

Estimating Recombination Rate Distribution by Optimal Quantization

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Abstract

We obtain recombination rate distribution functions for all human chromosomes using an optimal quantization method. This non-parametric method allows us to control over-/under-fitting. The piece-wise constant recombination rate distribution functions are convenient to store and retrieve. Our experimental results showed more abrupt distribution functions than two recently published results. In the previous results, the over-/under-fitting issues were not addressed explicitly. Our estimation had greater log likelihood over a previous result using Parzen window. It suggests that the optimal quantization technique might be of great advantage for estimation of other genomic feature distributions.

1. Introduction

Recombination is the primary biological event pushing evolution. Biologists are interested in a high resolution recombination map that presents accurately how often a recombination event occurs at a specific location in a chromosome. Linear correlations have been established between recombination rate with factors such as Poly(A)/Poly(T) density, CpG density, GC content density, RefSeq gene count, PPY/PPU density, UniGene cluster count [2]; LINE density, SINE density, $(AC)_n$ density and chromosome position [4]. To understand accurately how recombination occurs, a recombination rate distribution (RRD) function can be used to quantify the recombination events at any location in a chromosome. The RRD functions of human chromo-

somes are first published in the Marshfield map [4]. The Iceland map [2] also obtained RRD functions but from a much larger sample size.

We find a RRD function that best reveals the information contained in the data. We propose to use optimal quantization [3], a non-parametric methodology, to estimate a piece-wise constant probability density function (p.d.f.). The estimated function is optimal in that over-/under-fitting are minimized by selecting the best control parameters. Comparisons made with other methods show the advantage of our approach in terms of the cross-validated log likelihood. In addition, the quantized p.d.f. representation is more convenient to use than other kernel methods such as Parzen window or k nearest neighbor, because it can be accessed as a table in logarithm time.

The paper is organized into five sections. In Section 1, we introduce the RRD estimation problem and our strategy. In Section 2, we explain the recombination and review methods to examine recombination events and estimate a RRD function. In Section 3, we describe the theoretical and algorithmic aspect of optimal quantization. In Section 4, we demonstrate RRDs obtained by optimal quantization and compare its performance quantitatively with the Parzen window results. Finally in Section 5, we conclude our study and describe some future work related to biological feature distribution estimation that can be done using optimal quantization.

2. Recombination Rate Distribution Function

Recombination plays a central role in molecular evolution. The mechanism of recombination can reveal directly

using the Parzen window method, that is:

$$\hat{p}(x) = \frac{1}{N} \sum_{i=1}^N k(x, x_i) \quad (3)$$

where

$$k(x, x_i) = \begin{cases} \frac{1}{\Delta}, & |x - x_i| \leq \frac{\Delta}{2} \\ 0, & \text{otherwise} \end{cases}$$

and Δ is the window width or bandwidth. Then they choose a sequence of M equally spaced locations $y_0, 2y_0, 3y_0, \dots, My_0$ to calculate the estimated p.d.f. values. In the end, they fit splines to these points to obtain a smooth p.d.f. The RRD is finally obtained by Eq. (1). The critical window width parameter Δ is 3 Mbps. The sample is drawn from 1257 meioses.

A previously published Marshfield RRD [4] used Eq. (2). In this approach, it is not necessary to know the exact location of each recombination event. They first compute the empirical c.d.f. $\hat{F}(x)$ from the observed recombination events, then fit cubic splines to $\hat{F}(x)$. They finally obtain the RRD function $R(x)$ by Eq. (2). In this study, only 184 meioses are analyzed to identify recombination events, which is a much smaller sample size compared to [2].

3. Estimating RRD by Optimal Quantization

Each RRD in [2] is a continuous function. They did not explain how the bandwidth is chosen in the Parzen window approach. In addition, all the splines have to be saved and evaluated before the rate at a certain location can be calculated. Optimal quantization, also a non-parametric technique, is an alternative to their approach. As we shall see, the advantages include that optimal quantization is both statistically and computationally efficient; it is as easy to use as table look-up; over-/under-fitting can be controlled in a systematic way. Optimal quantization finds the most effective representation of data in terms of both CPU cycles, the memory requirement and the targeted performance. Intuitively, an optimal quantization algorithm locates the most important regions which are then finely quantized, while less important regions are coarsely quantized. Importance determination relies on the pattern recognition task. It could be average log likelihood, entropy, or some combination of them. Other methods, e.g., kernel methods, treat everywhere in the space equally without the prioritized resource allocation. For the less important regions, there is the potential wasting of resources.

Our methodology obtains a variable bin width p.d.f. estimation by optimizing a quantizer measure defined on a finite sample, where all bins will have non-zero p.d.f. values. The measure combines convexly average log likelihood and entropy. We perform two steps to find a p.d.f. Dynamic programming is employed to find a quantization of the real

axis maximizing the quantizer measure. ensuring the adaptivity to data and overcoming the statistical inefficiency of an equal bin width histogram. The second step obtains a locally averaged p.d.f. estimate for each bin. We use a computationally efficient algorithm for smoothing, which guarantees the consistency of the p.d.f. estimates while avoiding the computation complexity of a kernel type smoothing method. The p.d.f. thus produced is optimal in both the adaptivity and consistency senses.

There are four parameters in our optimal quantization framework: W_J , the weight of log likelihood, W_H , the weight of entropy, number of quantization levels L , number of neighbors k . W_J , W_H and L control the over-/under-fitting in finding the optimal intervals; k controls the over-/under-fitting in estimating the p.d.f. value of each bin. We estimate these parameters by 5-fold cross-validation on the training data. This method is computationally intensive but it can find a reasonably good set of parameters in the spectrum from under- to over-fitting.

4. Experimental Results

We perform optimal quantization on the data from [2]. The genetic distances of the markers are given, corresponding to the empirical c.d.f. of the recombination events. In the optimal quantization experiment, we first obtain the control parameters W_J , W_H , L and k by a 5-fold cross-validation. The values of W_J and W_H range from 0 to 1 with a step of 0.1. The value of L ranges from 2 to 2^8 in the power of 2. The value of k ranges from 1 to 3^6 in the power of 3. Second, the p.d.f. is estimated, using the best parameters just obtained, on all the recombination events of each chromosome. The estimated RRD functions of chromosomes 3, 13, 22 and X are shown in Fig. 2 to 5. Recombination is much more active around the ends of chromosomes than the centers. Our RRD's change more drastically than the ones shown in [2, 4]. Since all our control parameters are cross-validated, it is very likely that the recombination rate changes indeed more abruptly than the much more smooth curves published before. To fit splines on our estimation result could make the curve smoother, but it requires further validation of the smoothness. We further compare quantitatively the performance of optimal quantization with Parzen window approach. We did not apply splines to make the comparison fair. The evaluation is done by a 5-fold cross-validation. The performance measure is the log likelihood of the left-out data reserved for test, using the p.d.f. estimated from the the data without the left-out data. The average and the standard deviation of the five log likelihoods for each chromosome are shown in Table 1. The average log likelihoods of the p.d.f. obtained by optimal quantization are consistently higher than those by Parzen window method. The standard deviations of both are sim-

ilar, with Parzen window results slightly better on most of the chromosomes. Therefore the optimization quantization approach provides a better RRD estimation than that of the Parzen window.

Table 1. Performance comparison between optimal quantization and Parzen window.

Chromosome	average log likelihood		standard deviation	
	Opt. Quant.	Parzen Window	Opt. Quant.	Parzen Window
1	-19.11	-19.17	0.03	0.01
2	-19.10	-19.21	0.05	0.02
3	-18.90	-19.05	0.04	0.04
4	-18.91	-18.98	0.03	0.02
5	-18.79	-18.91	0.04	0.03
6	-18.72	-18.88	0.05	0.03
7	-18.69	-18.87	0.03	0.02
8	-18.69	-18.78	0.02	0.01
9	-18.60	-18.78	0.04	0.03
10	-18.55	-18.52	0.05	0.03
11	-18.53	-18.65	0.06	0.03
12	-18.57	-18.63	0.03	0.04
13	-18.02	-18.32	0.06	0.04
14	-17.94	-18.14	0.07	0.07
15	-17.87	-18.17	0.06	0.07
16	-18.05	-18.18	0.07	0.04
17	-17.99	-18.14	0.05	0.05
18	-18.04	-18.16	0.08	0.06
19	-17.70	-17.95	0.09	0.05
20	-17.62	-17.70	0.09	0.03
21	-17.05	-17.28	0.06	0.05
22	-16.96	-17.16	0.08	0.05
X	-18.42	-18.53	0.04	0.03

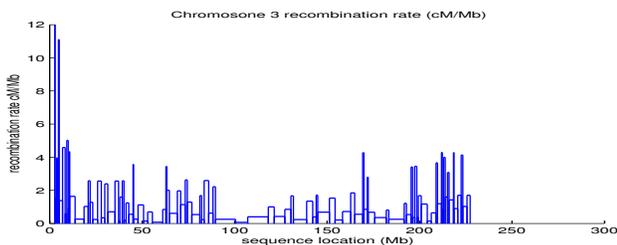


Figure 2. Chromosome 3

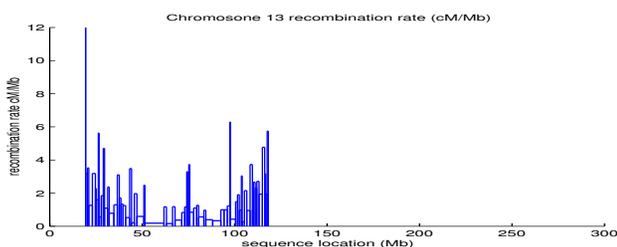


Figure 3. Chromosome 13

5. Conclusion and Future Work

Accurate estimation of the RRD across the entire genome is crucial to understand evolution quantitatively. For example, recombination rate has been known to be linearly correlated with the locations of retrotransposable elements such as long interspersed elements. In contrast to

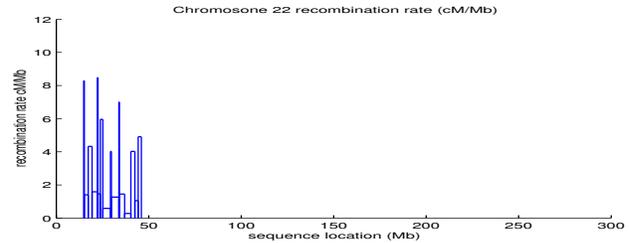


Figure 4. Chromosome 22.

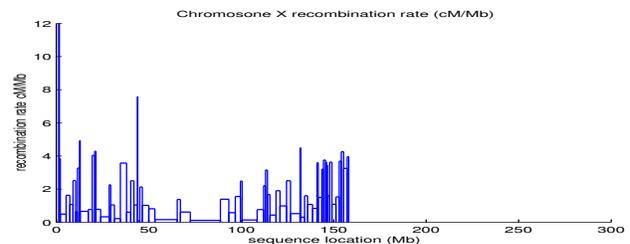


Figure 5. Chromosome X.

the Parzen window approach used in previously reported RRD's, we have used an optimal quantization approach to obtain piecewise constant RRD's. The optimal partition of each chromosome is obtained first and then the recombination rate in each bin is computed by a neighborhood averaging. Our 5-fold cross-validation result has shown that the performance of optimal quantization in terms of log likelihood is better than the Parzen window approach. The quantization approach produces RRD's that are much easier to use by table look-up than the continuous curves produced by Parzen window and splines. Quantization is an attractive approach to represent the genome-wide distributions of biological events, because of the controlled over-/under-fitting and the convenience of use. We further plan to obtain Guanine + Cytosine (*GC*) percentage distribution by this approach. Currently *GC* percentages are given by 20Kb windows which obviously is not the most efficient way to do the whole genome of 3 Gb. An even further goal is to use a multidimensional quantization approach to represent different biological features and to look at statistically significant relations revealed by the representation.

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