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OPTIMAL DESIGNS FOR TWO-COLOUR MICROARRAY EXPERIMENTS

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Microarrays facilitate the study of gene expression, that is, which genes are active in a given cell under pre-specified experimental conditions. Microarray technology enables the measurement of gene expression for many thousands of genes simultaneously. This has created the potential for significant advances in the field of bioinformatics. Careful statistical design is crucial to realize the full potential of microarray technology.

This thesis focuses on the recommendation of optimal designs for two-colour microarray experiments. The optimality criterion presented is based on the notion of Pareto optimal designs. Pareto optimality enables the recommendation of designs that are particularly efficient for the effects that are of scientific interest. This is relevant in the microarray context where analysis is typically carried out separately for those effects. The approach presented in this thesis allows for effects of interest that correspond to contrasts rather than solely considering parameters of the linear model. The approach is further developed to cater for additional experimental considerations such as contrasts that are of equal scientific interest. Further to this, the issue of gene-specific dye bias is addressed. The approach is illustrated in studies of leukaemia and breast cancer.

For large experiments, it is not feasible to examine all possible designs in an exhaustive search for Pareto optimal designs. This thesis presents an adaptation of the multiple objective metaheuristic method of Pareto simulated annealing to the microarray context. The aim of Pareto simulated annealing is to generate an approximation to the set of Pareto optimal designs in a relatively short time. At each iteration, a sample of generating designs is used to explore the design space in

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an efficient way. This involves the setting of a number of Pareto simulated annealing parameters and the development of appropriate quality measures. Algorithms are developed to search systematically for the optimal values of the tuning parameters based on Pareto simulated annealing and response surface methodology. The algorithms are demonstrated in the context of a factorial microarray experimental situation.

Finally, issues related to technical replication and other complex experiments are discussed.

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