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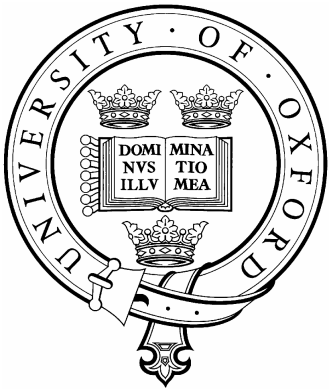

Multilocus sequence analysis of the pathogen *Neisseria meningitidis*

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ABSTRACT

Neisseria meningitidis is the bacterium responsible for meningococcal meningitis and septicaemia in humans. Meningococcal disease is primarily a disease of young children, characterized by rapid deterioration from first symptoms to death, with an 11% fatality rate and a global distribution. Patterns of genetic diversity in meningococcal populations provide an account of their evolutionary history and structure, which can be inferred by population genetics modelling. Understanding these phenomena can inform control and prevention strategies, and provides interesting case studies in evolution. The aim of this thesis is to develop population genetics techniques for inferring the evolutionary history of meningococci.

I begin by reviewing the field, and justifying the use of coalescent methods in modelling microparasite populations. Inference on carriage populations of meningococci under the standard neutral model and the neutral microepidemic model is performed using a modification to approximate Bayesian computation. AMOVA and Mantel tests are used to quantify the differentiation between carriage and disease populations, and the extent to which geography and host age structure carriage populations. The results are used to propose revised coalescent models for meningococcal evolution.

The role of natural selection in shaping meningococcal diversity is investigated using a novel method that utilises an approximation to the coalescent and reversible-jump Markov chain Monte Carlo to detect sites under selection in the presence of recombination. Having performed a simulation study to assess the statistical properties of the method, I apply it to the *porB* antigen locus and seven housekeeping loci in *N. meningitidis*. There is strong evidence for selection imposed by the host immune system in the antigen locus, but not the housekeeping loci which are functionally constrained. Finally I discuss the future direction of population genetic approaches to understanding infectious disease.

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