fiber data set and additional simulation scenarios. We offer reproducible implementations of both algorithms of this approach in the R package `mildsvm`.

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PROBABILISTIC CONTRASTIVE DIMENSION REDUCTION FOR CASE-CONTROL STUDY DATA

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Case-control experiments are essential to the scientific method, as they allow researchers to test biological hypotheses by looking for differences in outcome between cases and controls. It is then of interest to characterize variation that is enriched in a "foreground" (case) dataset relative to a "background" (control) dataset. For example, in a genomics context, the goal is to identify low-dimensional transcriptional structure unique to patients with certain disease (cases) vs. those without that disease (controls). In this work we propose probabilistic contrastive principal component analysis (PCPCA), a probabilistic dimension reduction method designed for case-control data. We describe inference in PCPCA through a contrastive likelihood and show that our model generalizes PCA, probabilistic PCA, and contrastive PCA. We discuss how to set the tuning parameter in theory and in practice, and we show several of PCPCA's advantages in the analysis of case-control data over related methods, including greater interpretability, uncertainty quantification and principled inference, robustness to noise and missing data, and the ability to generate "foreground-enriched" data from the model. We demonstrate PCPCA's performance on case-control data through a series of simulations, and we successfully identify variation specific to case data in genomic case-control experiments with data modalities, including gene expression, protein expression, and images.

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MODELING CURVES AND DERIVATIVES AS PREDICTORS FOR TRAFFIC BREAKDOWN PROBABILITIES

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Motivated by an interest in predicting the status of road traffic congestion within a short period, this paper presents a generalized functional linear regression model for predicting traffic breakdown probabilities. In this model, traffic congestion status is the response variable, and we utilize the observed traffic speed trajectories and their first two derivatives as functional predictors, representing different features of a random function. While the derivatives of a trajectory may contain useful information, they cannot be observed directly and so must be estimated. To address this challenge, we apply the Karhunen–Loève representation to individual functional predictors, including the trajectory and its derivatives. The regression model is reparameterized to represent both the integrated regression effect and the predictor-specific effects. The importance of these effects is indicated by the corresponding weight parameters. We also provide the consistency properties of the estimators relating to the derivative functional principal components and the regression parameter functions. In our simulation study, we find that the modeling approach is useful in its application to freeway traffic data; in particular, the use of speed trajectory derivatives as predictors for traffic status successfully enhances prediction accuracy.

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SURROGATE METHOD FOR PARTIAL ASSOCIATION BETWEEN MIXED DATA WITH APPLICATION TO WELL-BEING SURVEY ANALYSIS

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This paper is motivated by the analysis of a survey study focusing on college student well-being before and after the COVID-19 pandemic outbreak. A statistical challenge in well-being studies lies in the multidimensionality of outcome variables, recorded in various scales such as continuous, binary, or ordinal. The presence of mixed data complicates the examination of their relationships when adjusting for important covariates. To address this challenge, we propose a unifying framework for studying partial association between mixed data. We achieve this by defining a unified residual using the surrogate method. The idea is to map the residual randomness to a consistent continuous scale, regardless of the original scales of outcome variables. This framework applies to parametric or semiparametric models for covariate adjustments. We validate the use of such residuals for assessing partial association, introducing a measure that generalizes classical Kendall's tau to capture both partial and marginal associations. Moreover, our development advances the theory of the surrogate method by demonstrating its applicability without requiring outcome variables to have a latent variable structure. In the analysis of the college student well-being survey, our proposed method unveils the contingency of relationships between multidimensional well-being measures and micro personal risk factors (e.g., physical health, loneliness, and accommodation) as well as the macro disruption caused by COVID-19.

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AN INTEGRATIVE NETWORK-BASED MEDIATION MODEL (NMM) TO ESTIMATE MULTIPLE GENETIC EFFECTS ON OUTCOMES MEDIATED BY FUNCTIONAL CONNECTIVITY

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Functional connectivity of the brain, characterized by interconnected neural circuits across functional networks, is a cutting-edge feature in neuroimaging. It has the potential to mediate the effect of genetic variants on behavioral outcomes or diseases. Existing mediation analysis methods can evaluate the impact of genetics and brain structure/function on cognitive behavior or disorders, but they tend to be limited to single genetic variants or univariate mediators, without considering cumulative genetic effects and the complex matrix and group and network structures of functional connectivity. To address this gap, the paper presents an integrative network-based mediation model (NMM) that estimates the effect of multiple genetic variants on behavioral outcomes or diseases mediated by functional connectivity. The model incorporates group information of inter-regions at broad network level and imposes low-rank and sparse assumptions to reflect the complex structures of functional connectivity and selecting network mediators simultaneously. We adopt block coordinate descent algorithm to implement a fast and efficient solution to our model. Simulation results indicate the efficacy of the model in selecting active mediators and reducing bias in effect estimation. With application to the Human Connectome Project Youth Adult (HCP-YA) study of 493 young adults, two genetic variants (rs769448 and rs769449) on the *APOE4* gene are identified that lead to deficits in functional connectivity within visual networks and fluid intelligence.

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SEMIPARAMETRIC LINEAR REGRESSION WITH AN INTERVAL-CENSORED COVARIATE IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

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In longitudinal studies, investigators are often interested in understanding how the time since the occurrence of an intermediate event affects a future outcome. The intermediate event is often asymptomatic such that its occurrence is only known to lie in a time interval induced by periodic examinations. We propose a linear regression model that relates the time since the occurrence of the intermediate event to a continuous response at a future time point through a rectified linear unit activation function while formulating the distribution of the time to the occurrence of the intermediate event through the Cox proportional hazards model. We consider nonparametric maximum likelihood estimation with an arbitrary sequence of examination times for each subject. We present an EM algorithm that converges stably for arbitrary datasets. The resulting estimators of regression parameters are consistent, asymptotically normal, and asymptotically efficient. We assess the performance of the proposed methods through extensive simulation studies and provide an application to the Atherosclerosis Risk in Communities Study.

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SEMIPARAMETRIC MODELING OF SARS-COV-2 TRANSMISSION USING TESTS, CASES, DEATHS, AND SEROPREVALENCE DATA

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Mechanistic models fit to streaming surveillance data are critical for understanding the transmission dynamics of an outbreak as it unfolds in real-time. However, transmission model parameter estimation can be imprecise, sometimes even impossible, because surveillance data are noisy and not informative about all aspects of the mechanistic model. To partially overcome this obstacle, Bayesian models have been proposed to integrate multiple surveillance data streams. We devised a modeling framework for integrating SARS-CoV-2 diagnostics test and mortality time series data as well as seroprevalence data from cross-sectional studies and tested the importance of individual data streams for both inference and forecasting. Importantly, our model for incidence data accounts for changes in the total number of tests performed. We apply our Bayesian data integration method to COVID-19 surveillance data collected in Orange County, California, between March 2020 and February 2021 and find that 32–72% of the Orange County residents experienced SARS-CoV-2 infection by mid-January, 2021. Despite this high number of infections, our results suggest that the abrupt end of the winter surge in January 2021 was due to both behavioral changes and a high level of accumulated natural immunity.

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BAYESIAN JOINT MODELING OF HIGH-DIMENSIONAL DISCRETE MULTIVARIATE LONGITUDINAL DATA USING GENERALIZED LINEAR MIXED MODELS

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In routine cancer care, various patient- and clinician-reported symptoms are collected throughout treatment. This informs a crucial part of clinical research, particularly in studying the factors associated with symptom underascertainment. To jointly analyze such discrete, multivariate, and potentially high-dimensional repeated measures, we propose a Bayesian longitudinal generalized linear mixed model (BLGLMM). This model integrates three key methodologies: a low-rank matrix decomposition to approximate the high-dimensional regression coefficient matrix, a sparse factor model to capture the dependence among multiple outcomes, and random effects to account for the dependence among repeated responses. Posterior computation is performed using an efficient Markov chain Monte Carlo algorithm. We conduct simulations and provide an illustrative example examining the factors associated with symptom underascertainment in prostate cancer patients to demonstrate the efficacy and utility of our proposed method.

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ASSESSING AQUATIC TOXICITY ASSESSMENT VIA A CLUSTERED VARIANCE MODEL

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Motivated by the need to assess consistency in the outcomes of aquatic toxicity tests conducted by different labs at different time points, we propose a clustering of variance method in linear mixed models. The proposed method, referred as CVM, is able to identify the cluster structure of the variances and estimate model parameters simultaneously. In our proposed method, a penalized approach based on pairwise penalties is proposed to identify the cluster structure. We construct an optimization problem and develop an algorithm based on the alternating direction method of multipliers. Simulation studies show that the proposed approach can identify the cluster structure well and outperforms traditional methods based on k-means. In the end, the proposed approach is applied to the aquatic toxicity assessment data, which gives a more reasonable cluster structure than the traditional methods.

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A LATENT VARIABLE APPROACH FOR MODELING RELATIONAL DATA WITH MULTIPLE RECEIVERS

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Directional relational event data, such as email data, often contain unicast messages (i.e., messages of one sender toward one receiver) and multicast messages (i.e., messages of one sender toward multiple receivers). The Enron email data that is the focus in this paper consists of 31% multicast messages. Multicast messages contain important information about the roles of actors in the network, which is needed for better understanding social interaction dynamics. In this paper a multiplicative latent factor model is proposed to analyze such relational data. For a given message, all potential receiver actors are placed on a suitability scale, and the actors are included in the receiver set whose suitability score exceeds a threshold value. Unobserved heterogeneity in the social interaction behavior is captured using a multiplicative latent factor structure with latent variables for actors (which differ for actors as senders and receivers) and latent variables for individual messages. The model is referred to as the multicast additive and multiplicative effects network (mc-amen) model. A Bayesian computational algorithm, which relies on Gibbs sampling, is proposed for model fitting. Model assessment is done using posterior predictive checks. Numerical simulations show that the model is widely applicable for various scenarios involving multicast messages. Furthermore, a mc-amen model with a two-dimensional latent variable can accurately capture the empirical distribution of the cardinality of the receiver set and the composition of the receiver sets for commonly observed messages in the Enron email data. In the Enron network, actors have a comparable (but not identical) role as a sender and as a receiver in the network.

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SPARSE CLUSTERING FOR CUSTOMER SEGMENTATION WITH HIGH-DIMENSIONAL MIXED-TYPE DATA

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Customer segmentation has wide applications in business activities, such as personalized marketing and targeted product development. To realize customer segmentation, clustering methods are commonly used. However, modern customer segmentation encounters challenges characterized by high-dimensionality and mixed-type variables (i.e., the mixture of continuous variables and categorical variables). It brings great challenges to customer segmentation, because most existing clustering methods are only designed for data with one single type of variables. Furthermore, the existence of noise variables highlights the necessity of simultaneous variable selection and data clustering. Motivated by these issues, we develop a Davies–Bouldin index based sparse clustering (DBI-SC) method for customer segmentation with high-dimensional mixed-type data. In this method we define dissimilarity measures for continuous variables and categorical variables separately. Then an adjusted DBI criterion is designed to measure the contribution of each variable to clustering. For variable selection we apply the sparse clustering framework and introduce different penalty parameters for the mixed-type variables. The screening consistency property of the DBI-SC method is also investigated. Extensive simulation studies demonstrate the satisfactory performance of the DBI-SC method in both clustering and variable selection. Finally, a designated driving service dataset is analyzed for customer segmentation using the proposed method.

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EVALUATION OF TRANSPLANT BENEFITS WITH THE U.S. SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS BY SEMIPARAMETRIC REGRESSION OF MEAN RESIDUAL LIFE

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Kidney transplantation is the most effective renal replacement therapy for end stage renal disease patients. With the severe shortage of kidney supplies and for the clinical effectiveness of transplantation, patient's life expectancy posttransplantation is used to prioritize patients for transplantation; however, severe comorbidity conditions and old age are the most dominant factors that negatively impact posttransplantation life expectancy, effectively precluding sick or old patients from receiving transplants. It would be crucial to design objective measures to quantify the transplantation benefit by comparing the mean residual life with and without a transplant, after adjusting for comorbidity and demographic conditions. To address this urgent need, we propose a new class of semiparametric covariate-dependent mean residual life models. Our method estimates covariate effects semiparametrically efficiently and the mean residual life function nonparametrically, enabling us to predict the residual life increment potential for any given patient. Our method potentially leads to a more fair system that prioritizes patients who would have the largest residual life gains. Our analysis of the kidney transplant data from the U.S. Scientific Registry of Transplant Recipients also suggests that a single index of covariates summarize well the impacts of multiple covariates, which may facilitate interpretations of each covariate's effect. Our subgroup analysis further disclosed inequalities in survival gains across groups defined by race, gender and insurance type (reflecting socioeconomic status).

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SITE OCCUPANCY AND ABUNDANCE MODELS FOR ANALYZING MULTIPLE-VISIT DETECTION/NONDETECTION DATA

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We propose an enhanced site occupancy model for analyzing ecological detection/nondetection data obtained from multiple visits. The model distinguishes between abundance, occupancy, and detection probabilities. We allow for transient individuals through a community parameter, c, that characterizes the proportion of individuals fixed across visits. This parameter seamlessly transitions from the standard occupancy model ($c = 0$) to the N-mixture model ($c = 1$), enabling a more accurate analysis of site occupancy data. Through theoretical developments and simulation studies, we demonstrate how this model effectively addresses biases inherent in conventional approaches, particularly for c is not at 0 or 1. We apply the model to various datasets of mammal and bird species and compare it to current approaches.

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JOINT MODELING OF MULTISTATE AND NONPARAMETRIC MULTIVARIATE LONGITUDINAL DATA

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It is oftentimes the case in studies of disease progression that subjects can move into one of several disease states of interest. Multistate models are an indispensable tool to analyze data from such studies. The Environmental Determinants of Diabetes in the Young (TEDDY) is an observational study of at-risk children from birth to onset of type-1 diabetes (T1D) up through the age of 15. A joint model for simultaneous inference of multistate and multivariate nonparametric longitudinal data is proposed to analyze data and answer the research questions brought up in the study. The proposed method allows us to make statistical inferences, test hypotheses, and make predictions about future state occupation in the TEDDY study. The performance of the proposed method is evaluated by simulation studies. The proposed method is applied to the motivating example to demonstrate the capabilities of the method.

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LATENT LEVEL CORRELATION MODELING OF MULTIVARIATE DISCRETE-VALUED FINANCIAL TIME SERIES

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In high-frequency financial data, dynamic patterns of transaction counts in regular time intervals provide crucial insights into market microstructure, such as short-term trading activities and intermittent intensities of price oscillation. In this paper we propose a Bayesian hierarchical framework that incorporates correlated latent level and temporal effects to model multivariate count data during intraday transaction intervals. Built on the INLA method for implementation, our framework proves to be competitive with the traditional MCMC approach in terms of model inference and computational cost. We demonstrate the efficacy of our methodology by applying it to assets from three Global Industry Classification Standard (GICS) sectors, namely, healthcare, energy, and industrials. The analysis uncovers various microstructures of financial count data using our framework. Specifically, our model featuring a correlated latent effect structure adeptly captures the pattern of the empirical correlations within the count data patterns with additional statistical inference, such as assessing different associations between short-term averaged trading size as well as trading duration, the counts at different risk levels, and uncovering differential levels of uncertainty resulted from market temporal behavior and unobservable latent effects across the three sectors. We also discuss some potential applications of our framework in real-world scenarios.

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A FORENSIC STATISTICAL ANALYSIS OF FRAUD IN THE FEDERAL FOOD STAMP PROGRAM

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This study develops methods to detect anomalous transactions linked with fraud in food stamp purchases through order statistics methods. The methods detect clusters in the order statistics of the transaction amounts that merit further scrutiny. Our techniques use scan statistics to determine when an excessive number of transactions occur (cluster), which is historically linked to fraud. A scoring paradigm is constructed that ranks the degree in which detected clusters and individual transactions are anomalous among approximately 250 million total transactions.

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BAYESIAN SPARSE VECTOR AUTOREGRESSIVE SWITCHING MODELS WITH APPLICATION TO HUMAN GESTURE PHASE SEGMENTATION

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We propose a sparse vector autoregressive (VAR) hidden semi-Markov model (HSMM) for modeling temporal and contemporaneous (e.g., spatial) dependencies in multivariate nonstationary time series. The HSMM's generic state distribution is embedded in a special transition matrix structure, facilitating efficient likelihood evaluations and arbitrary approximation accuracy. To promote sparsity of the VAR coefficients, we deploy an l_1-ball projection prior, which combines differentiability with a positive probability of obtaining exact zeros, achieving variable selection within each switching state. This also facilitate posterior estimation via HMC. We further place nonlocal priors on the parameters of the HSMM dwell distribution improving the ability of Bayesian model selection to distinguish whether the data is better supported by the simpler hidden Markov model (HMM) or more flexible HSMM. Our proposed methodology is illustrated via an application to human gesture phase segmentation based on sensor data, where we successfully identify and characterize the periods of rest and active gesturing as well as the dynamical patterns involved in the gesture movements associated with each of these states.

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MIXTURE CONDITIONAL REGRESSION WITH ULTRAHIGH DIMENSIONAL TEXT DATA FOR ESTIMATING EXTRALEGAL FACTOR EFFECTS

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Testing judicial impartiality is a problem of fundamental importance in empirical legal studies for which standard regression methods have been popularly used to estimate the extralegal factor effects. However, those methods cannot handle control variables with ultrahigh dimensionality, such as those found in judgment documents recorded in text format. To solve this problem, we develop a novel mixture conditional regression (MCR) approach, assuming that the whole sample can be classified into a number of latent classes. Within each latent class, a standard linear regression model can be used to model the relationship between the response and a key feature vector, which is assumed to be of a fixed dimension. Meanwhile, ultrahigh dimensional control variables are then used to determine the latent class membership, where a naïve Bayes type model is used to describe the relationship. Hence, the dimension of control variables is allowed to be arbitrarily high. A novel expectation-maximization algorithm is developed for model estimation. Therefore, we are able to estimate the key parameters of interest as efficiently as if the true class membership were known in advance. Simulation studies are presented to demonstrate the proposed MCR method. A real dataset of Chinese burglary offenses is analyzed for illustration purposes.

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A FLEXIBLE MODEL FOR CORRELATED COUNT DATA, WITH APPLICATION TO MULTICONDITION DIFFERENTIAL EXPRESSION ANALYSES OF SINGLE-CELL RNA SEQUENCING DATA

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Detecting differences in gene expression is an important part of single-cell RNA sequencing experiments, and many statistical methods have been developed for this aim. Most differential expression analyses focus on comparing expression between two groups (e.g., treatment vs. control). But there is increasing interest in *multicondition differential expression analyses* in which expression is measured in many conditions and the aim is to accurately detect and estimate expression differences in all conditions. We show that directly modeling single-cell RNA-seq counts in all conditions simultaneously, while also inferring how expression differences are shared across conditions, leads to greatly improved performance for detecting and estimating expression differences compared to existing methods. We illustrate the potential of this new approach by analyzing data from a single-cell experiment studying the effects of cytokine stimulation on gene expression. We call our new method "Poisson multivariate adaptive shrinkage," and it is implemented in an R package available at https://github.com/stephenslab/poisson.mash.alpha.

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WEIGHTED BIOMARKER VARIABILITY IN JOINT ANALYSIS OF LONGITUDINAL AND TIME-TO-EVENT DATA

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Motivated by the clinical evidence that the biomarker variability may have prognostic value for a related disease, we extend the standard joint model for longitudinal and time-to-event outcomes to incorporate the weighted cumulative effects of both biomarker level and variability on the survival hazard. A mixed-effects model is specified for biomarker observations wherein the subject-specific trajectories are modelled by spline functions with random coefficients. Borrowing ideas from smoothing splines, we propose a new variability measure which characterizes the roughness of the subject-specific biomarker trajectory by the integrated amount of its second derivatives over time. The inclusion of weight functions in cumulative quantities permits the importance of biomarker history to vary with time. To reduce computational complexity, we confine the weight functions to a particular parametric family with scale parameters to be estimated. Asymptotic properties of maximum likelihood estimators are established with a discussion on the identification issue of the scale parameters. We use EM algorithm in estimation with initial values obtained from a two-stage method. Simulation studies have been conducted under different settings. Finally, we apply our model to investigate the weighted cumulative effects of systolic blood pressure level and variability on cardiovascular events in the Medical Research Council trial.

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BIVARIATE FUNCTIONAL PATTERNS OF LIFETIME MEDICARE COSTS AMONG ESRD PATIENTS

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In this work we study the lifetime Medicare spending patterns of patients with end-stage renal disease (ESRD). We extract the information of patients who started their ESRD services in 2007–2011 from the United States Renal Data System (USRDS). Patients are partitioned into three groups based on their kidney transplant status: 1-unwaitlisted and never transplanted, 2-waitlisted but never transplanted, and 3-waitlisted and then transplanted. To study their Medicare cost trajectories, we use a semiparametric regression model with both fixed and bivariate time-varying coefficients to compare groups 1 and 2 as well as a bivariate time-varying coefficient model with different starting times (time since the first ESRD service and time since the kidney transplant) to compare groups 2 and 3. In addition to demographics and other medical conditions, these regression models are conditional on the survival time, which ideally depict the lifetime Medicare spending patterns. For estimation we extend the profile weighted least squares (PWLS) estimator to longitudinal data for the first comparison and propose a two-stage estimating method for the second comparison. We use sandwich variance estimators to construct confidence intervals and validate inference procedures through simulations. Our analysis of the Medicare claims data reveals that waitlisting is associated with a lower daily medical cost at the beginning of ESRD service among waitlisted patients, which gradually increases over time. Averaging over lifespan, however, there is no difference between waitlisted and unwaitlisted groups. A kidney transplant, on the other hand, reduces the medical cost significantly after an initial spike.

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ARE MADE AND MISSED DIFFERENT? AN ANALYSIS OF FIELD GOAL ATTEMPTS OF PROFESSIONAL BASKETBALL PLAYERS VIA DEPTH BASED TESTING PROCEDURE

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In this paper we develop a novel depth-based testing procedure on spatial point processes to examine the difference in made and missed field goal attempts for NBA players. Specifically, our testing procedure can statistically detect the differences between made and missed field goal attempts for NBA players. We first obtain the depths of two processes under the polar coordinate system. A two-dimensional Kolmogorov–Smirnov test is then performed to test the difference between the depths of the two processes. Throughout extensive simulation studies, we show our testing procedure with good frequentist properties under both null hypothesis and alternative hypothesis. A comparison against the competing methods shows that our proposed procedure has better testing reliability and testing power. Application to the shot chart data of 191 NBA players in the 2017–2018 regular season offers interesting insights about these players' made and missed shot patterns.

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PREDICTION INTERVALS FOR ECONOMIC FIXED-EVENT FORECASTS

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The fixed-event forecasting setup is common in economic policy. It involves a sequence of forecasts of the same ("fixed") predictand so that the difficulty of the forecasting problem decreases over time. Fixed-event point forecasts are typically published without a quantitative measure of uncertainty. To construct such a measure, we consider forecast postprocessing techniques tailored to the fixed-event case. We develop regression methods that impose constraints motivated by the problem at hand and use these methods to construct prediction intervals for gross domestic product (GDP) growth in Germany and the U.S.

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INTEGRATING MENDELIAN RANDOMIZATION WITH CAUSAL MEDIATION ANALYSES FOR CHARACTERIZING DIRECT AND INDIRECT EXPOSURE-TO-OUTCOME EFFECTS

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Mendelian randomization (MR) assesses the total effect of exposure on outcome. With the rapidly increasing availability of summary statistics from genome-wide association studies (GWASs), MR leverages existing summary statistics and is widely used to study the causal effects among complex traits and diseases. The total effect in the population is a sum of indirect and direct effects. For complex disease outcomes with complicated etiologies and/or for modifiable exposure traits, there may exist more than one pathway between exposure and outcome. The direct effect and the indirect effect via a mediator of interest could be in opposite directions, and the total effect estimates may not be informative for treatment and prevention decision-making or may even be misleading for different subgroups of patients. Causal mediation analysis delineates the indirect effect of exposure on outcome operating through the mediator and the direct effect transmitted through other mechanisms. However, causal mediation analysis often requires individual-level data measured on exposure, outcome, mediator and confounding variables, and the power of the mediation analysis is restricted by sample size. In this work, motivated by a study of the effects of atrial fibrillation (AF) on Alzheimer's dementia, we propose a framework for Integrative Mendelian randomization and Mediation Analysis (IMMA). The proposed method integrates the total effect estimates from MR analyses based on large-scale GWASs with the direct and indirect effect estimates from mediation analysis based on individual-level data of a limited sample size. We introduce a series of IMMA models under the scenarios with or without exposure-mediator interaction and/or study heterogeneity. The proposed IMMA models improve the estimation and the power of inference on the direct and indirect effects in the population. Our analyses showed a significant positive direct effect of AF on Alzheimer's dementia risk not through the use of the oral anticoagulant treatment and a significant indirect effect of AF-induced anticoagulant treatment in reducing Alzheimer's dementia risk. The results suggested potential Alzheimer's dementia risk prediction and prevention strategies for AF patients and paved the way for future reevaluation of anticoagulant treatment guidelines for AF patients. A sensitivity analysis was conducted to assess the sensitivity of the conclusions to a key assumption of the IMMA approach.

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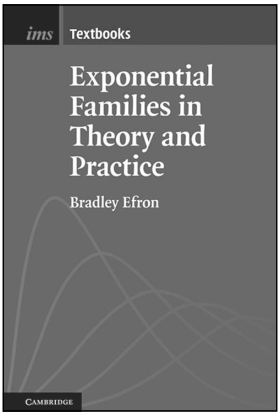

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