



## Bayesian statistics in medicine: A 25 year review<sup>†</sup>

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### SUMMARY

This review examines the state of Bayesian thinking as *Statistics in Medicine* was launched in 1982, reflecting particularly on its applicability and uses in medical research. It then looks at each subsequent five-year epoch, with a focus on papers appearing in *Statistics in Medicine*, putting these in the context of major developments in Bayesian thinking and computation with reference to important books, landmark meetings and seminal papers. It charts the growth of Bayesian statistics as it is applied to medicine and makes predictions for the future. From sparse beginnings, where Bayesian statistics was barely mentioned, Bayesian statistics has now permeated all the major areas of medical statistics, including clinical trials, epidemiology, meta-analyses and evidence synthesis, spatial modelling, longitudinal modelling, survival modelling, molecular genetics and decision-making in respect of new technologies. Copyright © 2006 John Wiley & Sons, Ltd.

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### 1. INTRODUCTION

An invitation to chart the growth of Bayesian statistics over 25 years for the 25th anniversary edition of *Statistics in Medicine* seemed a good opportunity to review areas of work I have much enjoyed, and to ensure that I was keeping up to date. I seriously underestimated how large a task this would be: from sparse beginnings, it seems there is now no area of medical statistics untouched by Bayesian approaches.

No review in the 21st century is complete without stating its methods. For the first 10 years of *Statistics in Medicine* I carried out a hand-search, and for the next 10 years was profoundly grateful to the annual indexers, looking at papers indexed by Bayes<sup>\*</sup>, BUGS, Computer packages<sup>\*</sup>, Full

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Bayes, Gibbs\*, Hierarchical Bayes, M(arkov) C(hain) M(onte) C(arlo), Posterior, Prior, Utility\* and WinBUGS, although scanning titles and occasional following back of references yielded some extra papers. Because the indexing became briefer, I returned to hand searching for 2002—mid 2006. I also hand-searched *Statistical Science* from 1986 to mid 2006, the review journal *Statistical Methods in Medical Research* from 1992 to mid 2006, and discussion papers of the Royal Statistical Society, the proceedings at the Valencia meetings 1–7, as well as collected volumes, and other key papers and reports of which I was aware. I did not carry out other systematic searching, partly for lack of resources, but mainly because any major trends were likely to have been represented in the main sources for this review.

This review starts by examining the state of Bayesian thinking as *Statistics in Medicine* was launched, reflecting particularly on its applicability and uses in medical research. It then looks at each 5-year epoch, with a focus on papers appearing in *Statistics in Medicine*, putting these in the context of major developments in Bayesian thinking and computation with reference to important books, landmark meetings and seminal papers. It aims to chart the growth of Bayesian statistics as it is applied to medicine: rather than giving a comprehensive introduction to Bayesian methods, key ideas emerge as they permeated into medical research with the references serving as a resource for those wanting more detail.

## 2. 1763–1981: A BRIEF HISTORY OF BAYESIAN STATISTICS

The Rev Thomas Bayes published his paper on ‘An essay towards solving a problem in the doctrine of chances’ [1] posthumously, thanks to the efforts of his friend Richard Price. At heart this is a simple result that most statistics students are taught as part of an early course in probability theory, but from the perspective of statistical inference Cox and Hinckley [2] describe it as providing a way of combining a prior distribution for a parameter with the likelihood to provide a posterior distribution for the parameter. They go on to explain that the mathematics can be made tractable by using conjugate distributions, which have the property that for a particular distribution for the data, the distributional form of the conjugate prior distribution and the posterior distribution are the same, with updated parameters. Three interpretations can be given to prior distributions: as frequency distributions based perhaps on previous data, as normative and objective representations of what it is rationale to believe about a parameter, or a subjective measure of what a particular individual actually believes. There are Bayesian versions of interval estimation, point estimation and significance testing. For large samples the posterior density is asymptotically normal, with a mean and variance that depends on the likelihood and not the prior.

The preceding paragraph pretty much summarizes my total formal education on the subject of Bayesian inference, having being studied in approximately three lectures in 1980 on an inference course based on Cox and Hinckley, which devoted one chapter to Bayesian inference. This does, in a brief paragraph, reference the work of Jeffreys, Good, Savage, de Finetti, de Groot and Lindley, whom I have learned since were influential figures in the development of Bayesian thinking. I did not know about texts such as Lindley [3, 4], Box and Tiao [5] or Raiffa and Schlaiffer [6] from which I could have studied further. Indeed, Cornfield had been advocating a Bayesian outlook in clinical trials since the 1960s [7–10]. A paper in 1981 [11] built on the work of Good and Card to develop ways of assessing utilities for clinical decision-making, foreshadowing much current work. However, as somebody starting her career in medical statistics just as *Statistics in Medicine* was in the planning stages, I suspect my knowledge of Bayesian thinking was fairly typical. Certainly

I learned no more about Bayesian statistics on a Master's degree in Medical Statistics; our course text, Armitage [12] contained just a couple of pages devoted to Bayes' theorem, including an application to medical diagnosis of congenital heart disease, and another couple of pages on likelihood from a Bayesian point of view. As an applied statistician I was soon more concerned with the practicalities of carrying out multiple regression and logistic regression on large samples than I was with alternative schools of inference that only seemed practicable in low-dimensional situations.

At a few other institutions, including University College, London, Bayesian statistics was being more thoroughly discussed during the 1970s. Bernardo [13] has documented the meetings of statisticians from different countries interested in Bayesian statistics, which prompted a meeting in Valencia in 1979, which was to be the first of a regular series. The proceedings of that meeting [14] show that much work presented was foundational or computational, but medical applications did feature in two papers, one on change-point problems including monitoring of kidney transplant patients and performance on a daily psychological test with a treatment switch at an unknown time-point [15], and the other on 'more ethical clinical trials', where allocation depends on clinical opinion for particular patients [16].

### 3. 1982–1986

In 1982 *Statistics in Medicine* was launched. In the same year, Peter Armitage gave his Presidential Address to the Royal Statistical Society on *Trials and Errors: The Emergence of Clinical Statistics* [17] highlighting the emergence of new journals in the areas, and also two new societies: the Society for Clinical Trials, and the International Society for Clinical Biostatistics. In proposing the vote of thanks, the previous President, David Cox, said, 'The spectacular growth of medical statistics recorded in the final sections of the address is very pleasing, intellectually exciting and, one trusts, socially valuable.' There was no mention of Bayesian statistics. In the same year, John Lewis read a paper to the Royal Statistical Society on '*Clinical trials: Statistical developments of practical benefit to the pharmaceutical industry*' [18]: the only allusion to Bayesian methods came from Newman's contribution to the discussion in which he made a plea for the use of prior probabilities and losses. In a paper [19] on geographic variations in cardiovascular mortality, neither the authors nor a single discussant raised the possibility of a Bayesian approach.

Despite this lack of profile, applied Bayesian work in medicine was starting to emerge. In 1982 the Institute of Statisticians had held their Annual Conference on Practical Bayesian Statistics, which was the first of several conferences on this theme. Papers subsequently published in 1983 in *The Statistician* covered a range of areas including education, insurance, law and hydrology. Medical applications included the monitoring of kidney transplant patients to detect discontinuities in creatinine levels signalling rejection [20], another on change-point models to detect ovulation [21], a paper on pre-screening of Beta-Thalassaemia carriers [22] and two papers on the assessment of subjective opinion, one in the context of developing stopping rules for clinical trials [23], one more general [24]. In 1984 Spiegelhalter and Knill-Jones [25] read a paper on clinical decision-support jointly to the Royal Statistical Society and the Computer Committee of the Royal College of Physicians. It uses, *inter alia*, independent Bayes, with weights of evidence as the logarithms of the Bayes factor and was the culmination of much collaborative work in the area.

In 1983, the second Bayesian meeting in Valencia was held. In the proceedings [26], again, many of the papers were foundational, with little medical work, beyond brief examples of data

sets such as time to vaginal cancer in rats [27], medical prescription data [28] and classifying infants' health on the basis of bilirubin [29]. A paper on survival analysis of cancer patients [30] was a more substantial attempt at a medical application, although criticized in the discussion on computational grounds.

The 150th anniversary of the Royal Statistical Society in 1984 was celebrated by a conference at which leading statisticians were charged with surveying their fields. David Newell's review of 'Medical Statistics' [31] was wide-ranging but made few comments on theoretical matters. However in his discussion of that paper, David Spiegelhalter advocated using available clinical judgement through a practical subjective Bayesian approach. Adrian Smith's review of 'Bayesian Statistics' [32] was largely foundational, but he also considered implementation, concluding that '...efficient numerical integration procedures are the key to the more widespread use of Bayesian statistics', conjecturing that Monte Carlo methodology and 'adaptive quadrature rules exploiting statistically motivated kernels' would lead to user-friendly packages, perhaps by 1990, and predicted that 'Bayes's theorem plus computer graphics would be the accepted form of statistical practice by the end of the century'. A landmark paper for Bayesian medical statistics was published in 1986 on applications of Bayesian methods in the pharmaceutical industry, showing applications to LD50 experiments, cross-over trials, historical information in bioequivalence studies and non-linear random-effects models in pharmacodynamic and pharmacokinetic modelling [33].

### 3.1. *Statistics in Medicine*

So given that Bayesian work on diagnostic systems, clinical monitoring and on various aspects of pharmaceutical work and clinical trials was beginning to appear, how much featured in *Statistics in Medicine*? The first volume in 1982 contained a paper proposing a Bayesian criterion for which patients to exclude from clinical trials [34]. 1983 and 1984 were follow years, apart from the use of Bayes theorem in a paper on clinical decision-aids [35]. However, in 1985, four papers used Bayes in contrasting ways: empirical Bayes was used to estimate cancer mortality rates in Missouri cities, shrinking estimates whilst accounting for age, sex and water source, although not spatial distribution [36]. Methods for follow-up used Bayesian Weibull models [37]. Two papers [38, 39] looked at issues in clinical trials: optimal designs for dichotomous responses and a comparison of Bayesian and classical approaches to interim analyses. The papers on cancer mortality rates and on interim analyses were each the first Bayesian papers in *Statistics in Medicine* on topics that would prove popular. 1986 seemed to be the breakthrough year for Bayesian statistics in *Statistics in Medicine*; the volume started with a paper on selecting the size of clinical trials [40] and included further papers on clinical trials explored decision-theoretic approaches [41] and probabilistic prediction [42]. One paper [43] made the case for Bayesian approaches to case-control studies, drawing on earlier work of Bayesian analyses of  $2 \times 2$  tables, and others continued the theme of computer-aided diagnosis [44–46].

Reviewing this work of this period, I am struck by the breadth of applications. However, it is also fair to say that most of the work was illustrative rather than the primary means of analysing the data, and was hampered by the lack of computational power affecting both the nature of the problems tackled, and in the depth to which analysis could be pursued.

## 4. 1987–1991

In 1987, *The Statistician* published another collection of papers arising from the second Institute of Statisticians meeting on Practical Bayesian Statistics. Work on computational approaches

needed to tackle realistic problems focused on numerical integration techniques [47], and Monte Carlo integration [48, 49]. Medical applications included hierarchical models in kidney transplantation [50], preclinical and clinical trials in the pharmaceutical industry [51, 52], expert systems [53] and survival data [54].

*Statistical Science*, which started in 1986, commissioned substantial articles on important topics, to be published with invited discussions. Breslow's 'Biostatistics and Bayes' [55] argued that Bayesian approaches were particularly appropriate for decision-making and regulatory contexts. Ware [56] described two controversial clinical trials of ECMO therapy in newborns, carrying out a Bayesian analysis. The discussion reveals deep division between Bayesians who believed that randomization was always unethical, and those who believed it had a role in the presence of uncertainty. In medical read papers to the Royal Statistical Society, Bayesian thinking was also beginning to appear: in a review of statistical methods to assess disease near a putative source of pollution, various discussants raised the possibility of Bayesian approaches [57], and in a paper on a repeated confidence interval approach to interim analyses, several discussants advocated the benefits of Bayesian perspectives [58].

#### 4.1. *Statistics in Medicine*

Despite the promise of 1986, 1987 was a lean year for Bayes in *Statistics in Medicine*, with only two papers, both developing the theme of the use of 'independent Bayes' for diagnosis [59, 60]. In 1988 there were papers, based on Normal approximations, advocating using a Bayesian approach to avoid a biased effect estimate after stopping a trial early [61], considering computational aspects of a Bayesian approach to two by two summaries from case-control studies, illustrating these with example of alcohol and oesophageal cancer, and DES and vaginal cancer [62] and on diagnosis of multiple diseases, avoiding assumption of independence [63]. Another [64] attempted a more highly dimensional problem of estimating treatment effects from 24-hour ambulatory blood-pressure monitoring, but could only adopt a 'partial empirical Bayes' approach because software could not deal with full empirical Bayes for an unbalanced experimental design. The floodgates now were opened, and from then on, Bayesian ideas featured regularly in papers in *Statistics in Medicine* either as the main approach, or as one approach being compared with others. The next three years saw work on diagnosis [65–67], screening [68], estimating disease prevalence from screening, or from administrative lists [69], describing and predicting the AIDS epidemic [70–72] predicting corneal transplants [73], comparisons of experimental techniques [74], phase III clinical trials [75–77], pharmacovigilance [78], ecologic regression [79], spatial and temporal mapping of cancer rates [80, 81], case-control studies [82], multiple testing [83], longitudinal data [84], change-point analysis for detection of ovulation [85] and investigation of respiratory effects of an environmental accident [86], renewal process [87] and large databases [88–90].

In papers written for the 10th anniversary of *Statistics in Medicine*, Simon commented in his review of 'Statistical Methods for Clinical Trials' [91] that the Bayesian debate seemed to be shifting from one of acrimony to a climate where highly respected and experienced clinical trial statisticians were exploring Bayesian ideas, although they had not yet achieved wide usage. In his parallel review of 'Statistical Methods in Epidemiology' [92], Gail flagged up Bayesian and empirical Bayes methods among statistical topics of potential importance for epidemiological modelling.

What had bought about these developments in medical statistics? It is instructive to compare the proceedings of the third [93] and fourth [94] Valencia meetings, respectively, held in 1987 and

1991. At the former, there had been a panel session on computation and Bayesian software: despite numerous programs available for various tasks [95], there was still a perceived need for general purpose software for various levels of sophistication of the user, but there was a sense that, with rapid developments in computing power, this might be about to happen [96, 97]. There were two medical papers, one advocating a Bayesian approach to randomized clinical trials [98], the other on analysis of LD50 experiments [99], each having derived methods for analysing the problems therein. In between, two key papers were published. The first, a read paper to the Royal Statistical Society [100], developed the work on expert systems presented to the Institute of Statisticians [53]. This laid the foundations for computations on graphical structures that would underpin modelling across a range of applications. The other [101] described the use of a technique known as Gibbs sampling, which, together with graphical modelling, would revolutionize computation and allow arbitrarily complex problems to be tackled.

By the 1991 Valencia meeting, the use of the Gibbs sampler was being thoroughly explored and exploited [102–108] and perhaps most significantly for applied statisticians, a computer package, BUGS, was launched [109], which combined graphical modelling [100] with the use of Gibbs sampling for carrying out the computations. Medical applications of Gibbs sampling included hierarchical models for meta-analysis [110], analysis of air pollution on health using logistic regression models allowing for measurement error [111] and to predictions of cancer in the lymph nodes based on five binary variables, and modelling infant sleep patterns [112]; other medical applications at the meeting included more on expert systems [113], and when to terminate a trial of an influenza vaccine [114].

## 5. 1992–1996

This was a time of serious expansion of applied Bayesian work. A third Institute of Statisticians Conference on Applied Bayesian Statistics was held in 1992, with the proceedings running to three issues of *The Statistician*. Medical application included graphical elicitation of priors for clinical trials [115], monitoring of clinical trials [116], drug safety [117], case-control studies in cancer epidemiology [118], back-calculation of the numbers infected in the HIV epidemic [119], dosage regimens in population pharmaco-kinetics [120], analysis of binary cross-over data [121] and modelling heterogeneity in environmental epidemiology [122].

This period was one of consolidation in a number of respects. For theory, two definitive works appeared in 1994 [123, 124]. For computational advances, a meeting at the Royal Statistical Society on the use of the Gibbs sampler covered both technical aspects [125] and applications in immunology, pharmacology, transplantation, cancer screening, industrial epidemiology and genetic epidemiology [126], the latter showing how such apparently diverse applications can be approach in a uniform way, building complex models from simple building blocks using conditional independence modelling. A subsequent edited volume showed the power of Markov chain Monte Carlo in practice [127]. And, after much debate, a Bayesian society was launched in 1992: the International Society for Bayesian Analysis.

There was also a sense of consolidation of thinking on some medical issues. In clinical trials, a Royal Statistical Society read paper on Bayesian analyses of randomized trials, using largely analytically tractable Normal approximations, bought together much of the work and thinking of that time on parallel group trials [128], and work on two-treatment cross-over trials had developed to account for one or two baselines, and an extra period [129]. An edited volume on Bayesian

Biostatistics [130] covered a general introduction and introductions to trials and epidemiology, as well as chapters on assigning probabilities, several on decision problems, on design, on model selection, and several examples of hierarchical models.

The fifth Valencia meeting was held in 1994 [131]. Although foundational and computational work was still prominent, applications were far more fully explored. A quick flick through the figures in the volume shows just how popular graphical modelling had become. A case study in breast cancer [132] raised the problem of working with disparate sources of information. A paper on meta-analysis [133], using both trial and observational examples, explored model-fit using cross-validation. Another used hierarchical models to identify extremes, including an application to hospital data [134]. Model uncertainty in survival analysis was explored using data from a lung cancer trial [135]. The flexibility of the conditional independence modelling using the BUGS package was illustrated with examples on a case-control study of cervical cancer, and spatial smoothing of lip cancer rates [136]. Pharmaceutical applications included dynamic longitudinal modelling [137] and hierarchical modelling of dose-ranging studies [138].

### 5.1. Clinical trials

In the next quinquennium *Statistics in Medicine* picked up many of these themes, and explored them further. It started with four papers on Bayesian analysis of cancer clinical trials [139–143], and carried papers from a meeting on ‘Methodological and Ethical Issues in Clinical Trials’ in 1992 where a major theme had been the Bayesian-frequentist debate [144–150]. A workshop on ‘Early Stopping Rules in Cancer Clinical Trials’ included Bayesian approaches [151–154]. Other papers on clinical trials covered dose-finding [155–160], monitoring phase I studies [161], screening treatments prior to phase II evaluation [162], sample size for phase II [163], selecting treatments for phase III evaluation [164, 165], monitoring phase II trials [166] bioequivalence [167, 168], sample sizes for equivalence trials [169], two-period cross-over allowing for baseline [170], randomization [171], adaptive assignment [172], monitoring of trials [173, 174], replication of evidence [175], reporting of clinical trials [176] and general commentaries [177]. In the regulatory context, European Notes for Guidance were published [178], which stated ‘Although this Note for Guidance is written largely from the classical (frequentist) viewpoint, the use of Bayesian or other well-argued approaches is quite acceptable’.

### 5.2. Meta-analysis

An early Bayesian paper on meta-analysis [179] was to be the first of many in *Statistics in Medicine*, using a model similar to a previously published analysis of multi-centre trials [77]. These and others [180] were early examples of the emergence of hierarchical models in the medical field, addressed more generally by Lange, whose expository paper outlined the connection between graphical models and GIBBS sampling [181]. Connections between the computational methods from the EM algorithm to Gibbs sampling, particularly in the context of longitudinal and random-effects models, were discussed [182], and their application to longitudinal data reviewed [183]. Jones [184] reviewed computational issues in meta-analysis, highlighting that empirical Bayes [185] had been used for some time, but that full Bayes was becoming available in convenient implementations [109, 186]. The use of meta-analysis in the design and monitoring of trials was illustrated with an obstetric example [187].

### 5.3. Empirical Bayes

Empirical Bayes was used or compared to other methods in applications to an audit of cervical smears [188], occupational cancer mortality [189, 190], cancer mapping [191], mortality in small geographic areas [192, 193], mapping mortality in the Netherlands [194], mapping Hepatitis B in Berlin [195], mapping mortality in Missouri [196] and mapping knee replacement rates in the U.S. [197] with extra-Poisson variation, mapping prevalence of non-rare conditions that do not follow a Poisson distribution [198] age-adjustment for mapping death-rates [199], estimating hospital-specific rates in the U.S. [200], multiple exposures [201], measurement errors in dietary assessments [202, 203], random effects models with binary response, repeated measures [204] longitudinal studies [205–208], analysis of dependent survival data in dentistry [209], prognostic modelling for kidney graft survival [210], modelling seasonal changes in seasonal affective disorder [211] estimating the HIV infection curve [212], modelling CD4 trajectories in HIV [213] and cross-over trial [214]. Links between empirical Bayes and penalized likelihood techniques were reviewed in the context of smoothing of gastric cancer rates in Nova Scotia [215].

### 5.4. Markov chain Monte Carlo

The advances in GIBBS sampling and related techniques opened up new possibilities and started to appear in papers including work on suppressor genes in bladder cancer [216], transition rates between disease states in coronary heart disease [217, 183], analysing a series of  $2 \times 2$  tables from a case-control study [218], predicting HIV status from a diagnostic test and covariates [219], screening for HIV using variety of sampling schemes [220], estimating the CD4 distribution at the time of AIDS diagnosis [221], modelling the effect of zidovudine on CD4 counts in HIV [222], modelling CD4 counts and censored survival times in AIDS simultaneously [223], within-family transmission of HiB bacteria [224], measurement error in epidemiological studies [225], bivariate survival data [226] survival on multiple time scales (age-period cohort models) [227], missing data in hazard regression [228], random coefficient regression modelling [229], repeated measures experiments [230], and pharmacokinetic and pharmacodynamic modelling [231]. A special issue devoted to the growing area of spatial disease patterns illustrated the impact of powerful flexible Bayesian modelling in smoothing, modelling heterogeneity and clustering and accounting for temporal as well as spatial trends [232–237]. Gibbs sampling enabled the modelling of population risk in meta-analysis, avoiding the problems of bias due to measurement error [238], and the incorporation of external trials to the meta-analysis to better estimate the heterogeneity [239]. A fully worked example of meta-analysis compared both non-Bayesian and Bayesian approaches [240], providing one of the first medical examples of a complex analysis using the general-purpose Bayesian package, BUGS [109].

### 5.5. Other applications

Other Bayesian papers included medical diagnosis [241], modelling birth-weight distribution [242], estimating vaccine efficiency [243], screening for an autologous tumour vaccine trial [244], more on understanding or treating the AIDS epidemic [245–247], predictive models for cardiac death [248], repeated-measures data on multiple reaction time [249], misclassification of cause of death in competing risk models [250], model choice in a depression prevention trial [251], multiple comparisons [252], optimal experimental design [253–255] and interpreting medical studies [256].



These 5 years were seminal in the development of applied Bayesian work in medicine, with a rapid shift from reasonably straightforward conjugate analyses, through to problems characterized by complex structures. At the end of this epoch, in 1996 van Houwelingen [257] gave an invited talk at the International Society for Clinical Biostatistics entitled 'The Future of Biostatistics: Expecting the Unexpected' in which he saw that graphical chain modelling, random effects modelling and faster computational methods including Markov chain Monte Carlo would play an important role. Although computational advances were revolutionizing statistical work on many fronts, Bayesian techniques were now competing with them, and offering advantages in terms of flexibility and coherence.

## 6. 1997–2001

The sixth Valencia meeting was held in 1998 [258]. Computation continued to be an important theme at the meeting, but with increasing model complexity, issues of model checking, choice, comparison and diagnostics were also becoming more prominent. There were relatively few medical examples, although work on spatial modelling included medical examples [259, 260]. Decision-making was applied to screening for breast cancer [261] and to sequential methods for clinical trials [262].

In contrast, meetings and read papers from the Royal Statistical Society at this time show statisticians using Bayes to address genuinely complex medical applications: a meeting on analysis of complex sample surveys included a contribution on longitudinal binary data from a two-phase survey of dementia, showing how conditional independence models can cope with both the sampling and missing data [263]. Another meeting on disease clusters and ecological studies included various Bayesian developments [264–266]. A read paper showed a very detailed examination of projections of the AIDS epidemic [267], and another used hierarchical modelling to combine evidence on air pollution and daily mortality in the 20 largest U.S. cities [268]. In the burgeoning area of molecular population genetics, another read paper compared algorithms based on importance sampling and Markov chain Monte Carlo in making inference [269]. In contrast to earlier read papers on clinical trials, one focusing on trials in the pharmaceutical industry addressed head on the Bayesian-frequentist debate and the extent to which Bayesian methods were or were not making inroads [270]. The review journal *Statistical Methods in Medical Research* included a comprehensive review of Bayesian meta-analysis, meta-regression and the newer area of evidence synthesis where all pertinent studies are directly and jointly modelled, even if they are of contrasting design [271]. The seriousness with which Bayesian methods were being taken was exemplified by the commissioning of a review of Bayesian methods in Health Technology Assessment by the new U.K. Health Technology assessment programme. The resulting report [272] was subsequently developed into a book [273].

### 6.1. *Statistics in Medicine*

In papers in *Statistics in Medicine* for this period, the explosion in Bayesian work really became apparent. Conventional territory was revisited from a Bayesian perspective, including sample size for experiments [274], analysis of  $2 \times 2$  tables using relative risk, odds ratio and attributable risk [275] and the proportional hazards model [276]. Work on diagnosis using independent Bayes compared it with the more recent Classification and Regression Tree methodology [277]. But the

areas of clinical trial, meta-analysis and spatial analysis had each spawned a range of work in the journal; these are reviewed in turn, before looking at the rapid developments in computational techniques.

### 6.2. *Clinical trials*

Work on clinical trials continued with accrual strategies for phase I trials [278], optimal design for dose-response experiments [279], more work on the continual reassessment method [280–283], patient specific dosing in phase I cancer trials [284], dose-escalation when the event is lagged [285], interim analysis of phase II cancer clinical trials [286, 287], evaluation of results in a subgroup [288], allocation of significance levels for multiple endpoints based on prior information [289] and choice of sample size and allocation taking into account utilities [290], or sample size based on costs [291], and bias reduction in vaccine trials [292]. Implementation of Bayesian data-monitoring for phase III trials was becoming a reality [293], with new work on quantifying and documenting prior beliefs for use in monitoring [294] and on predicting analysis times [295]. A radical departure was the monitoring of an ‘open’ trial where results were regularly fed back to investigators [296]. Group-sequential methods for cure rate models were developed [297]. Cost-effectiveness analysis could be incorporated [298, 299]. Bayesian methods were developed for cluster-randomized trials with continuous [300] and binary responses [301], and could incorporate pre-intervention data [302]. The analysis of ordinal data was illustrated with a trial of treatments for allergic rhinitis [303].

In the drug regulatory context, the European guidelines [178] had formed the basis of international guidelines [304]. Although still predominantly classical in flavour, the Bayesian section was expanded slightly: ‘the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust’ Bayesian approaches were defined in the glossary as ‘Approaches to data analysis that provide a posterior probability distribution for some parameter (for example, treatment effect) derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is used as a basis for statistical inference’.

### 6.3. *Meta-analysis*

Meta-analyses could deal with increasing complexity including grouping trials such as open and closed trials in epilepsy [305], and evaluating surrogate markers for AIDS [306]. An application for paired binary data comparing the effect of radiation with surgery on recurrences in the treatment of rectal cancer showed the advantages of Bayes over other methods in dealing with nuisance parameters [307]. Heterogeneity was a developing theme, starting with testing for heterogeneity using Bayes factors [308]. A paper on underlying risk as a source of heterogeneity in meta-analysis in trials of sclerotherapy for cirrhosis continued this theme, but used the freely available general purpose package BUGS which the authors claimed made the technology ‘realistically available to applied researchers undertaking meta-analysis’ [309]. This work was then developed further [310] with a tutorial on meta-analysis comparing different approaches [311] and a method comparison for explaining heterogeneity in meta analysis [312]. Incorporation of prior data, especially in a regulatory setting, can provide challenges [313]. Hierarchical models lend themselves to meta-analyses using continuous [314] and ordinal [315] individual patient data. Meta-analysis of diagnostic tests was considered [316]. Building on meta-analysis, which is used to combine similar studies, the idea of generalized evidence synthesis

was emerging, where disparate sources of data could be combined, for example to evaluate breast cancer screening using randomized and non-randomized studies in a hierarchical model [317]. Multi-centre trials have a hierarchical structure similar to meta-analyses; a review of methods [318], method comparisons [319], and an exploration of institutional effects [320] showed the impact of Bayesian methods in their analysis. The idea of institutional rankings began to emerge, with both empirical Bayes and full Bayes giving the means to produce shrunk estimates which lead to more robust rankings [321] and hierarchical models used to capture different levels of variation in health service research for cardiac procedure utilization following myocardial infarction [322].

#### 6.4. Spatial analysis

Spatial data was another rich area for Bayesian development although mapping estimates, Bayesian or not, are not without their problems [323]. A review of issues in the analysis of small area health data shows the impact Bayesian methods have made in providing a systematic framework [324]. Work included identifying geographical areas with excess incidence of leukaemia [325], mapping of lung cancer mortality in Ohio with errors in covariates [326], and combining longitudinal and spatial data [327] built on previous work on mapping spatial smoothing of survival from breast cancer and malignant melanoma [328]. Other applications included spatio-temporal analysis of lung cancer rates in Missouri [329]. Conditionally autoregressive models, which allow each site to 'borrow strength' from its neighbours were used for lip cancer in Scotland [330], and asthma mortality in Taiwan [331]. A special issue of *Statistics in Medicine* on 'Disease Mapping with a Focus on Evaluation' included many papers describing Bayesian modelling [332–349], in several cases presenting reanalyses of the lip cancer data. These data featured, along with breast cancer data from Sardinia and infant mortality data from British Columbia in methodology using mixture models to identify high-risk areas [350]. An analysis of diffusion and prediction of Leishmaniasis in Brazil used hierarchical models to explore space–time interactions [351] and Bayesian testing for the presence of a cluster was proposed [352]. It was no surprise that Bayesian methods featured strongly in a *Statistics in Medicine* tutorial paper on disease mapping [353].

#### 6.5. Computational developments

As the wish to deal with large complex problems grew, computation continued to prove a challenge, trying to find a balance between efficient procedures and the still slow Markov chain Monte Carlo approaches, for example for hierarchical models for cancer mortality [354] and for meta-analysis [355]. In a review of methods for ordinal categorical data, the large number of nuisance parameters were still considered an issue for Bayesian modelling [356]. Microsimulation was used to investigate timing of prostate specific antigen screening on prostate cancer mortality rates [357]. An approximate Bayesian bootstrap was used to analysis interval censored data from a trial of different treatments for breast cancer [358].

Empirical Bayes was still appearing, either as the main thrust of the paper, or as an adjunct to more classical analyses: examples include multiple outcomes in large epidemiological studies [359], adjusting for measurement error in biomarkers using empirical Bayes-like estimators [360], parametric models for survival times in HIV when examination times and survival are not independent [361] estimating the number of HIV—infected individuals in hidden and elusive populations [362] modelling overweight prevalence whilst adjusting for sample selection [363], in a clinical trial

of beta-interferon for multiple sclerosis using robust mixed linear models [364], genetic analysis of the age at menopause [365], in quality control for longitudinal studies [366], reliability of cognitive tests for Alzheimer's disease [367] measuring cognitive change in patients with Alzheimer's disease [368], and modelling bivariate measures with different change-points in Alzheimer's disease [369].

More complex designs or issues were increasingly being studied mainly by full Bayesian approaches based on Markov chain Monte Carlo techniques including population pharmacokinetic modelling [370], population approaches to dose selection [371], prevalence estimates for depression in adolescents from two-stage sampling [372], bivariate survival models to jointly model hospital stay and community stay in assessing the effect of insurance policies on mental health care [373], hierarchical models to examine predictors of results in oral practice examinations in anaesthesiology [374], prevalence surveys in HIV accounting for imprecision in sensitivity and specificity [375], developing medical guidelines for coronary angiography following acute MI [376], back-calculating the time of transmission of HIV from mother to child [377], back-calculating age-specific incidence of HiB [378], classifying individuals based on predictors of random effects in HIV/AIDS [379] and risk of HIV infection as a function of duration of intravenous drug use [380]. Longitudinal models were developed further to cope with unequally spaced observations [381], and shrinkage estimates of immunological progression rates in HIV [382]. Semi-parametric random-effects models that could handle non-normal correlated errors was illustrated using data on the presence or absence of respiratory infection in Indonesian children [383]. Discrete-time Markov models were used for progression of diabetic retinopathy to assess costs and benefits of screening and treatment strategies [384]. Errors-in-measurement was a continuing theme, with work on mis-specification of priors [385] and analysis of change-points with measurement error [386], as was incomplete or missing data [387–392]. Analysis of hyperparathyroidism in haemodialysis patients required mixed models for bivariate response data that could also account for missing data due to drop-outs [393]. Optimal design for timing of stem cell collections could use longitudinal random-effects modelling [394]. Hierarchical change-point models were used for prostate specific antigen as a marker for prostate cancer [395], modelling cumulative false-positive rates for repeated breast screening [396] and detecting interactions in covariates in case-control studies in cancer [397]. A partial Bayes approach was used for the assessment of drug dissolution equivalence [398]. Dynamic linear modelling was used for forecasting hepatitis A and malaria rates [399]. Causal modelling began to appear with work on generalized population attributable fraction [400].

Papers using BUGS software in a variety of modelling began to appear although for some problems, other algorithms would still be needed [401]. Examples of BUGS or the newer WinBUGS included work on binary longitudinal data [402, 403], autoregressive models for handling non-linear changes in peak flow rates [404], analysis of ambulatory blood pressure monitor data allowing for heterogeneous within-subject variances [405], back-calculating age-specific cancer incidence rates from cancer mortality rates [406] and genetic markers for recurrent fetal loss [407]. Determination of sample size in hierarchical models was illustrated by a study of quality of care in congestive heart failure [408]. Some of the work already referred to in clinical trials [285, 298, 300–303] and much of that in meta-analysis [307, 309–312, 314–317] and spatial modelling [328, 331, 336, 345, 348, 350, 351] also used BUGS or WinBUGS. Despite computational advances there were still advocates for data augmentation techniques which enable Bayesian and semi-Bayes analyses through conventional software packages [354].

### 6.6. *Model critique*

With increasing model complexity, model criticism and model selection becomes more challenging. Work included assessing the goodness-of-fit of longitudinal models examining influences on infant weight-gain in Ethiopia [409], Bayes factors for hierarchical models [410], for mixture likelihoods, for example to identify low birth weight babies in the Third World [411] to choose among survival models for time to natural abortion for dairy cows [412] and for analysis of survival model with a surviving fraction [413]. Even prior to its publication, the Deviation Information Criteria [414] also began to make an appearance, for spatio-temporal data [335]. Variable selection and model averaging was demonstrated in a case-control study of cervical cancer [415].

A review of quality of life with missing data in cancer clinical trials [416] reviewed Bayesian as well as non-Bayesian techniques. A review of advances in HIV/AIDS statistical methodology showed that Bayesian thinking had become a part of the mainstream for complex problems [417]. More generally, the Bayesian paradigm was argued to be a natural statistical framework for evidence-based medicine [418]. Despite the proliferation of applied Bayesian work in the statistical literature, and its acceptance, at least in principle, by international drug regulatory authorities, Altman [419], in a review of recent trends in the medical literature, could find little evidence of Bayesian work, although using a wider selection of search terms than Bayes\* might have yielded a few more articles. However, given the explosion of Bayesian work in *Statistics in Medicine* over this 5-year epoch, it seems highly fitting that the last issue of volume 20 should open with an introduction to Bruno de Finetti and his work [420].

## 7. 2002–2006

Previous sections have started by reviewing general developments, and then seen what *Statistics in Medicine* had covered. The work in this epoch is largely applications-driven, and so it is easier to review it chiefly through the work in *Statistics in Medicine*, bringing in work published elsewhere from time to time.

### 7.1. *Clinical trials*

In *Statistics in Medicine*, Bayesian approaches to clinical trials from early phases onwards now appear regularly. A review of phase I designs included Bayesian approaches. Further work continued on the continual reassessment method [421], appropriate interval estimation for the probability of toxicity at the maximum tolerated dose from CRM designs [422] and adaptive dose-finding [423]. Hierarchical modelling was used for population toxokinetic analysis [424]. Optimal designs with utilities were used to choose doses of chemotherapy in lung cancer [425]. Dose escalation with overdose control was proposed in cancer phase I trials [426]. Concomitant information in bioassay can be incorporated in a semi-parametric model [427]. Dose-finding designs accounted for two endpoints using utilities [428, 429] and Bayesian designs for dose-escalation studies in healthy volunteers were compared [430]. Bayesian phase II designs were compared to Simon two-stage designs [431]. A hierarchical model allowing for subtypes is used for phase II trials in diseases with multiple subtypes such as sarcoma [432]. Outcome-adaptive randomization is proposed to overcome ethical dilemmas of patients being randomly allocated to inferior treatments [433].

In phase III, a Bayesian approach was used to estimate the proportion of treatment effect captured by a surrogate marker [434] and for assessment and monitoring of trials with

distinctive survival curves uses Bayesian Weibull modelling [435]. Markov chain Monte Carlo allowed models to include the joint response of quality of life and survival [436]. Complexities in AIDS clinical trials handled using Bayes included longitudinal modelling for monitoring of MCV to assess compliance to AZT [437], and non-linear mixed-effects modelling of viral load allowing for missing data [438]. Missing repeated-measures data in asthma trials was modelled using BUGS [439]. Treatment failures could be handled using a counter-factual approach [440]. In a paper assessing reproducibility of trials for regulatory submissions, a Bayesian approach was one of three tried [441]. In active equivalence trials in breast cancer and heart disease, a Bayesian approach was used to model the efficacy of control over placebo and thereby indirectly assess the probability of the efficacy of the new treatment [442]. Bayesian subset analysis was illustrated with treatment-by-gender interactions in trials [443]. Prior opinions on the influence of patient characteristics could be used to look at subgroup analyses of clinical trials [444]. A model for ordinal response in a multi-centre trial of therapies for MI was used to demonstrate heterogeneity across centres that limited generalizability [445]. Heterogeneity in treatment effect over centres was investigated in a trial in bladder cancer [446]. A Bayesian approach for multivariate mixed outcomes was used to set objective performance criteria against which to judge medical devices in single arm trials, illustrated by stenting in diabetics [447]. Futility analyses were used to stop unpromising trials to redirect resources [448], for repair of inguinal hernias [449] and for schizophrenia [450]. Cost data was modelled parametrically [451]. Binary data from cluster randomized trials could be analysed directly on the risk scale [452] and adjusting for baseline imbalances in repeated cross-sectional cluster randomized trials could account for baseline heterogeneity [453]. Imprecision of the intracluster correlation coefficient was allowed for in design of cluster randomized trials [454], and interval estimates obtained from modelling [455]. Bayesian methods provided a way of analysing rate-ratios of repeated events in cluster-randomized trials against trachoma [456]. Ideas of value of information were used to choose sample size [457]. A cost-related approach was used to evaluate whether to continue with a drug development program [458], and costs of technologies such as asthma treatments were modelled using ideas from analyses of extreme values [459]. Adaptive randomization in a sarcoma trial was achieved using covariate-adjusted randomization [460]. Multiple imputation under smoothed pattern-mixture models was used for non-ignorable drop-out in clinical trials [461]. A hierarchical logistic regression was used for binary longitudinal outcomes in a trial of severe chronic constipation with non-linear treatment effects, heterogeneity and a high proportion of non-responders [462]. In addition, reviews in *Statistical Methods in Medical Research* showed different approaches to Bayesian sample size determination [463]; approaches to phase II design were explored [464], as were approaches to multi-centre trials [465]. There was still relatively little about safety, but multi-item gamma Poisson shrinkage was used to analyse vaccine adverse event reports [466].

## 7.2. Meta-analysis, meta-regression and evidence synthesis

Meta-analysis in clinical trials using Bayesian techniques was by now well-established, and papers in *Statistics in Medicine* for this epoch were mainly exploring extensions to the basic model. Bayesian fixed effects models were proposed as a way of avoiding complexity [467]. The Bayesian fixed effects model performed well in a comparison of methods for sparse-data in meta-analysis [468]. Meta-analysis using intrinsic priors were proposed [469]. When carrying out meta-analysis of binary data, advantages included being able to model directly on the

risk difference and risk scales, if required [470]. Mixed treatment comparisons, combining direct and indirect evidence were illustrated using data on non-surgical treatments in cirrhosis [471]. The sensitivity of meta-analysis to varying degrees of vagueness in priors was assessed [472]. The analysis of *N*-of-1 trials, both within and between patients was handled in a hierarchical model [473]. A paper proposing measures of heterogeneity in meta-analysis included Bayesian versions which performed well in comparison to other approaches [474]. Meta-analysis of heterogeneously reported trials was handled within a fully Bayesian model [475]. Meta-analysis of observational studies allowed investigation of association of genetic factors with heart disease [476]. Extensions to multivariate meta-analysis allowed joint modelling of the effects of parental smoking on both asthma and lower respiratory disease [477]. Multivariate meta-analysis was also used to combine genetic studies using Mendelian randomization [478]. A tutorial paper on meta-regression included Bayesian hierarchical modelling [479]. Work on interpretation of meta-regression took a Bayesian stance [480]. Multiparameter evidence synthesis, which generalizes meta-analysis, was illustrated by combinations of data on thrombolytic therapy following MI [481]. Uncertainty about cost-effectiveness data could be included, as could sensitivity analyses [482].

### 7.3. *Observational studies*

Bayesian approaches were used in a variety of observational studies, from non-randomized animal experiments, through conventional epidemiology to health service data. Log-normal modelling was used for hearing loss in evaluation of surgery on guinea-pigs [483]. Latent mixture modelling for multivariate categorical data was used to compare tooth cleaning efficiency with different brushes [484]. Most analyses of case-control studies use a 'rare-disease' assumption, but Bayesian methods were proposed to enable more direct estimation of quantities of interest [485]. Bayesian model averaging was used as an alternative to stepwise logistic regression for prediction of coronary heart disease [486]. Logistic regression was extended to cope with diffuse interactions when looking at numerous explanatory variables for heart disease [487]. Models for assessing the role of mediators, through which risk factors exert their effect, in observational epidemiology compared Bayesian approaches to those from Structural Equation Modelling [488]. A simultaneous equations modelling framework was used to show birthweight has little structural or causal effects on early childhood development outcomes [489]. Hierarchical modelling was used to account for different levels of variation in peak expiratory flow data in atopic and non-atopic children [490]. Complex modelling could allow for bivariate ordinal data in diabetic retinopathy [491, 492]. Vaccine efficiency was estimated based on auxiliary outcome data, and a small validation sample [493]. Design of observational health care studies allowing for clustering was addressed [494]. A Bayesian Box-Cox random coefficients model was used for risk-adjustment of hospital costs [495]. Assessing the impact of provider-level ascertainment bias when profiling nursing homes uses data from a reliability study [496]. At the seventh Valencia meeting held in 2002 [497] medical work included causal inference with a medical application to the effect of maternal smoking on her child's birthweight [498].

### 7.4. *Longitudinal*

Modelling of longitudinal data is handled naturally using conditional independence models, and this was a real growth area. Poisson modelling was used to explain differences in small area hospitalization rates for respiratory conditions [499]. Time-series modelling was used for voluntary

abortion data from Italy [500]. Hierarchical models were used for longitudinal profiles of health care providers [501]. Binary latent variable modelling was used to assess the impact of air pollution on multiple binary outcomes in Hong Kong [502]. The Bayesian information criterion was used for model comparison of generalized linear mixed models from a longitudinal study of the health effects of air pollution, and a set of retrospective studies on lung cancer and pollution [503]. Generalized monotonic regression with random changepoints was used to model expression of a leukaemia surface antigen in relation to prognostic factors [504]. Modelling of a random effects covariance matrix was used in longitudinal studies of depression [505]. A hierarchical Bayesian birth cohort analysis was used for trends in the age of onset of Type I diabetes [506]. Tolerance intervals for reference ranges were developed for tracking viral load in people in different populations infected with HIV [507]. Non-linear random-effect models with continuous time autoregressive errors were used for modelling plasma volume on gestational age in pregnancy [508]. Adherence to medicines was modelled using structural equation modelling for dichotomous variables [509]. Stochastic modelling was used for transmission between disease states to model effect of risk factors on progression to leukoplakia then oral cancer [510]. Calibration of a change of machinery during a longitudinal study was applied for bone mineral density estimation [511]. Graphical models were used to model multivariate time series from intensive care monitoring [512].

### *7.5. Survival modelling*

Bayesian models for survival data had been used for along while. This theme continued, but often in conjunction with modelling other features of the data. An observational study modelled survival and pulmonary function in cystic fibrosis allowing for non-ignorable non-response using Empirical Bayes [513]. Joint modelling of non-linear longitudinal biomarkers and event time outcomes were used to predict cancer recurrence in prostate cancer from PSA levels [514]. Modelling of bovine abortion and foetal survival used mixture modelling allowing for herd effects and incompletely observed data [515]. Survival data with a non-susceptible fraction and dual censoring mechanisms were used in Huntingdon's disease, where not everyone inherits the gene [516]. Discrete time survival modelling was used for registry data on haemodialysis patients [517]. Estimation of cost-effectiveness from censored data was applied in cardiovascular disease [518]. A neural-Bayesian approach was used to improve predictions from Cox survival analysis [519]. The clinical course of bone metastases in women with advanced breast cancer was investigated using models for multivariate interval censored recurrent events [520]. Modelling risks of a second complication following a first complication of diabetes used conditional modelling and survival models [521]. Recurrent events such as infections in patients with an inherited immune disease were modelled using time-dependent frailties [522]. Correlated frailty models were used to analyse risk factors in bilateral corneal graft rejection [523]. Proportional hazards models with time-varying regression coefficients were illustrated in a study of ovarian cancer patients [524]. Dental restorations involving clustered grouped survival data were modelled using multilevel Cox regression [525]. A pattern-mixture model was used for repeated measures quality of life with right-censored survival times in a trial of congestive heart failure [526].

### *7.6. Missing data and misclassification*

Another theme that continued to be developed is that of missing data and misclassified data, where conditional independence models can allow for this aspect in addition to the main underlying model. Full-likelihood modelling allowed for misclassification of an exposure in matched



case-control studies [527]. Misclassification in binary outcome variables was assessed using prior data and expert opinion, to improve the modelling of effects of a smoking cessation program among pregnant women [528] and modelled via a validation substudy for a study of smoking and myocardial infarction [529]. Measurement error and missing data in a case-control study of radon exposure and leukaemia were handled via hierarchical models [530]. Other work on missing data included complete imputation of missing repeated measures data [531] and comparisons of methods including Bayesian least squares [532]; other work on measurement error included imperfectly observed transitions in a study of depression in adolescents [533] and on-ignorable non-response in binary data [534], and in  $r \times c$  tables [535]. A case-study of informative drop-out, non-ignorable non-compliance and repeated measures was presented on a trial of different psychotherapies [536]. Imperfect ascertainment in cancer studies was handled by extending latent class methodology [537]. Misclassification in binary risk factors in prospective studies was handled via a three-part model for disease, exposure and misclassification [538]. Analysis of risk factors for anovulation employed models that allow for imperfect measure of outcome [539]. Intuition about the effect of misclassification was shown to be in conflict with the results of a full Bayesian analysis [540].

### 7.7. *Diagnosis and screening*

Diagnosis and screening are areas for which conditional probabilities are fundamental, so Bayesian approaches are very natural. Tumour grading from magnetic resonance spectroscopy was approached using multivariate Bayesian selection [541]. Prediction of an individual's disease status and population prevalence, using several similar diagnostic tests, used robust Bayesian prediction [542]. Estimation of diagnostic test accuracy for tuberculosis and *toxoplasma gondii* were compared using various distributional assumptions [543]. Multivariate hierarchical transformation models were used for ROC analysis for biopsies in prostate cancer [544]. Diagnosis avoiding the use of cut-offs was applied to detecting abortion in cattle [545]. Estimating disease prevalence in the absence of a gold standard test was carried out using conditional independence modelling using the results of two diagnostic tests [546] and using prior information and stratification [547]. Sample size calculations could be performed in the same situation [548]. Estimating the proportion of women with gestational diabetes based on two sources employed capture-recapture sampling whilst allowing for measurement error [549]. Evaluation of breast cancer screening synthesized data from two studies [550] and examined accuracy of screening mammography uses an event order model [551]. Bayesian regression model averaging was used to estimate the false negative fraction in a two-stage multiple screening test for bowel cancer [552].

### 7.8. *Spatial and spatio-temporal modelling*

Work in disease mapping continued, and increasing modelled both spatial [553] and spatio-temporal [554] aspects. A model for fertility schedules allowing for space-varying parameter was used to model low-fertility behaviour in Brazil [555]. Spatial smoothing was used to investigate geographical variation in late detection of breast and colorectal cancer [556], in modelling of small areas rates of non-rare diseases [557], and in short-term prognosis after acute myocardial infarction [558]. Spatial effects in time-to-event data were used to look at effect of area of residence on time to coronary artery bypass grafts while adjusting for individual level covariates [559]. Cross-validatory predictive checking was illustrated for disease-mapping models, but is applicable to hierarchical models more generally [560]. Reversible jump MCMC was used to allow for fixed

clustering effects associate with certain areas for leukaemia [561]. Controlling for multiple health providers was included in a study of respiratory disease near cokeworks [562]. Child mortality in Nigeria was analysed using geoadaptive discrete time survival models [563]. The time-lag between socioeconomic factors and lung cancer mortality was investigated using space–time models with time-dependent covariates [564]. Colorectal cancer incidence was modelled using a semi-parametric temporal spatial model incorporating age and gender effects [565]. Simulation was used to compare three Bayesian procedures for cluster detection diagnostics [566]. Simultaneous inference on multiple scales in spatial epidemiology was illustrated by Tuscan gastric cancer data at various levels of aggregation [567, 568]. A cluster model for space–time disease counts used reversible jump Markov chain Monte Carlo in Japanese breast cancer mortality [569]. The impact of prior choice on local Bayes factor for cluster detection was compared on breast cancer incidence from Wisconsin [570]. A novel approach to cluster modelling was proposed for environmental surveillance [571]. A special issue of *Statistical Methods in Medical Research* was published, with empirical and full Bayes, [572] and extensions to joint mapping of multiple diseases [573–575]. At the 7th Valencia meeting held in 2002 [497] spatial modelling was extended to spatio-temporal survival modelling in multiple cancers [576].

### 7.9. Infectious disease modelling

Modelling of the HIV epidemic continued [577]; Markov modelling was used for changes in HIV-specific cytotoxic T-lymphocytes in untreated patients [578] and back-calculation using a multi-state model is used to estimate HIV incidence [579]. For other infectious diseases, hierarchical modelling was used for spatio-temporal modelling of influenza [580]. A method for estimating heterogeneous transmission with multiple infectives was illustrated for secondary attacks of pertussis following vaccination [581]. Estimating incidence of subclinical infections with Legionnaire's disease used data augmentation [582]. Prediction of meningococcal disease outbreaks in structured populations was used to inform information collection in the event of an actual outbreak [583]. Time to colonization of MRSA in an intensive care unit was modelled using priors on the first or second difference to smooth the hazard function [584]. Transmission of influenza was modelled within households [585], and transmission of gastroenteritis within schools [586]. Estimating the duration of malaria infection when detectability of the parasite was imperfect was achieved via immigration-death modelling [587]. The SARS epidemic prompted modelling of the probability of failing to detect and infectious disease at entry points to a country [588].

### 7.10. Molecular genetics

At the 7th Valencia meeting held in 2002 [497] a major theme was analysis of data generated from genetic microarray technology [589–593]. Elsewhere, statistical work in gene expression in microarray data [594], and DNA sequence segmentation [595] showed the power of modern Bayesian methods to deal with these highly structured problems, which in turn lead to further computational challenges [596].

In *Statistics in Medicine* this work has not yet made a big impact, but data from DNA microarrays were analysed using empirical Bayes to reduce the dimensionality whilst allowing for relative lack of replication [597, 598], tree-based models for homogeneous groupings of multinomials were illustrated on genetic sequence data [599] and genetic model-free approach was used for the meta-analysis of genetic association studies [600].

### 7.11. Decision-making

The development of Bayesian statistics is closely related to formal decision-making, but applications have been relatively rare so far. In clinical decision-making, Bayesian procedures were tested against other in detection of acute disease events in lung transplant patients, and found to perform well [601]. The additional value of information provided by axillary lymph node detection on breast cancer was assessed using an expected utility approach [602]. More generally, Bayesian methods for decision-making in health were reviewed [603] and proposals were made for bridging the gap between statistical analysis and decision-making in public health [604]. A review in *Statistical Methods for Medical Research* highlighted the development of cost-effectiveness modelling [605], with Bayesian approaches playing a strong role in accounting for uncertainty in these complex models [606]. The decision-making aspects of a Bayesian approach, for which many have argued, are coming into their own here [607, 608].

### 7.12. Other applications

One of the most striking features of Bayesian work in *Statistics in Medicine* in the epoch was the range of applications. Among the less standard applications were quantitative antimicrobial assays for assessing the efficacy of chemical germicides [609]. Optimal designs using the Michaelis-Menton equation had application in enzymology [610]. Modelling of pre-malignant lesions found MCMC was more efficient than maximum likelihood in the presence of heterogeneity [611]. Modelling of infection and recovery rates for parasites uses hidden Markov models [612]. Adaptive regression splines were extended to analyse the activity of neurons in the brain [613]. Spline smoothing in linear mixed models had applications in areas such as modelling mammographic density versus age and using pedigree data to model risk of bronchial hyperresponsiveness [614]. Bayes factors proved more powerful than a modified Hotellings  $T^2$  test in small samples testing the equality of two Poisson functions from neurophysiological applications [615] and procedures for detecting extra-Binomial variability use Bayes factors [616]. Neural networks for bivariate binary data were used in a prostate cancer study [617]. Queuing theory was used to analysis a renal transplant waiting list [618]. Glucose and insulin homeostatis, modelled via differential equations, were now modelled via a population-based hierarchical model [619]. In fact, much of the work cited in this review is part of a more general trend towards hierarchical modelling, and an overview included Bayesian methods alongside more classical approaches [620].

## 8. THE FUTURE

It is now over 300 years since the birth of Thomas Bayes [621]. At the time of writing, the 8th Valencia meeting has just been held in summer 2006, and the proceedings are now in preparation. Bayesian statistics is a standard part of many undergraduate and postgraduate degrees in statistics, at least in the U.K. Twenty-five years ago, Bayesian statistics barely got mentioned in the same breath as medical statistics; now the two are completely intertwined. No conference on Bayesian statistics is complete without medical applications, no conference on medical statistics is complete without some Bayesian approaches. The FDA has just issued a draft guideline on 'Use of Bayesian Statistics for Medical Device Clinical Trials'. So what will the future bring?

It is safe to say that applied Bayesian statistics is not a passing fad. The range of applications in this review, and the diversity of statisticians now using Bayesian approaches mean Bayes is firmly

in the mainstream of applied statistics. The ability to think in terms of structuring the scientific problem, and then bringing relevant data and assumptions to bear, rather than starting with a data set and a restricted set of models that can be fitted, have fundamentally changed the way that statisticians are thinking. My belief is that the next frontier is the medical literature. Altman's review [419] may have found little evidence of Bayesian statistics in medical journals in 2000, but one does not have to look far to find recent examples in the top medical journals, such as in the *New England Journal of Medicine* [622], the *BMJ* [623, 624] and the *Lancet* [625]. These are still the exception rather than the rule, but are encouraging signs for the future. I also predict that, following trends in previous major developments such as logistic regression and survival analysis, Bayes will be used increasingly by those who do not class themselves as statisticians, as well as those who do. Beyond that, I would predict that Bayes will be most used in newer and rapidly developing areas, where flexibility and innovation are required, rather than conventional areas where traditional methods are well-ensconced. In particular, the exploitation of the recent advances in the understanding of the human genome will provide fruitful areas. I look forward to both reading and writing about such developments over the next 25 years of *Statistics in Medicine*.

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