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HOSPITAL QUALITY RISK STANDARDIZATION VIA APPROXIMATE BALANCING WEIGHTS

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Comparing outcomes across hospitals, often to identify underperforming hospitals, is a critical task in health services research. However, naive comparisons of average outcomes, such as surgery complication rates, can be misleading because hospital case mixes differ—a hospital's overall complication rate may be lower simply because the hospital serves a healthier population overall. In this paper we develop a method of "direct standardization" where we reweight each hospital patient population to be representative of the overall population and then compare the weighted averages across hospitals. Adapting methods from survey sampling and causal inference, we find weights that directly control for imbalance between the hospital patient mix and the target population, even across many patient attributes. Critically, these balancing weights can also be tuned to preserve sample size for more precise estimates. We also derive principled measures of statistical uncertainty and use outcome modeling and Bayesian shrinkage to increase precision and account for variation in hospital size. We demonstrate these methods using claims data from Pennsylvania, Florida, and New York, estimating standardized hospital complication rates for general surgery patients. We conclude with a discussion of how to detect low performing hospitals.

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ESTIMATION OF GAUSSIAN DIRECTED ACYCLIC GRAPHS USING PARTIAL ORDERING INFORMATION WITH APPLICATIONS TO DREAM3 NETWORKS AND DAIRY CATTLE DATA

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Estimating a directed acyclic graph (DAG) from observational data represents a canonical learning problem and has generated a lot of interest in recent years. Research has focused mostly on the following two cases: when no information regarding the ordering of the nodes in the DAG is available and when a domain-specific complete ordering of the nodes is available. In this paper, motivated by a recent application in dairy science, we develop a method for DAG estimation for the middle scenario, where partition-based partial ordering of the nodes is known based on domain-specific knowledge. We develop an efficient algorithm that solves the posited problem, coined Partition-DAG. Through extensive simulations, using the DREAM3 Yeast networks, we illustrate that Partition-DAG effectively incorporates the partial ordering information to improve both speed and accuracy. We then illustrate the usefulness of Partition-DAG by applying it to recently collected dairy cattle data, and inferring relationships between various variables involved in dairy agroecosystems.

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ROBUST SENSIBLE ADVERSARIAL LEARNING OF DEEP NEURAL NETWORKS FOR IMAGE CLASSIFICATION

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The idea of robustness is central and critical to modern statistical analysis. However, despite the recent advances of deep neural networks (DNNs), many studies have shown that DNNs are vulnerable to adversarial attacks. Making imperceptible changes to an image can cause DNN models to make the wrong classification with high confidence, such as classifying a benign mole as a malignant tumor and a stop sign as a speed limit sign. The tradeoff between robustness and standard accuracy is common for DNN models. In this paper we introduce sensible adversarial learning and demonstrate the synergistic effect between pursuits of standard natural accuracy and robustness. Specifically, we define a sensible adversary, which is useful for learning a robust model, while keeping high natural accuracy. We theoretically establish that the Bayes classifier is the most robust multiclass classifier with the $0-1$ loss under sensible adversarial learning. We propose a novel and efficient algorithm that trains a robust model using implicit loss truncation. We apply sensible adversarial learning for large-scale image classification to a handwritten digital image dataset, called MNIST, and an object recognition colored image dataset, called CIFAR10. We have performed an extensive comparative study to compare our method with other competitive methods. Our experiments empirically demonstrate that our method is not sensitive to its hyperparameter and does not collapse even with a small model capacity while promoting robustness against various attacks and keeping high natural accuracy. The sensible adversarial learning software is available as a Python package at https://github.com/JungeumKim/SENSE.

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ESTIMATING THE EFFECTS OF A CALIFORNIA GUN CONTROL PROGRAM WITH MULTITASK GAUSSIAN PROCESSES

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Gun violence is a critical public safety concern in the United States. In 2006, California implemented a unique firearm monitoring program, the Armed and Prohibited Persons System (APPS), to address gun violence in the state. The APPS program first identifies those firearm owners who become prohibited from owning one, due to federal or state law, then confiscates their firearms. Our goal is to assess the effect of APPS on California murder rates using annual, state-level crime data across the U.S. for the years before and after the introduction of the program. To do so, we adapt a nonparametric Bayesian approach, multitask Gaussian processes (MTGPs), to the panel data setting. MTGPs allow for flexible and parsimonious panel data models that nest many existing approaches and allow for direct control over both dependence across time and dependence across units as well as natural uncertainty quantification. We extend this approach to incorporate non-Normal outcomes, auxiliary covariates, and multiple outcome series, which are all important in our application. We also show that this approach has attractive Frequentist properties, including a representation as a weighting estimator with separate weights over units and time periods. Applying this approach, we find that the increased monitoring and enforcement from the APPS program substantially decreased homicides in California. We also find that the effect on murder is driven entirely by declines in gun-related murder with no measurable effect on non-gun murder. Estimated cost per murder avoided are substantially lower than conventional estimates of the value of a statistical life, suggesting a very high benefit-cost ratio for this enforcement effort.

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ROBUST JOINT MODELLING OF LEFT-CENSORED LONGITUDINAL DATA AND SURVIVAL DATA WITH APPLICATION TO HIV VACCINE STUDIES

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In jointly modelling longitudinal and survival data, the longitudinal data may be complex in the sense that they may contain outliers and may be left censored. Motivated from an HIV vaccine study, we propose a robust method for joint models of longitudinal and survival data, where the outliers in longitudinal data are addressed using a multivariate t-distribution for b-outliers and using an M-estimator for e-outliers. We also propose a computationally efficient method for approximate likelihood inference. The proposed method is evaluated by simulation studies. Based on the proposed models and method, we analyze the HIV vaccine data and find a strong association between longitudinal biomarkers and the risk of HIV infection.

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BAYESIAN DECISION THEORY FOR TREE-BASED ADAPTIVE SCREENING TESTS WITH AN APPLICATION TO YOUTH DELINQUENCY

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Crime prevention strategies based on early intervention depend on accurate risk assessment instruments for identifying high-risk youth. It is important in this context that the instruments be convenient to administer, which means, in particular, that they should also be reasonably brief; adaptive screening tests are useful for this purpose. Adaptive tests constructed using classification and regression trees are becoming a popular alternative to traditional item response theory (IRT) approaches for adaptive testing. However, tree-based adaptive tests lack a principled criterion for terminating the test. This paper develops a Bayesian decision theory framework for measuring the trade-off between brevity and accuracy when considering tree-based adaptive screening tests of different lengths. We also present a novel method for designing tree-based adaptive tests, motivated by this framework. The framework and associated adaptive test method are demonstrated through an application to youth delinquency risk assessment in Honduras; it is shown that an adaptive test requiring a subject to answer fewer than 10 questions can identify high-risk youth nearly as accurately as an unabridged survey containing 173 items.

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BAYESIAN COX REGRESSION FOR LARGE-SCALE INFERENCE WITH APPLICATIONS TO ELECTRONIC HEALTH RECORDS

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The Cox model is an indispensable tool for time-to-event analysis, particularly in biomedical research. However, medicine is undergoing a profound transformation, generating data at an unprecedented scale, which opens new frontiers to study and understand diseases. With the wealth of data collected, new challenges for statistical inference arise, as datasets are often high dimensional, exhibit an increasing number of measurements at irregularly spaced time points, and are simply too large to fit in memory. Many current implementations for time-to-event analysis are ill-suited for these problems, as inference is computationally demanding and requires access to the full data at once. Here, we propose a Bayesian version for the counting process representation of Cox's partial likelihood for efficient inference on large-scale datasets with millions of data points and thousands of time-dependent covariates. Through the combination of stochastic variational inference and a reweighting of the log-likelihood, we obtain an approximation for the posterior distribution that factorizes over subsamples of the data, enabling the analysis in big data settings. Crucially, the method produces viable uncertainty estimates for large-scale and high-dimensional datasets. We show the utility of our method through a simulation study and an application to myocardial infarction in the UK Biobank, where we characterize the multivariate effects of risk factors and replicate results from individual studies. Our framework extends the Cox model to new data sources, like biobanks and EHR, the combination of which can provide new insights into our understanding of diseases.

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CYTOPT: OPTIMAL TRANSPORT WITH DOMAIN ADAPTATION FOR INTERPRETING FLOW CYTOMETRY DATA

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The automated analysis of flow cytometry measurements is an active research field. We introduce a new algorithm, referred to as `CytOpT`, using regularized optimal transport to directly estimate the different cell population proportions from a biological sample characterized with flow cytometry measurements. We rely on the regularized Wasserstein metric to compare cytometry measurements from different samples, thus accounting for possible misalignment of a given cell population across samples (due to technical variability from the technology of measurements). In this work we rely on a supervised learning technique, based on the Wasserstein metric, that is used to estimate an optimal reweighting of class proportions in a mixture model from a source distribution (with known segmentation into cell sub-populations) to fit a target distribution with unknown segmentation. Due to the high dimensionality of flow cytometry data, we use stochastic algorithms to approximate the regularized Wasserstein metric to solve the optimization problem involved in the estimation of optimal weights representing the cell population proportions in the target distribution. Several flow cytometry data sets are used to illustrate the performances of `CytOpT` that are also compared to those of existing algorithms for automatic gating based on supervised learning.

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A TENSOR DECOMPOSITION MODEL FOR LONGITUDINAL MICROBIOME STUDIES

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Longitudinal microbiome studies can help delineate true biological signals from the high interindividual variability that is common in microbiome data. However, there are few methods available for unsupervised dimension reduction of time course microbial abundance observations. Existing methods do not fully observe the distribution characteristics of such data types, namely, zero inflation, compositionality, and overdispersion. We present a tensor decomposition model and a semiparametric quasi-likelihood estimation method for the decomposition of longitudinal microbiome data by generalizing existing approaches in tensor decomposition of Gaussian data. Optimization is performed through projected gradient descent, additionally allowing interpretability constraints. We show through simulation studies that our method is able to recover low-rank structures from microbiome time-course data better than existing approaches. Lastly, we apply our method to two existing longitudinal microbiome studies to detect global microbial changes associated with dietary and pharmaceutical effects as well as infant birth modes.

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A ROTATION-BASED FEATURE AND BAYESIAN HIERARCHICAL MODEL FOR THE FORENSIC EVALUATION OF HANDWRITING EVIDENCE IN A CLOSED SET

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Forensic handwriting examiners are often tasked with identifying the writer of a particular document. Examples of handwriting evidence include ransom notes, forged documents and signatures, and threatening letters. At present, examiners rely on visual inspection of similarities and differences between the questioned document and reference writing samples. Here, we propose a principled modeling approach to compute the posterior predictive probability of writership when the author of the questioned document is part of a closed set of writers. Given a handwritten document, we extract measurements, including rotation angles that are related to the slant of writing, which are the response variables in a multilevel model. We fit the model and test its posterior predictive performance using writing samples from the United States and from Europe. We find that, as long as the questioned document is longer than a sentence or two, it is possible to correctly associate a writer with a document that he or she wrote with high probability. Earlier versions of this work have been well received by the community of forensic document examiners.

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KNOCKOFFS WITH SIDE INFORMATION

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We consider the problem of assessing the importance of multiple variables or factors from a dataset when side information is available. In principle, using side information can allow the statistician to pay attention to variables with a greater potential which, in turn, may lead to more discoveries. We introduce an adaptive knockoff filter, which generalizes the knockoff procedure (*Ann. Statist.* **43** (2015) 2055–2085; *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **80** (2018) 551–577), in that it uses both the data at hand and side information to adaptively order the variables under study and focus on those that are most promising. The *adaptive knockoffs* procedure controls the finite-sample false discovery rate (FDR), and we demonstrate its power by comparing it with other structured multiple testing methods. We also apply our methodology to real genetic data in order to find associations between genetic variants and various phenotypes such as Crohn's disease and lipid levels. Here, the adaptive knockoffs method makes more discoveries than reported in previous studies on the same datasets.

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LATENT MULTIVARIATE LOG-GAMMA MODELS FOR HIGH-DIMENSIONAL MULTITYPE RESPONSES WITH APPLICATION TO DAILY FINE PARTICULATE MATTER AND MORTALITY COUNTS

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Precise estimation of daily fine particulate matter with a diameter ≤ 2.5 microns (PM2.5) and mortality in the U.S. is an important research challenge in public health because high levels of PM2.5 have been linked to several serious health problems, including lung disease, cardiovascular disease, and stroke. This motivates us to develop a joint Bayesian hierarchical model for bivariate spatial data to obtain precise spatial predictions of two types of responses, continuous skewed PM2.5 levels, and discrete mortality counts over U.S. counties. Our novel modeling framework address several challenges in the area of spatial prediction of mortality counts and PM2.5 levels. Specifically, our model allows for spatial variability and dependence of two types of responses, accommodate an unknown nonlinear spatial relationship between mortality and PM2.5 through basis function expansions, improve the precision of predictions at counties with undisclosed/missing observations, and allow for different missing data patterns for mortality and PM2.5. Furthermore, we introduce a new local measure of association for the cross-dependence between mortality and PM2.5 level. To address the burden of Bayesian computation for large databases, we use the dimension reduction tool and the shared conjugate structure between the Weibull distribution, Poisson distribution, and the multivariate log-gamma distribution. We provide a simulation study to illustrate the performance of our method. Our joint spatial model of "multitype responses" (discrete and continuous responses) and associated Bayesian method are used to analyze bivariate spatial data of daily averaged PM2.5 levels in air and mortality counts (due to diseases related to lung, cardiovascular, respiratory, and stroke) from the Centers for Disease Control and Prevention (CDC) database.

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IDENTIFICATION OF IMMUNE RESPONSE COMBINATIONS ASSOCIATED WITH HETEROGENEOUS INFECTION RISK IN THE IMMUNE CORRELATES ANALYSIS OF HIV VACCINE STUDIES

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In HIV vaccine/prevention research, probing into the vaccine-induced immune responses that can help to predict the risk of HIV infection provides valuable information for the development of vaccine regimens. Previous correlate analysis of the Thai vaccine trial aided the discovery of interesting immune correlates related to the risk of developing an HIV infection. The present study aimed to identify the combinations of immune responses associated with the heterogeneous infection risk. We explored a "change-plane" via combination of a subset of immune responses that could help separate vaccine recipients into two heterogeneous subgroups in terms of the association between immune responses and the risk of developing infection. Additionally, we developed a new variable selection algorithm through a penalized likelihood approach to investigate a parsimonious marker combination for the change-plane. The resulting marker combinations can serve as candidate correlates of protection and can be used for predicting the protective effect of the vaccine against HIV infection. The application of the proposed statistical approach to the Thai trial has been presented, wherein the marker combinations were explored among several immune responses and antigens.

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BAYESIAN ANALYSIS FOR IMBALANCED POSITIVE-UNLABELLED DIAGNOSIS CODES IN ELECTRONIC HEALTH RECORDS

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With the increasing availability of electronic health records (EHR), significant progress has been made on developing predictive inference and algorithms by health-data analysts and researchers. However, the EHR data are notoriously noisy, due to missing and inaccurate inputs, despite abundant information. One serious problem is that only a small portion of patients in the database has confirmatory diagnoses, while many other patients remain undiagnosed because they did not comply with the recommended examinations. The phenomenon leads to a so-called positive-unlabelled situation, and the labels are extremely imbalanced. In this paper we propose a model-based approach to classify the unlabelled patients by using a Bayesian finite mixture model. We also discuss the label switching issue for the imbalanced data and propose a consensus Monte Carlo approach to address the imbalance issue and improve computational efficiency simultaneously. Simulation studies show that our proposed model-based approach outperforms existing positive-unlabelled learning algorithms. The proposed method is applied on the Cerner EHR for detecting diabetic retinopathy (DR) patients using laboratory measurements. With only 3% confirmatory diagnoses in the EHR database, we estimate the actual DR prevalence to be 25% which coincides with reported findings in the medical literature.

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SURROGATE MARKER ASSESSMENT USING MEDIATION AND INSTRUMENTAL VARIABLE ANALYSES IN A CASE-COHORT DESIGN

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The identification of surrogate markers for gold standard outcomes in clinical trials enables future cost-effective trials that target the identified markers. Due to resource limitations, these surrogate markers may be collected only for cases and for a subset of the trial cohort, giving rise to what is termed the case-cohort design. Motivated by a COVID-19 vaccine trial, we propose methods of assessing the surrogate markers for a time-to-event outcome in a case-cohort design by using mediation and instrumental variable (IV) analyses. In the mediation analysis we decomposed the vaccine effect on COVID-19 risk into an indirect effect (the effect mediated through the surrogate marker such as neutralizing antibodies) and a direct effect (the effect not mediated by the marker), and we propose that the mediation proportions are surrogacy indices. In the IV analysis we aimed to quantify the causal effect of the surrogate marker on disease risk in the presence of surrogate-disease confounding which is unavoidable even in randomized trials. We employed weighted estimating equations derived from nonparametric maximum likelihood estimators (NPMLEs) under semiparametric probit models for the time-to-disease outcome. We plugged in the weighted NPMLEs to construct estimators for the aforementioned causal effects and surrogacy indices, and we determined the asymptotic properties of the proposed estimators. Finite sample performance was evaluated in numerical simulations. Applying the proposed mediation and IV analyses to a mock COVID-19 vaccine trial data, we found that 84.2% of the vaccine efficacy was mediated by 50% pseudovirus neutralizing antibody and that neutralizing antibodies had significant protective effects for COVID-19 risk.

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DETECTING DISTRIBUTIONAL DIFFERENCES IN LABELED SEQUENCE DATA WITH APPLICATION TO TROPICAL CYCLONE SATELLITE IMAGERY

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Our goal is to quantify whether, and if so how, spatiotemporal patterns in tropical cyclone (TC) satellite imagery signal an upcoming rapid intensity change event. To address this question, we propose a new nonparametric test of association between a time series of images and a series of binary event labels. We ask whether there is a difference in distribution between (dependent but identically distributed) 24-hour sequences of images preceding an event vs. a nonevent. By rewriting the statistical test as a regression problem, we leverage neural networks to infer modes of structural evolution of TC convection that are representative of the lead-up to rapid intensity change events. Dependencies between nearby sequences are handled by a bootstrap procedure that estimates the marginal distribution of the label series. We prove that type I error control is guaranteed as long as the distribution of the label series is well estimated which is made easier by the extensive historical data for binary TC event labels. We show empirical evidence that our proposed method identifies archetypes of infrared imagery associated with elevated rapid intensification risk, typically marked by deep or deepening core convection over time. Such results provide a foundation for improved forecasts of rapid intensification.

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A BAYESIAN ACCELERATED FAILURE TIME MODEL FOR INTERVAL CENSORED THREE-STATE SCREENING OUTCOMES

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Women infected by the human papillomavirus are at an increased risk to develop cervical intraepithelial neoplasia lesions (CIN). CIN are classified into three grades of increasing severity (CIN-1, CIN-2, and CIN-3) and can eventually develop into cervical cancer. The main purpose of screening is detecting CIN-2 and CIN-3 cases which are usually removed surgically. Screening data from the POBASCAM trial involving 1454 HPV-positive women are analyzed with two objectives, estimate: (a) the transition time from HPV diagnosis to CIN-3 and (b) the transition time from CIN-2 to CIN-3. The screening data have two key characteristics. First, the CIN state is monitored in an interval censored sequence of screening times. Second, a woman's progression to CIN-3 is only observed if the woman progresses to, both, CIN-2 and from CIN-2 to CIN-3 in the same screening interval. We propose a Bayesian accelerated failure time model for the two transition times in this three-state model. To deal with the unusual censoring structure of the screening data, we develop a Metropolis-within-Gibbs algorithm with data augmentation from the truncated transition time distributions.

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LOCUS: A REGULARIZED BLIND SOURCE SEPARATION METHOD WITH LOW-RANK STRUCTURE FOR INVESTIGATING BRAIN CONNECTIVITY

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Network-oriented research has been increasingly popular in many scientific areas. In neuroscience research, imaging-based network connectivity measures have become the key for understanding brain organizations, potentially serving as individual neural fingerprints. There are major challenges in analyzing connectivity matrices, including the high dimensionality of brain networks, unknown latent sources underlying the observed connectivity, and the large number of brain connections leading to spurious findings. In this paper we propose a novel blind source separation method with low-rank structure and uniform sparsity (LOCUS) as a fully data-driven decomposition method for network measures. Compared with the existing method that vectorizes connectivity matrices ignoring brain network topology, LOCUS achieves more efficient and accurate source separation for connectivity matrices using low-rank structure. We propose a novel angle-based uniform sparsity regularization that demonstrates better performance than the existing sparsity controls for low-rank tensor methods. We propose a highly efficient iterative node-rotation algorithm that exploits the block multiconvexity of the objective function to solve the nonconvex optimization problem for learning LOCUS. We illustrate the advantage of LOCUS through extensive simulation studies. Application of LOCUS to Philadelphia Neurodevelopmental Cohort neuroimaging study reveals biologically insightful connectivity traits which are not found using the existing method.

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SIMULATING FLOOD EVENT SETS USING EXTREMAL PRINCIPAL COMPONENTS

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Hazard event sets, a collection of synthetic extreme events over a given period, are important for catastrophe modelling. This paper addresses the issue of generating event sets of extreme river flow for northern England and southern Scotland, a region which has been particularly affected by severe flooding over the past 20 years. We start by analysing historical extreme river flow across 45 gauges, using methods from extreme value analysis, including the concept of extremal principal components. Our analysis reveals interesting connections between the extremal dependence structure and the region's topography/climate. We then introduce a framework which is based on modelling the distribution of the extremal principal components in order to generate synthetic events of extreme river flow. The generative framework is dimension-reducing in that it distinctly handles the principal components based on their contribution to describing the nature of extreme river flow across the study region. We also detail a data-driven approach to select the optimal dimension. Synthetic flood events are subsequently generated efficiently by sampling from the fitted distribution. Our results indicate good agreement between the observed and simulated extreme river flow dynamics and, therefore, illustrate the usefulness of our approach to practitioners. For the considered application, we also find that our approach outperforms existing statistical approaches for generating hazard event sets.

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ESTIMATING GLOBAL AND COUNTRY-SPECIFIC EXCESS MORTALITY DURING THE COVID-19 PANDEMIC

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Estimating the true mortality burden of COVID-19 for every country in the world is a difficult, but crucial, public health endeavor. Attributing deaths, direct or indirect, to COVID-19 is problematic. A more attainable target is the "excess deaths," the number of deaths in a particular period, relative to that expected during "normal times," and we develop a model for this endeavor. The excess mortality requires two numbers, the total deaths and the expected deaths, but the former is unavailable for many countries, and so modeling is required for such countries. The expected deaths are based on historic data, and we develop a model for producing estimates of these deaths for all countries. We allow for uncertainty in the modeled expected numbers when calculating the excess. The methods we describe were used to produce the World Health Organization (WHO) excess death estimates. To achieve both interpretability and transparency we developed a relatively simple overdispersed Poisson count framework within which the various data types can be modeled. We use data from countries with national monthly data to build a predictive log-linear regression model with time-varying coefficients for countries without data. For a number of countries, subnational data only are available, and we construct a multinomial model for such data, based on the assumption that the fractions of deaths in subregions remain approximately constant over time. Our inferential approach is Bayesian, with the covariate predictive model being implemented in the fast and accurate `INLA` software. The subnational modeling was carried out using MCMC in `Stan`. Based on our modeling, the point estimate for global excess mortality during 2020–2021 is 14.8 million, with a 95% credible interval of (13.2, 16.6) million.

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DYNAMIC RISK PREDICTION TRIGGERED BY INTERMEDIATE EVENTS USING SURVIVAL TREE ENSEMBLES

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With the availability of massive amounts of data from electronic health records and registry databases, incorporating time-varying patient information to improve risk prediction has attracted great attention. To exploit the growing amount of predictor information over time, we develop a unified framework for landmark prediction, using survival tree ensembles, where an updated prediction can be performed when new information becomes available. Compared to conventional landmark prediction with fixed landmark times, our methods allow the landmark times to be subject-specific and triggered by an intermediate clinical event. Moreover, the nonparametric approach circumvents the thorny issue of model incompatibility at different landmark times. In our framework, both the longitudinal predictors and the event time outcome are subject to right censoring, and thus existing tree-based approaches cannot be directly applied. To tackle the analytical challenges, we propose a risk-set-based ensemble procedure by averaging martingale estimating equations from individual trees. Extensive simulation studies are conducted to evaluate the performance of our methods. The methods are applied to the Cystic Fibrosis Foundation Patient Registry (CFFPR) data to perform dynamic prediction of lung disease in cystic fibrosis patients and to identify important prognosis factors.

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MIXED-FREQUENCY EXTREME VALUE REGRESSION: ESTIMATING THE EFFECT OF MESOSCALE CONVECTIVE SYSTEMS ON EXTREME RAINFALL INTENSITY

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Understanding and modeling the determinants of extreme hourly rainfall intensity is of utmost importance for the management of flash-flood risk. Increasing evidence shows that mesoscale convective systems (MCS) are the principal driver of extreme rainfall intensity in the United States. We use extreme value statistics to investigate the relationship between MCS activity and extreme hourly rainfall intensity in Greater St. Louis, an area particularly vulnerable to flash floods. Using a block maxima approach with monthly blocks, we find that the impact of MCS activity on monthly maxima is not homogeneous within the month/block. To appropriately capture this relationship, we develop a mixed-frequency extreme value regression framework accommodating a covariate sampled at a frequency higher than that of the extreme observation.

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LAGGED COUPLINGS DIAGNOSE MARKOV CHAIN MONTE CARLO PHYLOGENETIC INFERENCE

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Phylogenetic inference is an intractable statistical problem on a complex space. Markov chain Monte Carlo methods are the primary tool for Bayesian phylogenetic inference, but it is challenging to construct efficient schemes to explore the associated posterior distribution or assess their performance. Existing approaches are unable to diagnose mixing or convergence of Markov schemes jointly across all components of a phylogenetic model. Lagged couplings of Markov chain Monte Carlo algorithms have recently been developed on simpler spaces to diagnose convergence and construct unbiased estimators. We describe a contractive coupling of Markov chains targeting a posterior distribution over a space of phylogenetic trees with branch lengths, scalar parameters and latent variables. We use these couplings to assess mixing and convergence of Markov chains jointly across all components of the phylogenetic model on trees with up to 200 leaves. Samples from our coupled chains may also be used to construct unbiased estimators.

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CO-CLUSTERING OF SPATIALLY RESOLVED TRANSCRIPTOMIC DATA

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Spatial transcriptomics is a groundbreaking technology that allows the measurement of the activity of thousands of genes in a tissue sample and maps where the activity occurs. This technology has enabled the study of the spatial variation of the genes across the tissue. Comprehending gene functions and interactions in different areas of the tissue is of great scientific interest, as it might lead to a deeper understanding of several key biological mechanisms, such as cell-cell communication or tumor-microenvironment interaction. To do so, one can group cells of the same type and genes that exhibit similar expression patterns. However, adequate statistical tools that exploit the previously unavailable spatial information to more coherently group cells and genes are still lacking.

In this work we introduce SPARTACO, a new statistical model that clusters the spatial expression profiles of the genes according to a partition of the tissue. This is accomplished by performing a co-clustering, that is, inferring the latent block structure of the data and inducing two types of clustering: of the genes, using their expression across the tissue, and of the image areas, using the gene expression in the *spots* where the RNA is collected. Our proposed methodology is validated with a series of simulation experiments, and its usefulness in responding to specific biological questions is illustrated with an application to a human brain tissue sample processed with the 10X-Visium protocol.

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BALANCING WEIGHTS FOR REGION-LEVEL ANALYSIS: THE EFFECT OF MEDICAID EXPANSION ON THE UNINSURANCE RATE AMONG STATES THAT DID NOT EXPAND MEDICAID

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We predict the average effect of Medicaid expansion on the nonelderly adult uninsurance rate among states that did not expand Medicaid in 2014, as if they had expanded their Medicaid eligibility requirements. Using American Community Survey data aggregated to the region level, we estimate this effect by reweighting the expansion regions to approximately match the covariate distribution of the nonexpansion regions. Existing methods to estimate balancing weights often assume that the covariates are measured without error and do not account for dependencies in the outcome model. Our covariates have random noise that is uncorrelated with the outcome errors, and our assumed outcome model contains state-level random effects. To correct for measurement error induced bias, we propose generating weights on a linear approximation to the true covariates, extending an idea from the measurement error literature known as "regression calibration." This requires auxiliary data to estimate the measurement error variability. We also propose an objective function to reduce the variance of our estimator when the outcome model errors are homoskedastic and equicorrelated within states. We then estimate that Medicaid expansion would have caused a -2.33 (-3.54, -1.11) percentage point change in the adult uninsurance rate among states that did not expand Medicaid.

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SPATIOTEMPORAL LOCAL INTERPOLATION OF GLOBAL OCEAN HEAT TRANSPORT USING ARGO FLOATS: A DEBIASED LATENT GAUSSIAN PROCESS APPROACH

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The world ocean plays a key role in redistributing heat in the climate system and hence in regulating Earth's climate. Yet statistical analysis of ocean heat transport suffers from partially incomplete large-scale data intertwined with complex spatiotemporal dynamics as well as from potential model misspecification. We present a comprehensive spatiotemporal statistical framework tailored to interpolating the global ocean heat transport using in situ Argo profiling float measurements. We formalize the statistical challenges using latent local Gaussian process regression accompanied by a two-stage fitting procedure. We introduce an approximate expectation-maximization algorithm to jointly estimate both the mean field and the covariance parameters, and refine the potentially underspecified mean field model with a debiasing procedure. This approach provides data-driven global ocean heat transport fields that vary in both space and time and can provide insights into crucial dynamical phenomena, such as El Niño & La Niña, as well as the global climatological mean heat transport field which by itself is of scientific interest. The proposed framework and the Argo-based estimates are thoroughly validated with state-of-the-art multimission satellite products and shown to yield realistic subsurface ocean heat transport estimates.

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LATENT VARIABLE MODELS FOR MULTIVARIATE DYADIC DATA WITH ZERO INFLATION: ANALYSIS OF INTERGENERATIONAL EXCHANGES OF FAMILY SUPPORT

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Understanding the help and support that is exchanged between family members of different generations is of increasing importance, with research questions in sociology and social policy focusing on both predictors of the levels of help given and received, and on reciprocity between them. We propose general latent variable models for analysing such data, when helping tendencies in each direction are measured by multiple binary indicators of specific types of help. The model combines two continuous latent variables, which represent the helping tendencies, with two binary latent class variables which allow for high proportions of responses where no help of any kind is given or received. This defines a multivariate version of a zero-inflation model. The main part of the models is estimated using MCMC methods, with a bespoke data augmentation algorithm. We apply the models to analyse exchanges of help between adult individuals and their noncoresident parents, using survey data from the UK Household Longitudinal Study.

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A BAYESIAN PANEL VECTOR AUTOREGRESSION TO ANALYZE THE IMPACT OF CLIMATE SHOCKS ON HIGH-INCOME ECONOMIES

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In this paper we assess the impact of climate shocks on futures markets for agricultural commodities and a set of macroeconomic quantities for multiple high-income economies. To capture relations among countries, markets, and climate shocks, this paper proposes parsimonious methods to estimate high-dimensional panel vector autoregressions. We assume that coefficients associated with domestic lagged endogenous variables arise from a Gaussian mixture model while further parsimony is achieved using suitable global-local shrinkage priors on several regions of the parameter space. Our results point toward pronounced global reactions of key macroeconomic quantities to climate shocks. Moreover, the empirical findings highlight substantial linkages between regionally located shocks and global commodity markets.

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ESTIMATION AND INFERENCE FOR EXPOSURE EFFECTS WITH LATENCY IN THE COX PROPORTIONAL HAZARDS MODEL IN THE PRESENCE OF EXPOSURE MEASUREMENT ERROR

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Researchers are often interested in estimating the effects of time-varying exposures on health outcomes. The latency period, defined as the critical period of susceptibility, can be an important component of exposure effect assessment. Although it is widely known that many environmental, nutritional, and other exposure measurements are prone to error and are also likely to act only during a critical time window of susceptibility, no one has yet considered the impact of this on the estimation of latency parameters in survival models. In this paper we derived methods for point and interval estimation for the latency parameter and the regression coefficients in rare disease situations. Under a linear measurement model, although the estimated hazard ratios are biased, as has been previously demonstrated, we show that the latency parameter is approximately unbiased. Simulations and an illustrative example investigating the prospective association between $PM_{2.5}$ and lung cancer incidence in the Nurses' Health Study are included to evaluate the performance of our method.

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RANDOMIZATION INFERENCE FOR CLUSTER-RANDOMIZED TEST-NEGATIVE DESIGNS WITH APPLICATION TO DENGUE STUDIES: UNBIASED ESTIMATION, PARTIAL COMPLIANCE, AND STEPPED-WEDGE DESIGN

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In 2019, the World Health Organization identified dengue as one of the top 10 global health threats. For the control of dengue, the Applying *Wolbachia* to Eliminate Dengue (AWED) study group conducted a cluster-randomized trial in Yogyakarta, Indonesia, and used a novel design, called the cluster-randomized test-negative design (CR-TND). This design can yield valid statistical inference with data collected by a passive surveillance system and thus has the advantage of cost-efficiency compared to traditional cluster-randomized trials. We investigate the statistical assumptions and properties of CR-TND under a randomization inference framework, which is known to be robust for small-sample problems. We find that, when the differential healthcare-seeking behavior comparing intervention and control varies across clusters (in contrast to the setting of Dufault and Jewell (*Stat. Med.* **39** (2020a) 1429–1439) where the differential healthcare-seeking behavior is constant across clusters), current analysis methods for CR-TND can be biased and have inflated type I error. We propose the log-contrast estimator that can eliminate such bias and improve precision by adjusting for covariates. Furthermore, we extend our methods to handle partial intervention compliance and a stepped-wedge design, both of which appear frequently in cluster-randomized trials. Finally, we demonstrate our results by simulation studies and reanalysis of the AWED study.

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VARIATIONAL BAYESIAN ANALYSIS OF NONHOMOGENEOUS HIDDEN MARKOV MODELS WITH LONG AND ULTRALONG SEQUENCES

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Nonhomogeneous hidden Markov models (NHMMs) are useful in modeling sequential and autocorrelated data. Bayesian approaches, particularly Markov chain Monte Carlo (MCMC) methods, are principal statistical inference tools for NHMMs. However, MCMC sampling is computationally demanding, especially for long observation sequences. We develop a variational Bayes (VB) method for NHMMs, which utilizes a structured variational family of Gaussian distributions with factorized covariance matrices to approximate target posteriors, combining a forward-backward algorithm and stochastic gradient ascent in estimation. To improve efficiency and handle ultralong sequences, we further propose a subsequence VB (SVB) method that works on subsamples. The SVB method exploits the memory decay property of NHMMs and uses buffers to control for bias caused by breaking sequential dependence from subsampling. We highlight that the local nonhomogeneity of NHMMs substantially affects the required buffer lengths and propose the use of local Lyapunov exponents that characterize local memory decay rates of NHMMs and adaptively determine buffer lengths. Our methods are validated in simulation studies and in modeling ultralong sequences of customers' telecom records to uncover the relationship between their mobile Internet usage behaviors and conventional telecommunication behaviors.

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HOW CLOSE AND HOW MUCH? LINKING HEALTH OUTCOMES TO BUILT ENVIRONMENT SPATIAL DISTRIBUTIONS

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Built environment features (BEFs) refer to aspects of the human constructed environment which may, in turn, support or restrict health related behaviors and thus impact health. In this paper we are interested in understanding whether the spatial distribution and quantity of fast-food restaurants (FFRs) influence the risk of obesity in schoolchildren. To achieve this goal, we propose a two-stage Bayesian hierarchical modeling framework. In the first stage, examining the position of FFRs relative to that of some reference locations—in our case, schools—we model the distances of FFRs from these reference locations as realizations of inhomogenous Poisson processes (IPP). With the goal of identifying representative spatial patterns of exposure to FFRs, we model the intensity functions of the IPPs using a Bayesian nonparametric model, specifying a nested Dirichlet process prior. The second-stage model relates exposure patterns to obesity. We offer two different approaches to carry out the second stage; they differ in how they accommodate uncertainty in the exposure patterns. In the first approach, the odds of obesity at the school level is regressed on cluster indicators, each representing a major pattern of exposure to FFRs. In the second, we employ Bayesian kernel machine regression to relate the odds of obesity to the multivariate vector reporting the degree of similarity of a given school to all other schools. Our analysis on the influence of patterns of FFR occurrence on obesity among Californian schoolchildren has indicated that, in 2010, among schools that are consistently assigned to a cluster, there is a lower odds of obesity among ninth graders who attend schools with most distant FFR occurrences in a one-mile radius, as compared to others.

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TRUNCATED RANK-BASED TESTS FOR TWO-PART MODELS WITH EXCESSIVE ZEROS AND APPLICATIONS TO MICROBIOME DATA

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High-throughput sequencing technology allows us to test the compositional difference of bacteria in different populations. One important feature of human microbiome data is that it often includes a large number of zeros. Such data can be treated as being generated from a two-part model that includes a zero-point mass. Motivated by analysis of such nonnegative data with excessive zeros, we introduce several truncated rank-based two-group and multigroup tests, including a truncated rank-based Wilcoxon rank-sum test for two-group comparison and two truncated Kruskal–Wallis tests for multigroup comparisons. We show, both analytically through asymptotic relative efficiency analysis and by simulations, that the proposed tests have higher power than the standard rank-based tests in typical microbiome data settings, especially when the proportion of zeros in the data is high. The tests can also be applied to repeated measurements of compositional data via simple within-subject permutations. In a simple before-and-after treatment experiment, the within-subject permutation is similar to the paired rank test. However, the proposed tests handle the excessive zeros which leads to a better power. We apply the tests to compare the microbiome compositions of healthy children and pediatric Crohn's disease patients and to assess the treatment effects on microbiome compositions. We identify several bacterial genera that are missed by the standard rank-based tests.

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distinct: A NOVEL APPROACH TO DIFFERENTIAL DISTRIBUTION ANALYSES

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We present *distinct*, a general method for differential analysis of full distributions that is well suited to applications on single-cell data, such as single-cell RNA sequencing and high-dimensional flow or mass cytometry data. High-throughput single-cell data reveal an unprecedented view of cell identity and allow complex variations between conditions to be discovered; nonetheless, most methods for differential expression target differences in the mean and struggle to identify changes where the mean is only marginally affected. *distinct* is based on a hierarchical nonparametric permutation approach and, by comparing empirical cumulative distribution functions, identifies both differential patterns involving changes in the mean as well as more subtle variations that do not involve the mean. We performed extensive benchmarks across both simulated and experimental datasets from single-cell RNA sequencing and mass cytometry data, where *distinct* shows favourable performance, identifies more differential patterns than competitors, and displays good control of false positive and false discovery rates. *distinct* is available as a Bioconductor R package.

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THE RISK OF MATERNAL COMPLICATIONS AFTER CESAREAN DELIVERY: NEAR-FAR MATCHING FOR INSTRUMENTAL VARIABLES STUDY DESIGNS WITH LARGE OBSERVATIONAL DATASETS

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Cesarean delivery is used when there are problems with the placenta or umbilical cord, for twin pregnancies, and breech births. However, research has found that Cesarean delivery increases the risk of maternal complications like blood transfusions and admission to the intensive care unit. Here, using an instrumental variables study design to reduce bias from unobserved confounders, we study whether Cesarean delivery increases the risk of maternal complications. We use a variant of matching—near-far matching—to render our study design more plausible. In a near-far match the investigator seeks to strengthen the effect of the instrument on the exposure while balancing observable characteristics between groups of subjects with low and high values of the instrument. Extant near-far matching methods are computationally intensive for large data sets, and computing time can be very lengthy. To reduce the computational complexity of near-far matching in large observational studies, we apply an iterative form of Glover's algorithm for a doubly convex bipartite graph to determine an optimal reverse caliper for the instrument which reduces the number of candidate matches and allows for an optimal match in a large but much sparser graph. We also incorporate a variety of balance constraints, including exact matching, fine and near-fine balance, and covariate balance prioritization. We illustrate this new matching method using medical claims data from Pennsylvania, New York, and Florida. In our application we match on physician's preferences for delivery via Cesarean section which is the instrument in our study. We compare the computing time from our match to extant methods, and we find that we can reduce the computational time required for the match by more than 11 hours. If our matched sample came from a paired randomized experiment, we could conclude that Cesarean delivery elevates the risk of maternal complications and increases the time spent in the hospital. Sensitivity analysis shows that the estimates for complications could be the result of a minor amount of confounding due to an unobserved covariate. The effects on the length of stay outcome, however, are more insensitive to hidden confounders.

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INTEGRATING MULTIPLE BUILT ENVIRONMENT DATA SOURCES

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Studies examining the contribution of the built environment to health often rely on commercial data sources to derive exposure measures, such as the number of specific food outlets in study participants' neighborhoods. Data on the location of community amenities (e.g., food outlets) can be collected from multiple sources. However, these commercial listings are known to have ascertainment errors and thus provide conflicting claims about the number and location of amenities. We propose a method that integrates exposure measures from different databases, while accounting for ascertainment errors, and obtains unbiased health effects of latent exposure. We frame the problem of conflicting exposure measures as a problem of two contingency tables with partially known margins, with the entries of the tables modeled using a multinomial distribution. Available estimates of source quality were embedded in a joint model for observed exposure counts, latent exposures, and health outcomes. Simulations show that our modeling framework yields substantially improved inferences regarding the health effects. We used the proposed method to estimate the association between children's body mass index (BMI) and the concentration of food outlets near their schools when both the NETS and Reference USA databases are available.

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MARGINALLY CALIBRATED RESPONSE DISTRIBUTIONS FOR END-TO-END LEARNING IN AUTONOMOUS DRIVING

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End-to-end learners for autonomous driving are deep neural networks that predict the instantaneous steering angle directly from images of the street ahead. These learners must provide reliable uncertainty estimates for their predictions in order to meet safety requirements and to initiate a switch to manual control in areas of high uncertainty. However, end-to-end learners typically only deliver point predictions, since distributional predictions are associated with large increases in training time or additional computational resources during prediction. To address this shortcoming, we investigate efficient and scalable approximate inference for the deep distributional model of Klein, Nott and Smith (*J. Comput. Graph. Statist.* **30** (2021) 467–483) in order to quantify uncertainty for the predictions of end-to-end learners. A special merit of this model, which we refer to as implicit copula neural linear model (IC-NLM), is that it produces densities for the steering angle that are marginally calibrated, that is, the average of the estimated densities equals the empirical distribution of steering angles. To ensure the scalability to large n regimes, we develop efficient estimation based on variational inference as a fast alternative to computationally intensive, exact inference via Hamiltonian Monte Carlo. We demonstrate the accuracy and speed of the variational approach on two end-to-end learners trained for highway driving using the comma2k19 dataset. The IC-NLM is competitive with other established uncertainty quantification methods for end-to-end learning in terms of nonprobabilistic predictive performance and outperforms them in terms of marginal calibration for in-distribution prediction. Our proposed approach also allows the identification of overconfident learners and contributes to the explainability of black-box end-to-end learners by using the predictive densities to understand which steering actions the learner sees as valid.

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LEVERAGING HARDY–WEINBERG DISEQUILIBRIUM FOR ASSOCIATION TESTING IN CASE-CONTROL STUDIES

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Modern genome-wide association studies (GWAS) remove single nucleotide polymorphisms (SNPs) that are in Hardy–Weinberg disequilibrium (HWD), despite limited rigor for this practice. In a case-control GWAS, although HWD in the control sample is an evidence for genotyping error, a truly associated SNP may be in HWD in the case and/or control populations. We, therefore, develop a new case-control association test that: (i) leverages HWD attributed to true association to increase power, (ii) is robust to HWD caused by genotyping error, and (iii) is easy-to-implement at the genome-wide level. The proposed robust *allele-based* joint test incorporates the *difference* in HWD between the case and control samples into the traditional association measure to gain power. We provide the asymptotic distribution of the proposed test statistic under the null hypothesis. We evaluate its type 1 error control at the genome-wide significance level of 5×10^{-8} in the presence of HWD attributed to factors unrelated to phenotype-genotype association, such as genotyping error. Finally, we demonstrate that the power of the proposed allele-based joint test is higher than the standard association test for a variety of genetic models, through derivations of the noncentrality parameters of the tests, as well as simulation and application studies.

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BIVARIATE HIERARCHICAL BAYESIAN MODEL FOR COMBINING SUMMARY MEASURES AND THEIR UNCERTAINTIES FROM MULTIPLE SOURCES

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It is often of interest to combine available estimates of a similar quantity from multiple data sources. When the corresponding variances of each estimate are also available, a model should take into account the *uncertainty of the estimates* themselves as well as the *uncertainty in the estimation of variances*. In addition, if there exists a strong association between estimates and their variances, the correlation between these two quantities should also be considered. In this paper we propose a bivariate hierarchical Bayesian model that jointly models the estimates and their estimated variances, assuming a correlation between these two measures. We conduct simulations to explore the performance of the proposed bivariate Bayesian model and compare it to other commonly used methods under different correlation scenarios. The proposed bivariate Bayesian model has a wide range of applications. We illustrate its application in three very different areas: PET brain imaging studies, meta-analysis, and small area estimation.

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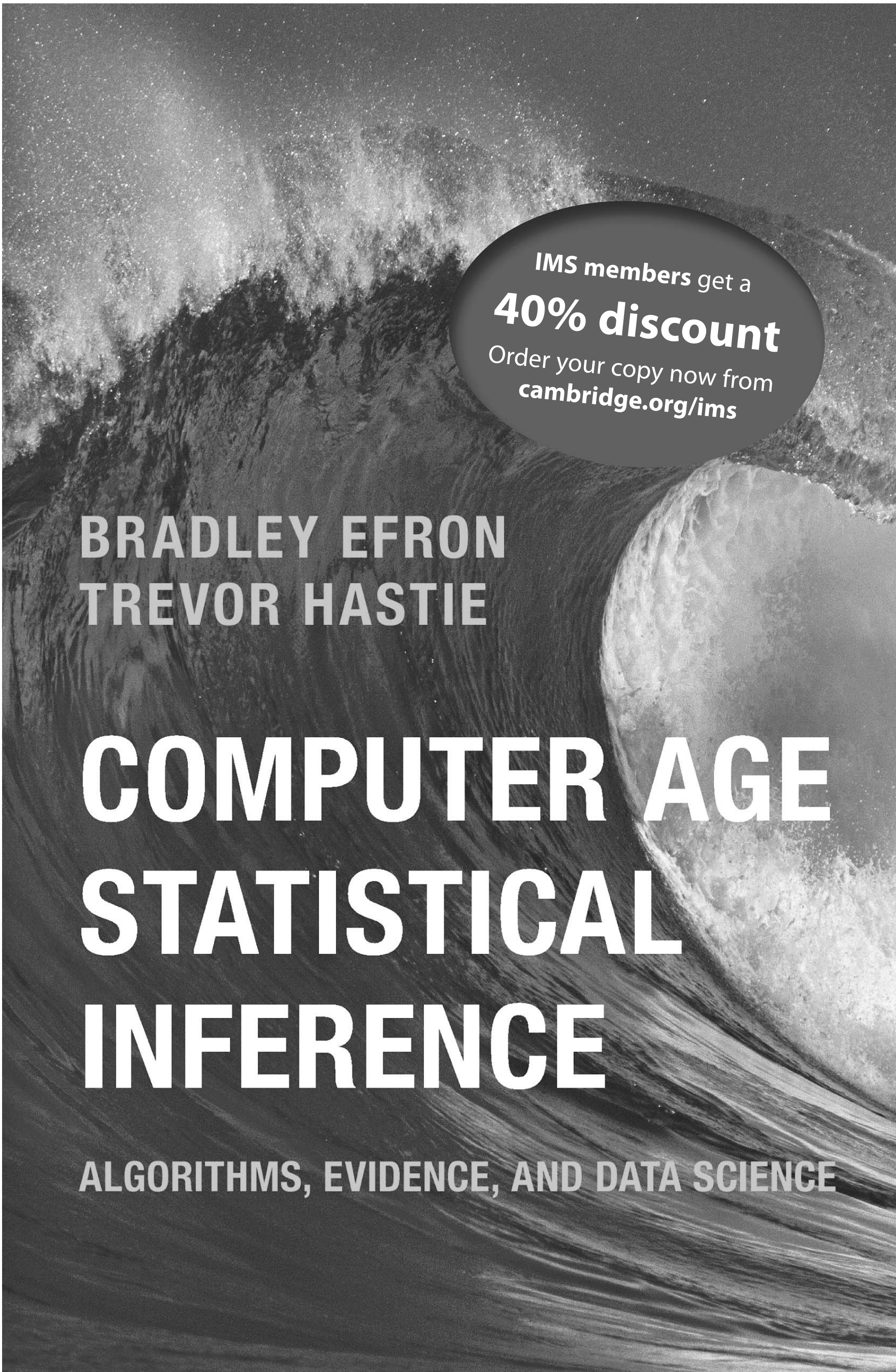
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