Application of Support Vector Machine to detect an association between a disease or trait and multiple SNP variations.

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Abstract

After the completion of human genome sequence was announced, it is evident that interpretation of DNA sequences is an immediate task to work on. For understanding their signals, improvement of present sequence analysis tools and developing new ones become necessary. Along this current trend, we attack one of the fundamental questions, which set of SNP (single nucleotide polymorphism) variations is related to a specific disease or trait is. For, in the whole DNA sequence, it is known that people have different DNAs only at SNP locations, and moreover, the total SNPs are less than 5 millions, finding an association between SNP variations and certain disease or trait is believed to be one of the essential steps not only for genetic researches but for drug design and discovery. In this paper, we are going to present a method of detecting whether there is an association between multiple SNP variations and a trait or disease. The method exploits the Support Vector Machine which has been attracting lots of attentions recently.

1 An introduction

Even though the DNA sequences are almost identical among people, they are slightly different in the respect with appearance, height, eye color, characters etc. Therefore it seems reasonable to believe that if there is no environmental
factor, each whole genome produce a unique person, and we assume that the mutations at the SNP locations makes people different, in other words, two persons with the same SNPs are identical.

The problem of determining whether a set of SNP variation cause a specific disease or trait could be formulated as follows. For a given disease or trait,

1. For each set of SNP variations, find its representation as a vector in a Euclidean space.(We will discuss this in the section 3)

2. Get a systematic way of distinguishing SNP genotypes of normal people from ones of people with the disease or trait. To do it, we will use the Support Vector Machine introduced by Vapnik, and we will describe its idea briefly in the next section.

We can explain why this Support Vector Machine is natural, by considering the examples in our real life. The current law prohibits a driver who has alcohol concentration in his/her blood over a certain number. This is an example of representation of a degree of "drunkenness" by a number. When we describe a basketball player, height and weight are mentioned most frequently and we trust those two numbers are indices for potential as a basketplayer. Enumeration of numbers such as (height, weight) is called a vector in mathematics and a generalization of a number enumeration of only one number. Once we have a representation, we have only to find out a way to separate into two groups. For the case of alcohol concentration, drunken drivers or not, depending on whether the concentration is greater than the number allowed legally. The role of the Support Vector Machine determining the boundary of two groups.

2 A review of Support Vector Machine

Let \( R^n \) be a \( n \)-dimensional Euclidean space and let \( A \) and \( B \) be two sets of finite number of points in \( R^n \). The basic and fundamental question is whether there is a systematic way of dividing \( R^n \) into two groups so that \( A \) and \( B \) are contained in different groups?

In mathematical terminologies, is there a way of obtaining a function \( f : R^n \rightarrow R \) such that

\[
    f(x) = \begin{cases} 
    1, & x \in A \\
    -1, & x \in B 
    \end{cases}
\]

The simplest function we may think of is a function of degree 1, i.e., linear function. Let’s assume that \( A \) and \( B \) are separable by such a function, which is of form \( w \cdot x + b = 0 \), where \( x \) is a variable and \( w \) and \( b \) are parameters for the hyperplane. (Here \( \cdot \) denotes the standard inner product in Euclidean space.) Since there are infinitely many hyperplanes separating \( A \) and \( B \), for practical implementation, we need to choose a specific one from those infinitely many candidates. Vapnik resolved this problem elegantly by introducing the definition of the Optimal hyperplane and connecting with nonlinear programming. It separate the sets \( A \) and \( B \) and the distance between the closest vectors of the
two sets to the plane is maximal. (For more details, see [4]).

The key step of obtaining the optimal plane is to form a nonlinear
programming problem, by imposing appropriate restrictions, and apply the Kuhn-
Tucker's necessary conditions. This nonlinear programming problem makes us
choose a unique expression for a plane. For example, 0.5 could be expressed
in infinitely many ways of fractions, i.e., $\frac{100}{200}, \frac{28}{56}, \ldots, \frac{4}{8}$. However, under the
constraint that numerator and denominator be relatively prime, then there is
a unique fractional expression, namely, $\frac{1}{2}$. In the same principle, though there
are infinitely many planes for separation, in the respect of separating a data
set into exactly same two groups, (even for a single plane, it has infinitely many
expressions. $x + y = 1$ and $2x + 2y = 2$ etc. represent the same line.), the
optimization problem deduced from an observation manages to get rid of this
ambiguity.

More precisely, it starts with the well-known distance form ula from a point
to a plane and, for simplicity, let $n = 2$.

Then the distance from a point $(x_0, y_0)$ to the plane $ax + by + c = 0$ in the
plane is given by

$$\frac{|ax_0 + by_0 + c|}{\sqrt{a^2 + b^2}}.$$

Observe that, if the condition $|ax_0 + by_0 + c| \geq 1$ is imposed, the distance
increases, as $\sqrt{a^2 + b^2}$ decreases. Thus, if we have $(0,2)$ and $(0,-2)$, we have to
solve the minimization problem under two restriction. The line $\frac{1}{2}y = 0$ will be
the optimal hyperplane. Intuitively, the optimal line should satisfy the maximal
distance from both points, which is the line passing through the middle point,
the origin.

In general, let $(x_1, y_1), (x_2, y_2), \ldots, (x_l, y_l)$ be a set of labelled vectors, where
each $y_i$ denotes where $x_i$ belongs and takes either $+1$ or $-1$. The formulation
from the observation can be stated as follows:

minimize $f(w) = \frac{1}{2}||w||^2$

under the constraints, $y_i[(x_i \cdot w) + b] \geq 1, i = 1, 2, \ldots, l$.

One way of solving this optimization problem is to use the associated La-
grangian whose definition is as follows:

**Definition 1** Given the following optimization problem

Minimize $f(x), x = (x_1, x_2, \ldots, x_n),$

under the constraints $g_i(x) \geq 0, i = 1, 2, \ldots, m,$

its associated Lagrangian is defined by

$L(x, \lambda) = f(x) - \sum_{i=1}^{m} \lambda_i g_i(x),$

where $\lambda = (\lambda_1, \lambda_2, \ldots, \lambda_m)$, Lagrangian multipliers.

Kuhn and Tucker proved the minimization problem is equivalent to solving
its associated Lagrangian functional (See [3]), i.e., finding a global saddle point
of its associated Lagrangian functional. In our case, the associated Lagrangian
is given by

$L(w, b, \alpha) = \frac{1}{2}||w||^2 - \sum_{i=1}^{l} \alpha_i [(x_i \cdot w + b) y_i - 1]$.
At the global saddle point, \( L \) should be minimized with respect to \( w \) and \( b \), and maximized with respect to \( \alpha_i \geq 0 \). As a result, we have familiar necessary conditions of first order derivatives, called Kuhn-Tucker necessary conditions. Substitution those conditions in the Lagrangian functional leads us to a quadratic programing:

\[
\text{maximize } W(\alpha) = \frac{1}{2} \sum_{i,j=1}^l y_i y_j \alpha_i \alpha_j (x_i \cdot x_j) - \sum_{i=1}^l \alpha_i \\
\text{under the constraints } \sum_{i=1}^l \alpha_i y_i = 0 \text{ and } \alpha_i \geq 0, \ i = 1, 2...l.
\]

To construct a hyperplane of the optimal type in the case when the data set is not separable linearly, we introduce non-negative slack variables \( \varepsilon_i \)'s to constraints to reduce the sum of ”distance of separation” errors.

\[
\text{minimize } f(w) = \frac{1}{2} ||w||^2 + C \sum_{i=1}^l \varepsilon_i \\
\text{under the constraints, } y_i[(x_i \cdot w) + b] \geq 1 - \varepsilon_i, \ i = 1, 2,...,l:
\]

Once again, the same arguments described above give the quadratic programming,

\[
\text{maximize } W(\alpha) = \frac{1}{2} \sum_{i,j=1}^l y_i y_j \alpha_i \alpha_j (x_i \cdot x_j) - \sum_{i=1}^l \alpha_i \\
\text{under the constraints } \sum_{i=1}^l \alpha_i y_i = 0 \text{ and } 0 \leq \alpha_i \leq C, \ i = 1, 2...l. \ C \text{ is a given constant.}
\]

The practical implementation of this quadratic optimization program was discussed in some details. (See [1])

3 A representation of multiple SNP variations as a vector

As we mentioned in section 1, in this section, we propose a vector representation of multiple SNP variations for the Support Vector Machine. The basic concept is simple. As is often the case, comparison data with other data is the best strategy and a reference is required. Height, weight, blood alcohol concentration etc. are examples of association with numbers that express quantities with respect to the standardize metric scale. Here is a basic scheme we propose.

**Scheme**

Given each disease or trait, and a collection of SNP data which possibly related to it,

1. Assume that there is no environmental factor.
2. SNP locations are assumed to be known for the disease or trait.
3. Assume there is a reference SNP data.
4. By giving scores based on difference from the reference data, assign a vector to each SNP data. At each SNP location, take average of those scores over the reference data set. The collection of difference scores, ordered numbers, may be considered as a vector in a Euclidean space, whose dimension is the number of SNPs to be related to the disease or trait.
5. A training set is chosen for the disease or trait, in other words, SNP genotype data of normal and sick population.

6. By using Step 4, compute the SNP vectors of all training data set. This would be a set of labelled vectors, \( \{(x_i, y_i)\} \) as described in section 2

7. Use the Support Vector Machine to get a hyperplane dividing into two groups, a control and a case group.

**Remark 2** The reference data can be built by collecting SNP genotypes from the healthy normal population. For example, choose 10000 ordinary and over 60 years old people who have good health records. Depending on race, sex, region etc., the reference data should be distinguished into several different groups.

**Remark 3** At each SNP location, we might give a difference score uniformly. For example,

\[
\text{diff}(w/w, w/m) = 0.25, \text{diff}(w/m, m/m) = 0.75 \text{ and} \\
\text{diff}(w/w, m/m) = 1
\]

Here \( w \) and \( m \) represent wild and mutation genotypes respectively.

**Remark 4** The hyperplane obtained can be considered as a criterion, and, given a new data set, it can be used for testing whether the person of the data is susceptible to the disease or trait.

**Remark 5** Representation of an object as a vector might be critical for making use of the Support Vector Machine. How to make domain knowledge contained in vector representations is one of the major issues. For best performance, the difference scores may be adjusted with training data set and, even at each SNP location, such as giving weights on each SNP, normalization. We implicitly used the fact those SNPs are related, i.e., linked each other. In other words, they are dependent in the sense of statistical probability, but independent in terms of linear algebra. (For this concept and an interesting vector representation, see [3])

**Remark 6** The idea of difference scoring could be applied to other data sets, in particular, to haplotype data and to find out a linkage among SNP variations etc.

**Remark 7** Once a group of SNP patterns are identified, it would be worth investigating and computing contribution score of each of those SNP to the disease or trait.
4 Inseparable Case

For the inseparable case, the iterated use of support vector machine enables us to divide a collection of labelled vectors into several clustering groups.

1. Set a threshold value. Say, 80 percent.
2. Use support vector machine to separate a collection of labelled vectors into two groups $A$, $B$.
3. Check if the groups contain more than 80 percent of either +1 or -1 labelled vectors. Suppose $A$ is not such one. Then use support vector machine to $A$ again to separate into two subgroups.
4. Repeat this procedure until each subgroup has a majority of more than 80 percent. This will make each subgroup having a major set of labelled vectors.
5. For each subgroup, figure out a range, i.e., its center and radius. For example, averages and standard deviations of major labelled vectors may give information on the range.

References

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