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REFINING CELLULAR PATHWAY MODELS USING AN ENSEMBLE OF HETEROGENEOUS DATA SOURCES[1]

BY ALEXANDER M. FRANKS, FLORIAN MARKOWETZ[2,3] AND EDOARDO M. AIROLDI[3]

University of California, Santa Barbara, University of Cambridge and Temple University

Improving current models and hypotheses of cellular pathways is one of the major challenges of systems biology and functional genomics. There is a need for methods to build on established expert knowledge and reconcile it with results of new high-throughput studies. Moreover, the available sources of data are heterogeneous, and the data need to be integrated in different ways depending on which part of the pathway they are most informative for. In this paper, we introduce a compartment specific strategy to integrate edge, node and path data for refining a given network hypothesis. To carry out inference, we use a local-move Gibbs sampler for updating the pathway hypothesis from a compendium of heterogeneous data sources, and a new network regression idea for integrating protein attributes. We demonstrate the utility of this approach in a case study of the pheromone response MAPK pathway in the yeast *S. cerevisiae*.

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STATISTICAL SHAPE ANALYSIS OF SIMPLIFIED NEURONAL TREES

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Neuron morphology plays a central role in characterizing cognitive health and functionality of brain structures. The problem of quantifying neuron shapes and capturing statistical variability of shapes is difficult because neurons differ both in geometry and in topology. This paper develops a mathematical representation of neuronal trees, restricting to the trees that consist of: (1) a main branch viewed as a parameterized curve in $\mathbb{R}^3$, and (2) some number of secondary branches—also parameterized curves in $\mathbb{R}^3$—which emanate from the main branch at arbitrary points. It imposes a metric on the representation space, in order to compare neuronal shapes, and to obtain optimal deformations (geodesics) across arbitrary trees. The key idea is to impose certain equivalence relations that allow trees with different geometries and topologies to be compared efficiently. The combinatorial problem of matching side branches across trees is reduced to a linear assignment with well-known efficient solutions. This framework is then applied to comparing, clustering, and classifying neurons using fully automated algorithms. The framework is illustrated on three datasets of neuron reconstructions, specifically showing geodesics paths and cross-validated classification between experimental groups.

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TPRM: TENSOR PARTITION REGRESSION MODELS WITH APPLICATIONS IN IMAGING BIOMARKER DETECTION

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Medical imaging studies have collected high-dimensional imaging data to identify imaging biomarkers for diagnosis, screening, and prognosis, among many others. These imaging data are often represented in the form of a multi-dimensional array, called a tensor. The aim of this paper is to develop a tensor partition regression modeling (TPRM) framework to establish a relationship between low-dimensional clinical outcomes (e.g., diagnosis) and high-dimensional tensor covariates. Our TPRM is a hierarchical model and efficiently integrates four components: (i) a partition model, (ii) a canonical polyadic decomposition model, (iii) a principal components model, and (iv) a generalized linear model with a sparse inducing normal mixture prior. This framework not only reduces ultra-high dimensionality to a manageable level, resulting in efficient estimation, but also optimizes prediction accuracy in the search for informative sub-tensors. Posterior computation proceeds via an efficient Markov chain Monte Carlo algorithm. Simulation shows that TPRM outperforms several other competing methods. We apply TPRM to predict disease status (Alzheimer versus control) by using structural magnetic resonance imaging data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.

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COMPLEX-VALUED TIME SERIES MODELING FOR IMPROVED ACTIVATION DETECTION IN FMRI STUDIES

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A complex-valued data-based model with pth order autoregressive errors and general real/imaginary error covariance structure is proposed as an alternative to the commonly used magnitude-only data-based autoregressive model for fMRI time series. Likelihood-ratio-test-based activation statistics are derived for both models and compared for experimental and simulated data. For a dataset from a right-hand finger-tapping experiment, the activation map obtained using complex-valued modeling more clearly identifies the primary activation region (left functional central sulcus) than the magnitude-only model. Such improved accuracy in mapping the left functional central sulcus has important implications in neurosurgical planning for tumor and epilepsy patients. Additionally, we develop magnitude and phase detrending procedures for complex-valued time series and examine the effect of spatial smoothing. These methods improve the power of complex-valued data-based activation statistics. Our results advocate for the use of the complex-valued data and the modeling of its dependence structures as a more efficient and reliable tool in fMRI experiments over the current practice of using only magnitude-valued datasets.

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OPTIMAL MULTILEVEL MATCHING USING NETWORK FLOWS: AN APPLICATION TO A SUMMER READING INTERVENTION

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Many observational studies of causal effects occur in settings with clustered treatment assignment. In studies of this type, treatment is applied to entire clusters of units. For example, an educational intervention might be administered to all the students in a school. We develop a matching algorithm for multilevel data based on a network flow algorithm. Earlier work on multilevel matching relied on integer programming, which allows for balance targeting on specific covariates but can be slow with larger data sets. Although we cannot directly specify minimal levels of balance for individual covariates, our algorithm is fast and scales easily to larger data sets. We apply this algorithm to assess a school-based intervention through which students in treated schools were exposed to a new reading program during summer school. In one variant of the algorithm, where we match both schools and students, we change the causal estimand through optimal subset matching to better maintain common support. In a second variant, we relax the common support assumption to preserve the causal estimand by only matching on schools. We find that the summer intervention does not appear to increase reading test scores. In a sensitivity analysis, however, we determine that an unobserved confounder could easily mask a larger treatment effect.

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TOPOLOGICAL DATA ANALYSIS OF SINGLE-TRIAL ELECTROENCEPHALOGRAPHIC SIGNALS

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Epilepsy is a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. Statistical analysis of neurophysiological recordings, such as electroencephalography (EEG), facilitates the understanding of epileptic seizures. Standard statistical methods typically analyze amplitude and frequency information in EEG signals. In the current study, we propose a topological data analysis (TDA) framework to analyze single-trial EEG signals. The framework denoises signals with a weighted Fourier series (WFS), and tests for differences between the topological features—persistence landscapes (PLs) of denoised signals through resampling in the frequency domain. Simulation studies show that the test is robust for topologically similar signals while bearing sensitivity to topological tearing in signals. In an application to single-trial epileptic EEG signals, EEG signals in the diagnosed seizure origin and its symmetric site are found to have similar PLs before and during a seizure attack, in contrast to signals at other sites showing significant statistical difference in the PLs of the two phases.

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JOINT SIGNIFICANCE TESTS FOR MEDIATION EFFECTS OF SOCIOECONOMIC ADVERSITY ON ADIPOSITY VIA EPIGENETICS[1]

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Academia Sinica

Mediation analysis has become a popular practice in biomedical research. We conduct mediation analyses to investigate whether epigenetic variations mediate the effect of socioeconomic disadvantage on adiposity. Mediation effects can be expressed as a product of two parameters: one for the exposure-mediator association and the other for the mediator-outcome association conditional on the exposure. Under multi-mediator models, we study joint significance tests which examine the two parameters separately and compare with the widely used product significance tests which focus on the product of two parameters. Normal approximation of product significance tests depends on both effect size and sample size. We show that joint significance tests are intersection-union tests with size α and asymptotically more powerful than the normality-based product significance tests. Based on the theoretical results, we construct powerful testing procedures for gene-based mediation analyses and path-specific analyses. Advantage of joint significance tests is supported by simulation as well as the results of locus-based and gene-based mediation analyses of chromosome 17. Our analyses suggest that methylation of *FASN* gene mediates the effect of socioeconomic adversity on adiposity.

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ADAPTIVE-WEIGHT BURDEN TEST FOR ASSOCIATIONS BETWEEN QUANTITATIVE TRAITS AND GENOTYPE DATA WITH COMPLEX CORRELATIONS

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High throughput sequencing has often been used to screen samples from pedigrees or with population structure, producing genotype data with complex correlations caused by both familial relation and linkage disequilibrium. With such data it is critical to account for these genotypic correlations when assessing the contribution of multiple variants by gene or pathway. Recognizing the limitations of existing association testing methods, we propose *Adaptive-weight Burden Test* (ABT), a retrospective, mixed model test for genetic association of quantitative traits on genotype data with complex correlations. This method makes full use of genotypic correlations across both samples and variants and adopts "data driven" weights to improve power. We derive the ABT statistic and its explicit distribution under the null hypothesis and demonstrate through simulation studies that it is generally more powerful than the fixed-weight burden test and family-based SKAT in various scenarios, controlling for the type I error rate. Further investigation reveals the connection of ABT with kernel tests, as well as the adaptability of its weights to the direction of genetic effects. The application of ABT is illustrated by a gene-based association analysis of fasting glucose using data from the NHLBI "Grand Opportunity" Exome Sequencing Project.

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BAYESIAN AGGREGATION OF AVERAGE DATA: AN APPLICATION IN DRUG DEVELOPMENT

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Throughout the different phases of a drug development program, randomized trials are used to establish the tolerability, safety and efficacy of a candidate drug. At each stage one aims to optimize the design of future studies by extrapolation from the available evidence at the time. This includes collected trial data and relevant external data. However, relevant external data are typically available as averages only, for example, from trials on alternative treatments reported in the literature. Here we report on such an example from a drug development for wet age-related macular degeneration. This disease is the leading cause of severe vision loss in the elderly. While current treatment options are efficacious, they are also a substantial burden for the patient. Hence, new treatments are under development which need to be compared against existing treatments.

The general statistical problem this leads to is *meta-analysis*, which addresses the question of how we can combine data sets collected under different conditions. Bayesian methods have long been used to achieve partial pooling. Here we consider the challenge when the model of interest is complex (hierarchical and nonlinear) and one data set is given as raw data while the second data set is given as averages only. In such a situation, common meta-analytic methods can only be applied when the model is sufficiently simple for analytic approaches. When the model is too complex, for example, nonlinear, an analytic approach is not possible. We provide a Bayesian solution by using simulation to approximately reconstruct the likelihood of the external summary and allowing the parameters in the model to vary under the different conditions. We first evaluate our approach using fake data simulations and then report results for the drug development program that motivated this research.

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BAYCOUNT: A BAYESIAN DECOMPOSITION METHOD FOR INFERRING TUMOR HETEROGENEITY USING RNA-SEQ COUNTS

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Tumors are heterogeneous. A tumor sample usually consists of a set of subclones with distinct transcriptional profiles and potentially different degrees of aggressiveness and responses to drugs. Understanding tumor heterogeneity is therefore critical for precise cancer prognosis and treatment. In this paper we introduce BayCount—a Bayesian decomposition method to infer tumor heterogeneity with highly over-dispersed RNA sequencing count data. Using negative binomial factor analysis, BayCount takes into account both the between-sample and gene-specific random effects on raw counts of sequencing reads mapped to each gene. For the posterior inference, we develop an efficient compound Poisson-based blocked Gibbs sampler. Simulation studies show that BayCount is able to accurately estimate the subclonal inference, including the number of subclones, the proportions of these subclones in each tumor sample, and the gene expression profiles in each subclone. For real world data examples, we apply BayCount to The Cancer Genome Atlas lung cancer and kidney cancer RNA sequencing count data and obtain biologically interpretable results. Our method represents the first effort in characterizing tumor heterogeneity using RNA sequencing count data that simultaneously removes the need of normalizing the counts, achieves statistical robustness, and obtains biologically/clinically meaningful insights. The R package `BayCount` implementing our model and algorithm is available for download.

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EXPLORING THE CONFORMATIONAL SPACE FOR PROTEIN FOLDING WITH SEQUENTIAL MONTE CARLO

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Computational methods for protein structure prediction from amino acid sequence are of vital importance in modern applications, for example protein design in biomedicine. Efficient sampling of conformations according to a given energy function remains a bottleneck, yet is a vital step for energy-based structure prediction methods. While the Protein Data Bank of experimentally determined 3-D protein structures has steadily increased in size, structure predictions for new proteins tend to be unreliable in the amino acid segments where there is low sequence similarity with known structures. In this paper we introduce a new method for building such segments of protein structures, inspired by sequential Monte Carlo methods. We apply our method to examples of real 3-D structure predictions and demonstrate its promise for improving low confidence segments. We also provide applications to the prediction of reconstructed segments in known structures, and to the assessment of energy function accuracy. We find that our method is able to produce conformations that have both low energies and good coverage of the conformational space and hence can be a useful tool for protein design and structure prediction.

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SEQUENTIAL DOUBLE CROSS-VALIDATION FOR ASSESSMENT OF ADDED PREDICTIVE ABILITY IN HIGH-DIMENSIONAL OMIC APPLICATIONS

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Enriching existing predictive models with new biomolecular markers is an important task in the new multi-omic era. Clinical studies increasingly include new sets of omic measurements which may prove their added value in terms of predictive performance. We introduce a two-step approach for the assessment of the added predictive ability of omic predictors, based on sequential double cross-validation and regularized regression models. We propose several performance indices to summarize the two-stage prediction procedure and a permutation test to formally assess the added predictive value of a second omic set of predictors over a primary omic source. The performance of the test is investigated through simulations. We illustrate the new method through the systematic assessment and comparison of the performance of transcriptomics and metabolomics sources in the prediction of body mass index (BMI) using longitudinal data from the Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study, a population-based cohort from Finland.

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JOINING THE INCOMPATIBLE: EXPLOITING PURPOSIVE LISTS FOR THE SAMPLE-BASED ESTIMATION OF SPECIES RICHNESS

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The lists of species obtained by purposive sampling by field ecologists can be used to improve the sample-based estimation of species richness. A new estimator is here proposed as a modification of the difference estimator in which the species inclusion probabilities are estimated by means of the species frequencies from incidence data. If the species list used to support the estimation is complete the estimator guesses the true richness without error. In the case of incomplete lists, the estimator provides values invariably greater than the number of species detected by the combination of sample-based and purposive surveys. An asymptotically conservative estimator of the mean squared error is also provided. A simulation study based on two artificial communities is carried out in order to check the obvious increase in accuracy and precision with respect to the widely applied estimators based on the sole sample information. Finally, the proposed estimator is adopted to estimate species richness in the Maremma Regional Park, Italy.

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A GENERAL FRAMEWORK FOR ASSOCIATION ANALYSIS OF HETEROGENEOUS DATA

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Multivariate association analysis is of primary interest in many applications. Despite the prevalence of high-dimensional and non-Gaussian data (such as count-valued or binary), most existing methods only apply to low-dimensional data with continuous measurements. Motivated by the Computer Audition Lab 500-song (CAL500) music annotation study, we develop a new framework for the association analysis of two sets of high-dimensional and heterogeneous (continuous/binary/count) data. We model heterogeneous random variables using exponential family distributions, and exploit a structured decomposition of the underlying natural parameter matrices to identify shared and individual patterns for two data sets. We also introduce a new measure of the strength of association, and a permutation-based procedure to test its significance. An alternating iteratively reweighted least squares algorithm is devised for model fitting, and several variants are developed to expedite computation and achieve variable selection. The application to the CAL500 data sheds light on the relationship between acoustic features and semantic annotations, and provides effective means for automatic music annotation and retrieval.

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CONFIDENT INFERENCE FOR SNP EFFECTS ON TREATMENT EFFICACY

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Our research is for finding SNPs that are predictive of treatment efficacy, to decide which subgroup (with enhanced treatment efficacy) to target in drug development. Testing SNPs for lack of association with treatment outcome is inherently challenging, because any linkage disequilibrium between a noncausal SNP with a causal SNP, however small, makes the zero-null (no association) hypothesis technically false. Control of Type I error rate in testing such null hypotheses are therefore difficult to interpret. We propose a completely different formulation to address this problem. For each SNP, we provide simultaneous confidence intervals directed toward detecting possible dominant, recessive, or additive effects. Across the SNPs, we control the expected number of SNPs with at least one false confidence interval coverage. Since our confidence intervals are constructed based on pivotal statistics, the false coverage control is guaranteed to be exact and unaffected by the true values of test quantities (whether zero or nonzero). Our method is applicable to the therapeutic areas of Diabetes and Alzheimer's diseases, and perhaps more, as a step toward confidently targeting a patient subgroup in a tailored drug development process.

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NONPARAMETRIC BAYESIAN LEARNING OF HETEROGENEOUS DYNAMIC TRANSCRIPTION FACTOR NETWORKS

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Gene expression is largely controlled by transcription factors (TFs) in a collaborative manner. Therefore, an understanding of TF collaboration is crucial for the elucidation of gene regulation. The co-activation of TFs can be represented by networks. These networks are dynamic in diverse biological conditions and heterogeneous across the genome within each biological condition. Existing methods for construction of TF networks lack solid statistical models, analyze each biological condition separately, and enforce a single network for all genomic locations within one biological condition, resulting in low statistical power and misleading spurious associations. In this paper, we present a novel Bayesian nonparametric dynamic Poisson graphical model for inference on TF networks. Our approach automatically teases out genome heterogeneity and borrows information across conditions to improve signal detection from very few replicates, thus offering a valid and efficient measure of TF co-activations. We develop an efficient parallel Markov chain Monte Carlo algorithm for posterior computation. The proposed approach is applied to study TF associations in ENCODE cell lines and provides novel findings.

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ESTIMATING AND COMPARING CANCER PROGRESSION RISKS UNDER VARYING SURVEILLANCE PROTOCOLS[1]

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Outcomes after cancer diagnosis and treatment are often observed at discrete times via doctor-patient encounters or specialized diagnostic examinations. Despite their ubiquity as endpoints in cancer studies, such outcomes pose challenges for analysis. In particular, comparisons between studies or patient populations with different surveillance schema may be confounded by differences in visit frequencies. We present a statistical framework based on multistate and hidden Markov models that represents events on a continuous time scale given data with discrete observation times. To demonstrate this framework, we consider the problem of comparing risks of prostate cancer progression across multiple active surveillance cohorts with different surveillance frequencies. We show that the different surveillance schedules partially explain observed differences in the progression risks between cohorts. Our application permits the conclusion that differences in underlying cancer progression risks across cohorts persist after accounting for different surveillance frequencies.

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ANALYSING PLANT CLOSURE EFFECTS USING TIME-VARYING MIXTURE-OF-EXPERTS MARKOV CHAIN CLUSTERING[1]

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In this paper we study data on discrete labor market transitions from Austria. In particular, we follow the careers of workers who experience a job displacement due to plant closure and observe—over a period of 40 quarters—whether these workers manage to return to a steady career path. To analyse these discrete-valued panel data, we apply a new method of Bayesian Markov chain clustering analysis based on inhomogeneous first order Markov transition processes with time-varying transition matrices. In addition, a mixture-of-experts approach allows us to model the probability of belonging to a certain cluster as depending on a set of covariates via a multinomial logit model. Our cluster analysis identifies five career patterns after plant closure and reveals that some workers cope quite easily with a job loss whereas others suffer large losses over extended periods of time.

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USING MISSING TYPES TO IMPROVE PARTIAL IDENTIFICATION WITH APPLICATION TO A STUDY OF HIV PREVALENCE IN MALAWI

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Frequently, empirical studies are plagued with missing data. When the data are missing not at random, the parameter of interest is not identifiable in general. Without additional assumptions, we can derive bounds of the parameters of interest, which, unfortunately, are often too wide to be informative. Therefore, it is of great importance to sharpen these worst-case bounds by exploiting additional information. Traditional missing data analysis uses only the information of the binary missing data indicator, that is, a certain data point is either missing or not. Nevertheless, real data often provide more information than a binary missing data indicator, and they often record different types of missingness. In a motivating HIV status survey, missing data may be due to the units' unwillingness to respond to the survey items or their hospitalization during the visit, and may also be due to the units' temporarily absence or relocation. It is apparent that some missing types are more likely to be missing not at random, but other missing types are more likely to be missing at random. We show that making full use of the missing types results in narrower bounds of the parameters of interest. In a real-life example, we demonstrate substantial improvement of more than 50% reduction in bound widths for estimating the prevalence of HIV in rural Malawi. As we illustrate using the HIV study, our strategy is also useful for conducting sensitivity analysis by gradually increasing or decreasing the set of types that are missing at random. In addition, we propose an easy-to-implement method to construct confidence intervals for partially identified parameters with bounds expressed as the minimums and maximums of finite parameters, which is useful for not only our problem but also many other problems involving bounds.

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A COUPLED ETAS-I^{2}GMM POINT PROCESS WITH APPLICATIONS TO SEISMIC FAULT DETECTION[1]

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Epidemic-type aftershock sequence (ETAS) point process is a common model for the occurrence of earthquake events. The ETAS model consists of a stationary background Poisson process modeling spontaneous earthquakes and a triggering kernel representing the space–time-magnitude distribution of aftershocks. Popular nonparametric methods for estimation of the background intensity include histograms and kernel density estimators. While these methods are able to capture local spatial heterogeneity in the intensity of spontaneous events, they do not capture well patterns resulting from fault line structure over larger spatial scales. Here we propose a two-layer infinite Gaussian mixture model for clustering of earthquake events into fault-like groups over intermediate spatial scales. We introduce a Monte Carlo expectation-maximization (EM) algorithm for joint inference of the ETAS-I^{2}GMM model and then apply the model to the Southern California Earthquake Catalog. We illustrate the advantages of the ETAS-I^{2}GMM model in terms of both goodness of fit of the intensity and recovery of fault line clusters in the Community Fault Model 3.0 from earthquake occurrence data.

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FUNCTIONAL PRINCIPAL VARIANCE COMPONENT TESTING FOR A GENETIC ASSOCIATION STUDY OF HIV PROGRESSION

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HIV-1C is the most prevalent subtype of HIV-1 and accounts for over half of HIV-1 infections worldwide. Host genetic influence of HIV infection has been previously studied in HIV-1B, but little attention has been paid to the more prevalent subtype C. To understand the role of host genetics in HIV-1C disease progression, we perform a study to assess the association between longitudinally collected measures of disease and more than 100,000 genetic markers located on chromosome 6. The most common approach to analyzing longitudinal data in this context is linear mixed effects models, which may be overly simplistic in this case. On the other hand, existing flexible and nonparametric methods either require densely sampled points, restrict attention to a single SNP, lack testing procedures, or are cumbersome to fit on the genome-wide scale. We propose a functional principal variance component (FPVC) testing framework which captures the nonlinearity in the CD4 and viral load with low degrees of freedom and is fast enough to carry out thousands or millions of times. The FPVC testing unfolds in two stages. In the first stage, we summarize the markers of disease progression according to their major patterns of variation via functional principal components analysis (FPCA). In the second stage, we employ a simple working model and variance component testing to examine the association between the summaries of disease progression and a set of single nucleotide polymorphisms. We supplement this analysis with simulation results which indicate that FPVC testing can offer large power gains over the standard linear mixed effects model.

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ESTIMATING A COMMON COVARIANCE MATRIX FOR NETWORK META-ANALYSIS OF GENE EXPRESSION DATASETS IN DIFFUSE LARGE B-CELL LYMPHOMA[1]

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The estimation of covariance matrices of gene expressions has many applications in cancer systems biology. Many gene expression studies, however, are hampered by low sample size and it has therefore become popular to increase sample size by collecting gene expression data across studies. Motivated by the traditional meta-analysis using random effects models, we present a hierarchical random covariance model and use it for the meta-analysis of gene correlation networks across 11 large-scale gene expression studies of diffuse large B-cell lymphoma (DLBCL). We suggest to use a maximum likelihood estimator for the underlying common covariance matrix and introduce an EM algorithm for estimation. By simulation experiments comparing the estimated covariance matrices by cophenetic correlation and Kullback–Leibler divergence the suggested estimator showed to perform better or not worse than a simple pooled estimator. In a posthoc analysis of the estimated common covariance matrix for the DLBCL data we were able to identify novel biologically meaningful gene correlation networks with eigengenes of prognostic value. In conclusion, the method seems to provide a generally applicable framework for meta-analysis, when multiple features are measured and believed to share a common covariance matrix obscured by study dependent noise.

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TREE-BASED REINFORCEMENT LEARNING FOR ESTIMATING OPTIMAL DYNAMIC TREATMENT REGIMES[1]

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Dynamic treatment regimes (DTRs) are sequences of treatment decision rules, in which treatment may be adapted over time in response to the changing course of an individual. Motivated by the substance use disorder (SUD) study, we propose a tree-based reinforcement learning (T-RL) method to directly estimate optimal DTRs in a multi-stage multi-treatment setting. At each stage, T-RL builds an unsupervised decision tree that directly handles the problem of optimization with multiple treatment comparisons, through a purity measure constructed with augmented inverse probability weighted estimators. For the multiple stages, the algorithm is implemented recursively using backward induction. By combining semiparametric regression with flexible tree-based learning, T-RL is robust, efficient and easy to interpret for the identification of optimal DTRs, as shown in the simulation studies. With the proposed method, we identify dynamic SUD treatment regimes for adolescents.

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A FREQUENCY-CALIBRATED BAYESIAN SEARCH FOR NEW PARTICLES

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The statistical procedure used in the search for new particles is investigated in this paper. The discovery of the Higgs particles is used to lay out the problem and the existing procedures. A Bayesian hierarchical model is proposed to address inference about the parameters of interest while incorporating uncertainty about the nuisance parameters into the model. In addition to inference, a decision making procedure is proposed. A loss function is introduced that mimics the important features of a discovery problem. Given the importance of controlling the "false discovery" and "missed detection" error rates in discovering new phenomena, the proposed procedure is calibrated to control for these error rates.

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BAYESIAN RANDOMIZED RESPONSE TECHNIQUE WITH MULTIPLE SENSITIVE ATTRIBUTES: THE CASE OF INFORMATION SYSTEMS RESOURCE MISUSE[1]

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The randomized response technique (RRT) is a classical and effective method used to mitigate the distortion arising from dishonest answers. The traditional RRT usually focuses on the case of a single sensitive attribute, and discussion of the case of multiple sensitive attributes is limited. Here, we study a business case to identify some individual and organizational determinants driving information systems (IS) resource misuse in the workplace. People who actually engage in IS resource misuse are probably not willing to provide honest answers, given the sensitivity of the topic. Yet, to develop the causal relationship between IS resource misuse and its determinants, a version of the RRT for multivariate analysis is required. To implement the RRT with multiple sensitive attributes, we propose a Bayesian approach for estimating covariance matrices with incomplete information (resulting from the randomization procedure in the RRT case). The proposed approach (i) accommodates the positive definite condition and other intrinsic parameter constraints in the posterior to improve statistical precision, (ii) incorporates Bayesian shrinkage estimation for covariance matrices despite incomplete information, and (iii) adopts a quasi-likelihood method to achieve Bayesian semiparametric inference for enhancing flexibility. We show the effectiveness of the proposed method in a simulation study. We also apply the Bayesian RRT method and structural equation modeling to identify the causal relationship between IS resource misuse and its determinants.

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DIRECT LIKELIHOOD-BASED INFERENCE FOR DISCRETELY OBSERVED STOCHASTIC COMPARTMENTAL MODELS OF INFECTIOUS DISEASE[1]

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Stochastic compartmental models are important tools for understanding the course of infectious diseases epidemics in populations and in prospective evaluation of intervention policies. However, calculating the likelihood for discretely observed data from even simple models—such as the ubiquitous susceptible-infectious-removed (SIR) model—has been considered computationally intractable, since its formulation almost a century ago. Recently researchers have proposed methods to circumvent this limitation through data augmentation or approximation, but these approaches often suffer from high computational cost or loss of accuracy. We develop the mathematical foundation and an efficient algorithm to compute the likelihood for discretely observed data from a broad class of stochastic compartmental models. We also give expressions for the derivatives of the transition probabilities using the same technique, making possible inference via Hamiltonian Monte Carlo (HMC). We use the 17th century plague in Eyam, a classic example of the SIR model, to compare our recursion method to sequential Monte Carlo, analyze using HMC, and assess the model assumptions. We also apply our direct likelihood evaluation to perform Bayesian inference for the 2014–2015 Ebola outbreak in Guinea. The results suggest that the epidemic infectious rates have decreased since October 2014 in the Southeast region of Guinea, while rates remain the same in other regions, facilitating understanding of the outbreak and the effectiveness of Ebola control interventions.

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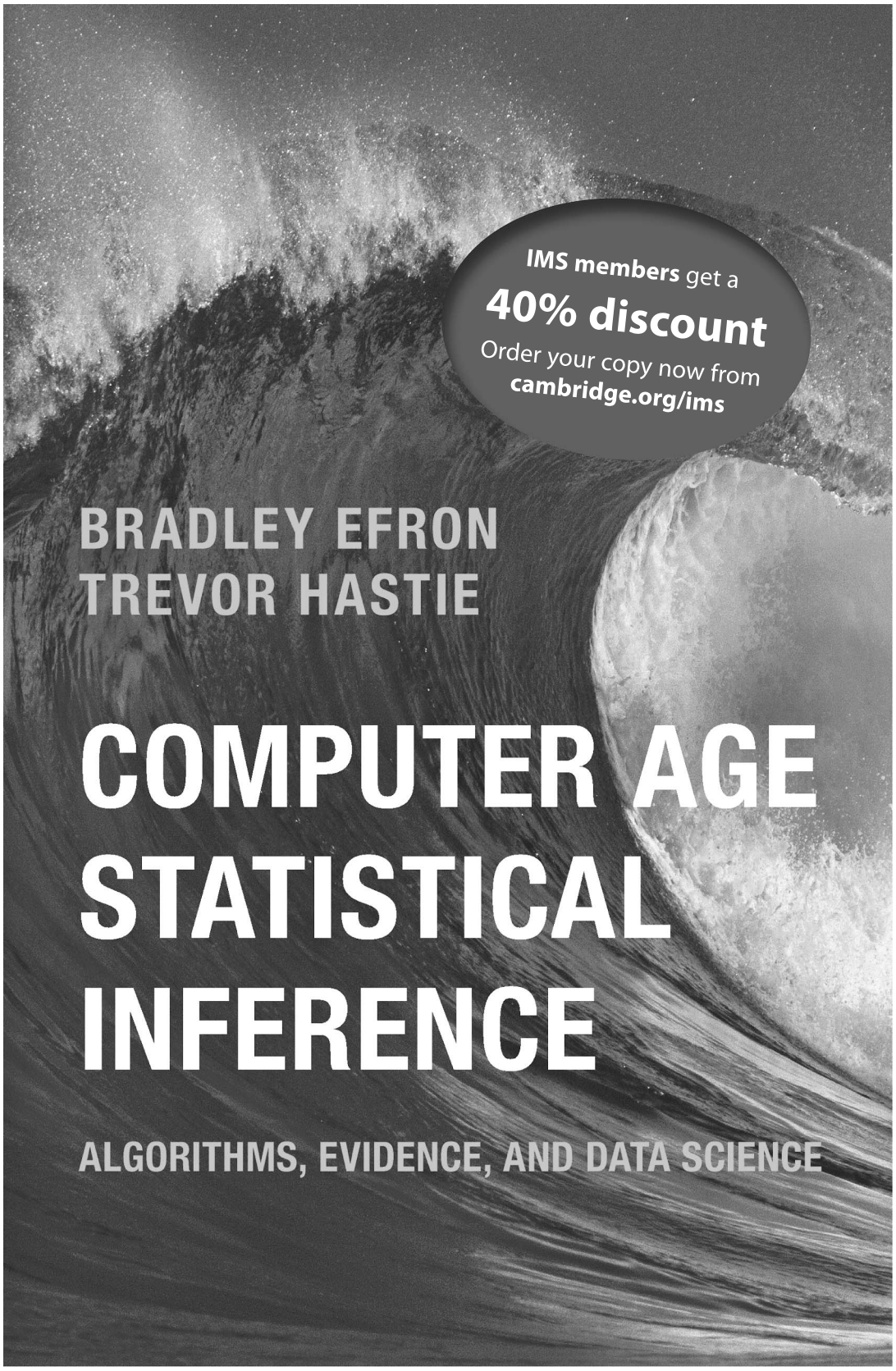
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