

Genetics and population analysis

GeneRecon—a coalescent based tool for fine-scale association mapping

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ABSTRACT

Summary: GeneRecon is a tool for fine-scale association mapping using a coalescence model. GeneRecon takes as input case–control data from phased or unphased SNP and microsatellite genotypes. The posterior distribution of disease locus position is obtained by Metropolis-Hastings sampling in the state space of genealogies. Input format, search strategy and the sampled statistics can be configured through the Guile Scheme programming language embedded in GeneRecon, making GeneRecon highly configurable.

Availability: The source code for GeneRecon, written in C++ and Scheme, is available under the GNU General Public License (GPL) at <http://www.birc.au.dk/~mailund/GeneRecon>

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1 INTRODUCTION

We have implemented a software package, GeneRecon, based on extensions of the shattered coalescence model of Morris *et al.* (2002) for Bayesian Markov chain Monte Carlo (MCMC) fine-scale linkage disequilibrium (LD) gene mapping. GeneRecon uses the coalescent model (Hein *et al.*, 2005) to explicitly model the genealogy of a sample of case chromosomes. The location of the mutation influencing the disease is inferred based on the observed LD at multiple genetic markers. Given the computational complexity of the problem, a Metropolis-Hastings algorithm is deployed to integrate over unknown population genetic parameters of the coalescence model and sample the marginal posterior probability density for the parameter(s) of interest.

2 THE MODEL

GeneRecon handles both SNP and microsatellite marker genotype or haplotype data from case/control design studies. Phenocopies and locus- and allele-heterogeneity are modeled in two ways. First, the ‘shattered’ coalescent allows genealogical independence of coalescent subtrees (Morris *et al.*, 2002). Second, cases are partitioned into two clusters, a ‘null’-cluster which is not evaluated by the model, and hence greatly reduces the search space, and a ‘mutation’-cluster of cases which is evaluated by the model (Liu *et al.*, 2001).

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3 IMPLEMENTATION

GeneRecon can be obtained from its homepage, where instructions for the installation are provided. The MCMC engine of GeneRecon is written in C++ and is available as a command-line executable for Linux. A ‘Getting started’ document provides an introduction to the functionality of GeneRecon, whereas a user’s manual provides examples of more advanced uses, including examples of using Guile Scheme.

4 FLEXIBILITY OF USING SCHEME

Using the Guile Scheme programming language as a front-end for input specifications and execution control allows a highly flexible interaction with the MCMC engine of GeneRecon. A collection of Guile modules allow easy changes to functionality specifications. Input file format, population genetic parameters, MCMC sampling strategy and output options can be configured. Prior knowledge of population genetic parameters, such as effective population size (N_e) or local recombination rates (ρ) may be explicitly defined, if available from independent sources such as HapMap or the DeCODE genetic map. At Present, sampling of the likelihood, disease location, effective population size, coalescent tree and cluster indices are supported. The MCMC sampling strategy is defined by the number of iterations, the burn-in period and the proposal densities of the sampled parameters. The choice of strategy will strongly affect the mixing properties of the Markov chain and convergence to a stationary distribution [for details on MCMC strategies see Gilks *et al.* (1995) or Liu (2001)].

5 PERFORMANCE

To evaluate the prediction capabilities of GeneRecon, we have conducted a large simulation study (Mailund *et al.*, 2005a), where sequence data were simulated under various parameters using the CoaSim tool (Mailund *et al.*, 2005b), and then analyzed using GeneRecon, with four independent runs for each dataset. Results for a Mendelian scenario, i.e. all cases carry the disease causing mutation and all controls are wild types, are shown in Table 1.

We have also tested GeneRecon on the $\Delta F508$ mutation for cystic fibrosis data from Kerem *et al.* (1989). The results from this analysis

Table 1. GeneRecon error, as measured by distance from the inferred to the true position of the disease locus of simulated haplotype SNP data from 100 cases and controls

| Setup | All diseased | | | 50% Diseased | | |
|--------------------|--------------|-----------|-----------|--------------|-----------|------------|
| | 50% | 75% | 95% | 50% | 75% | 95% |
| 20 Markers, 1 cM | 0.034 cM | 0.114 cM | 0.358 cM | 0.052 cM | 0.190 cM | 0.777 cM |
| 40 Markers, 1 cM | 0.058 cM | 0.241 cM | 0.564 cM | 0.137 cM | 0.377 cM | 0.727 cM |
| 20 Markers, 2 cM | 0.052 cM | 0.154 cM | 0.499 cM | 0.113 cM | 0.348 cM | 0.721 cM |
| 20 Markers, 0.1 cM | 0.0043 cM | 0.0073 cM | 0.0532 cM | 0.0062 cM | 0.0021 cM | 0.0372 cM |
| 40 Markers, 0.1 cM | 0.0072 cM | 0.0269 cM | 0.0532 cM | 0.0126 cM | 0.0302 cM | 0.0650 cM |
| 20 Markers, 0.2 cM | 0.0057 cM | 0.0283 cM | 0.0759 cM | 0.0084 cM | 0.0267 cM | 0.00618 cM |

The table shows the number of chains inferring a disease locus in the given distance from the true locus at the 50, 75 and 95% quantile, respectively. Six setups were explored in two GeneRecon settings. In setting one, all cases were considered by the coalescence model, whereas in setting two the fraction of cases evaluated by the model was 50%. In the first setup a region of 1 cM is covered by 20 markers of minor allele frequency (MAF) >10% and a trait locus with disease allele frequency of 20%, all placed at random, in the second setup the density of markers is doubled and in the third setup region is twice the size. Setup four to six follow this pattern, but in a smaller region (0.1 for setup four and five and 0.2 cM for setup six). That the accuracy is decreased when the number of markers are doubled, as seen in setup two and five, may seem counter-intuitive, but is a consequence of the increase in the search space. GeneRecon explored the search spaces of all setups for four CPU days each, regardless of the number of markers, so doubling of this number leads to the evaluation of a smaller fraction of the search space, causing the reduction in accuracy.

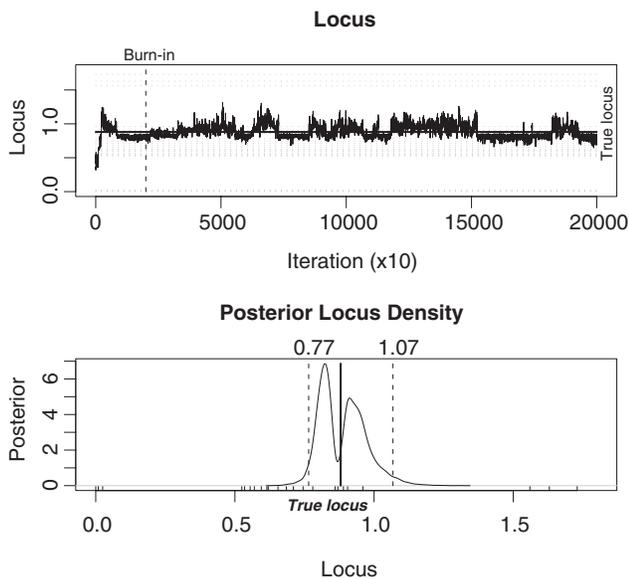


Fig. 1. Example of GeneRecon inferring the position of the $\Delta F508$ mutation for cystic fibrosis with data from Kerem *et al.* (1989). The MCMC was allowed to burn in for 20-000 iterations and the posterior was sampled from the following 180-000 iteration. In the posterior plot, the true position is indicated by the solid vertical line and the 95% credibility interval is indicated by dashed vertical lines. Ticks at the x -axis indicate the position of SNP markers.

are shown in Figure 1. GeneRecon compares favorably with other fine-mapping tools (Table 2).

6 CONCLUSION

GeneRecon is designed to allow flexible multimarker LD mapping using coalescent model. Adaptations and extensions of the various Scheme modules provided allow users to accommodate a wide range of scenarios, data types, sampling strategies and convergence diagnostics, without much loss of user friendliness compared to competing software.

Table 2. Comparison of location estimates of the $\Delta F508$ mutation for cystic fibrosis data Kerem *et al.* (1989) by GeneRecon and other coalescent-based fine mapping tools

| Method | Estimate | 95% Credibility interval |
|-----------------------------|----------|--------------------------|
| Liu <i>et al.</i> (2001) | 0.87 | 0.82–0.93 |
| Morris <i>et al.</i> (2002) | 0.85 | 0.65–1.00 |
| GeneRecon | 0.82 | 0.73–1.03 |

The mutation is located at 0.88.

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Conflict of Interest: none declared.

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