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Model-Based Approach to the Joint Analysis of Single-Cell Data on Chromatin Accessibility and Gene Expression

Zhixiang Lin, Mahdi Zamanighomi, Timothy Daley, Shining Ma and Wing Hung Wong

Abstract. Unsupervised methods, including clustering methods, are essential to the analysis of single-cell genomic data. Model-based clustering methods are under-explored in the area of single-cell genomics, and have the advantage of quantifying the uncertainty of the clustering result. Here we develop a model-based approach for the integrative analysis of single-cell chromatin accessibility and gene expression data. We show that combining these two types of data, we can achieve a better separation of the underlying cell types. An efficient Markov chain Monte Carlo algorithm is also developed.

Key words and phrases: Single-cell genomics, coupled clustering, Bayesian modeling, MCMC.

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Risk Models for Breast Cancer and Their Validation

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Abstract. Strategies to prevent cancer and diagnose it early when it is most treatable are needed to reduce the public health burden from rising disease incidence. Risk assessment is playing an increasingly important role in targeting individuals in need of such interventions. For breast cancer many individual risk factors have been well understood for a long time, but the development of a fully comprehensive risk model has not been straightforward, in part because there have been limited data where joint effects of an extensive set of risk factors may be estimated with precision. In this article we first review the approach taken to develop the IBIS (Tyrer–Cuzick) model, and describe recent updates. We then review and develop methods to assess calibration of models such as this one, where the risk of disease allowing for competing mortality over a long follow-up time or lifetime is estimated. The breast cancer risk model model and calibration assessment methods are demonstrated using a cohort of 132,139 women attending mammography screening in the State of Washington, USA.

Key words and phrases: Breast cancer, calibration, risk assessment, breast density, Tyrer–Cuzick model, IBIS model.

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Some Statistical Issues in Climate Science

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Abstract. Climate science is a field that is arguably both data-rich and data-poor. Data rich in that huge and quickly increasing amounts of data about the state of the climate are collected every day. Data poor in that important aspects of the climate are still undersampled, such as the deep oceans and some characteristics of the upper atmosphere. Data rich in that modern climate models can produce climatological quantities over long time periods with global coverage, including quantities that are difficult to measure and under conditions for which there is no data presently. Data poor in that the correspondence between climate model output to the actual climate, especially for future climate change due to human activities, is difficult to assess. The scope for fruitful interactions between climate scientists and statisticians is great, but requires serious commitments from researchers in both disciplines to understand the scientific and statistical nuances arising from the complex relationships between the data and the real-world problems. This paper describes a small fraction of some of the intellectual challenges that occur at the interface between climate science and statistics, including inferences for extremes for processes with seasonality and long-term trends, the use of climate model ensembles for studying extremes, the scope for using new data sources for studying space-time characteristics of environmental processes and a discussion of non-Gaussian space-time process models for climate variables. The paper concludes with a call to the statistical community to become more engaged in one of the great scientific and policy issues of our time, anthropogenic climate change and its impacts.

Key words and phrases: Statistical climatology, climate extremes, Argo network, non-Gaussian processes.

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A Tale of Two Parasites: Statistical Modelling to Support Disease Control Programmes in Africa

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Abstract. Vector-borne diseases have long presented major challenges to the health of rural communities in the wet tropical regions of the world, but especially in sub-Saharan Africa. In this paper, we describe the contribution that statistical modelling has made to the global elimination programme for one vector-borne disease, onchocerciasis.

We explain why information on the spatial distribution of a second vector-borne disease, Loa loa, is needed before communities at high risk of onchocerciasis can be treated safely with mass distribution of ivermectin, an antifiarial medication.

We show how a model-based geostatistical analysis of Loa loa prevalence survey data can be used to map the predictive probability that each location in the region of interest meets a WHO policy guideline for safe mass distribution of ivermectin and describe two applications: one is to data from Cameroon that assesses prevalence using traditional blood-smear microscopy; the other is to Africa-wide data that uses a low-cost questionnaire-based method.

We describe how a recent technological development in image-based microscopy has resulted in a change of emphasis from prevalence alone to the bivariate spatial distribution of prevalence and the intensity of infection among infected individuals. We discuss how statistical modelling of the kind described here can contribute to health policy guidelines and decision-making in two ways. One is to ensure that, in a resource-limited setting, prevalence surveys are designed, and the resulting data analysed, as efficiently as possible. The other is to provide an honest quantification of the uncertainty attached to any binary decision by reporting predictive probabilities that a policy-defined condition for action is or is not met.

Key words and phrases: Neglected tropical diseases, predictive disease mapping, spatial statistics.

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Quantum Science and Quantum Technology

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Abstract. Quantum science and quantum technology are of great current interest in multiple frontiers of many scientific fields ranging from computer science to physics and chemistry, and from engineering to mathematics and statistics. Their developments will likely lead to a new wave of scientific revolutions and technological innovations in a wide range of scientific studies and applications. This paper provides a brief review on quantum communication, quantum information, quantum computation, quantum simulation, and quantum metrology. We present essential quantum properties, illustrate relevant concepts of quantum science and quantum technology, and discuss their scientific developments. We point out the need for statistical analysis in their developments, as well as their potential applications to and impacts on statistics and data science.

Key words and phrases: Quantum communication, quantum information, quantum computation, quantum simulation, quantum annealing, quantum sensing and quantum metrology, quantum bit (qubit).

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Statistical Methodology in Single-Molecule Experiments

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Abstract. Toward the last quarter of the 20th century, the emergence of single-molecule experiments enabled scientists to track and study individual molecules' dynamic properties in real time. Unlike macroscopic systems' dynamics, those of single molecules can only be properly described by stochastic models even in the absence of external noise. Consequently, statistical methods have played a key role in extracting hidden information about molecular dynamics from data obtained through single-molecule experiments. In this article, we survey the major statistical methodologies used to analyze single-molecule experimental data. Our discussion is organized according to the types of stochastic models used to describe single-molecule systems as well as major experimental data collection techniques. We also highlight challenges and future directions in the application of statistical methodologies to single-molecule experiments.

Key words and phrases: Autocorrelation, continuous-time Markov chain, diffusion process, heterogeneity, hidden Markov model, molecular dynamics.

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Statistical Molecule Counting in Super-Resolution Fluorescence Microscopy: Towards Quantitative Nanoscopy

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Abstract. Super-resolution microscopy is rapidly gaining importance as an analytical tool in the life sciences. A compelling feature is the ability to label biological units of interest with fluorescent markers in (living) cells and to observe them with considerably higher resolution than conventional microscopy permits. The images obtained this way, however, lack an absolute intensity scale in terms of numbers of fluorophores observed. In this article, we discuss state of the art methods to count such fluorophores and statistical challenges that come along with it. In particular, we suggest a modeling scheme for time series generated by single-marker-switching (SMS) microscopy that makes it possible to quantify the number of markers in a statistically meaningful manner from the raw data. To this end, we model the entire process of photon generation in the fluorophore, their passage through the microscope, detection and photoelectron amplification in the camera, and extraction of time series from the microscopic images. At the heart of these modeling steps is a careful description of the fluorophore dynamics by a novel hidden Markov model that operates on two timescales (HTMM). Besides the fluorophore number, information about the kinetic transition rates of the fluorophore's internal states is also inferred during estimation. We comment on computational issues that arise when applying our model to simulated or measured fluorescence traces and illustrate our methodology on simulated data.

Key words and phrases: Molecule counting, super-resolution microscopy, quantitative nanoscopy, biophysics and computational biology, inhomogeneous hidden Markov models, statistical thinning.

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Data Denoising and Post-Denoising Corrections in Single Cell RNA Sequencing

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Abstract. Single cell sequencing technologies are transforming biomedical research. However, due to the inherent nature of the data, single cell RNA sequencing analysis poses new computational and statistical challenges. We begin with a survey of a selection of topics in this field, with a gentle introduction to the biology and a more detailed exploration of the technical noise. We consider in detail the problem of single cell data denoising, sometimes referred to as "imputation" in the relevant literature. We discuss why this is not a typical statistical imputation problem, and review current approaches to this problem. We then explore why the use of denoised values in downstream analyses invites novel statistical insights, and how denoising uncertainty should be accounted for to yield valid statistical inference. The utilization of denoised or imputed matrices in statistical inference is not unique to single cell genomics, and arises in many other fields. We describe the challenges in this type of analysis, discuss some preliminary solutions, and highlight unresolved issues.

Key words and phrases: Single cell biology, RNA sequencing, imputation, post-denoising inference, empirical Bayes, deep learning.

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Statistical Inference for the Evolutionary History of Cancer Genomes

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Abstract. Recent years have seen considerable work on inference about cancer evolution from mutations identified in cancer samples. Much of the modeling work has been based on classical models of population genetics, generalized to accommodate time-varying cell population size. Reverse-time, genealogical views of such models, commonly known as coalescents, have been used to infer aspects of the past of growing populations. Another approach is to use branching processes, the simplest scenario being the classical linear birth-death process. Inference from evolutionary models of DNA often exploits summary statistics of the sequence data, a common one being the so-called Site Frequency Spectrum (SFS). In a bulk tumor sequencing experiment, we can estimate for each site at which a novel somatic point mutation has arisen, the proportion of cells that carry that mutation. These numbers are then grouped into collections of sites which have similar mutant fractions. We examine how the SFS based on birth-death processes differs from those based on the coalescent model. This may stem from the different sampling mechanisms in the two approaches. However, we also show that despite this, they are quantitatively comparable for the range of parameters typical for tumor cell populations. We also present a model of tumor evolution with selective sweeps, and demonstrate how it may help in understanding the history of a tumor as well as the influence of data pre-processing. We illustrate the theory with applications to several examples from The Cancer Genome Atlas tumors.

Key words and phrases: Cancer evolution, coalescents, birth-death processes, site frequency spectrum, tumor heterogeneity, clonal selection, ploidy, bulk sequencing.

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Maximum Independent Component Analysis with Application to EEG Data

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Abstract. In many scientific disciplines, finding hidden influential factors behind observational data is essential but challenging. The majority of existing approaches, such as the independent component analysis (ICA), rely on linear transformation, that is, true signals are linear combinations of hidden components. Motivated from analyzing nonlinear temporal signals in neuroscience, genetics, and finance, this paper proposes the "maximum independent component analysis" (MaxICA), based on max-linear combinations of components. In contrast to existing methods, MaxICA benefits from focusing on significant major components while filtering out ignorable components. A major tool for parameter learning of MaxICA is an augmented genetic algorithm, consisting of three schemes for the elite weighted sum selection, randomly combined crossover, and dynamic mutation. Extensive empirical evaluations demonstrate the effectiveness of MaxICA in either extracting max-linearly combined essential sources in many applications or supplying a better approximation for nonlinearly combined source signals, such as EEG recordings analyzed in this paper.

Key words and phrases: Blind source separation, genetic algorithm, image analysis, nonlinear time series, optimization.

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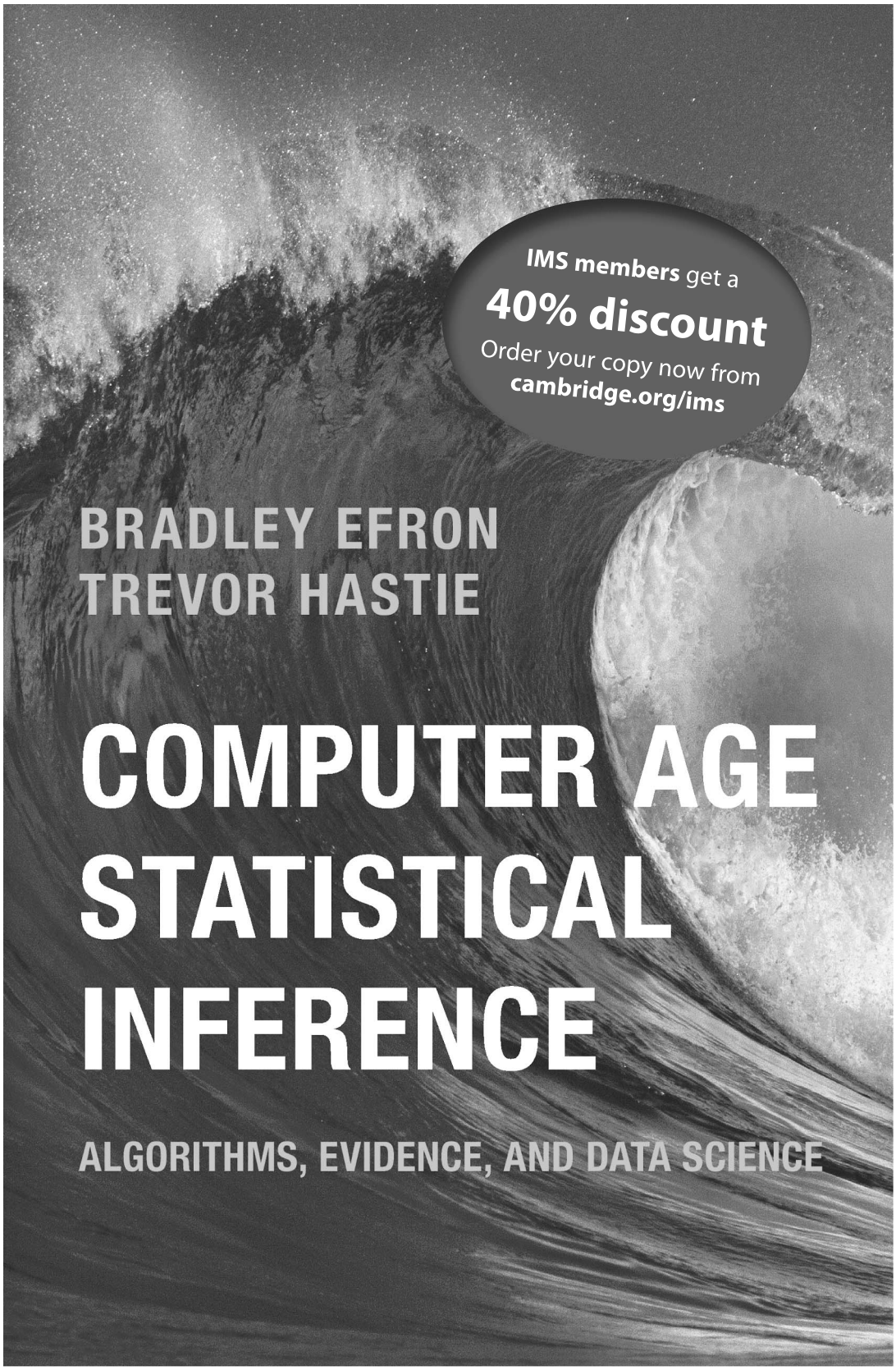
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