Weekly Homework 5

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Substitution Matrices in Bioinformatics

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In Bioinformatics, the concept of substitution matrices is used in order to determine how long it will take for one sequence to evolve into another one. These sequences are generally composed either by DNA or by amino acids. One of the easiest examples in which we can use matrix substitutions is in order to compute an alignment score for two different sequences of DNA. If we would take the first sequence as ATGACTGGA and the second sequence as ATATGA and, we could compute afterward the best alignment score. For the identity similarity matrix, we suppose that each nucleobase is similar only to itself and it cannot be transformed into any other one. In our example, we can choose different alignments since the second sequence has a smaller length than the first one. Therefore, an alignment such as ATGACTGGA and AT-A-TG-A would achieve 6 points, the maximum possible score since the second sequence only has 6 characters, which means at most 6 occurrences.

When it comes to amino acids, their sequences alignments scores can be computed much harder, since the alphabet now contains 20 characters, not only 4 as it did in the case of nucleobases. Also, there are several amino-acids that partially match in chemical properties and therefore those substitutions from one to another have higher chances of occurring. Therefore, scores of 0 and 1 are no longer able to clearly illustrate these probabilities. We will now have positive and negative scores with the significance that a positive value is more likely to occur than any random substitution and a negative value on the contrary.

Two of the most famous substitution matrices are BLOSUM and PAM. Both of these matrices are computed by observing substitutions of real-life protein alignments. The first

one, BLOSUM has its abbreviation from 'Block Substitution Matrix'. For computing its values, we should have a finite number of amino-acids and compute the frequency of each character from the whole table. Afterward, the second step is to compute for each pair of characters the number of occurrences if we would take any two amino-acids from the same column. Having these individual and pairwise frequencies calculated, we are now able to compute the final substitution probability for a given XY amino-acids pair in the following manner: it is equal to logarithm of relative value of X frequency multiplied by relative value of Y frequency, the result multiplied by 2 (because XY and YX have the same substitution probability) and everything divided by relative frequency of XY pair from the second step. In order for this matrices to be reliable and free of bias, each BLOSUM matrix has a threshold sequence identity. The block with no more than 50% of sequence identity is called BLOSUM50 and there are other alternatives as well such as BLOSUM62 and BLOSUM80. The second substitution matrix highly used is PAM, which states for 'Point Accepted Mutation'. The number attached to each PAM matrix, such as PAM1, represents the evolutionary distance between two amino-acids sequences. This evolutionary distance represents how, on average, the first sequence converted 1 in 100 amino-acids into the second sequence's amino acids. In practice, the most used options are PAM30 and PAM70.

As a conclusion, BLOSUM and PAM have different core principles from which they are computed and their scores should be distinctively interpreted.

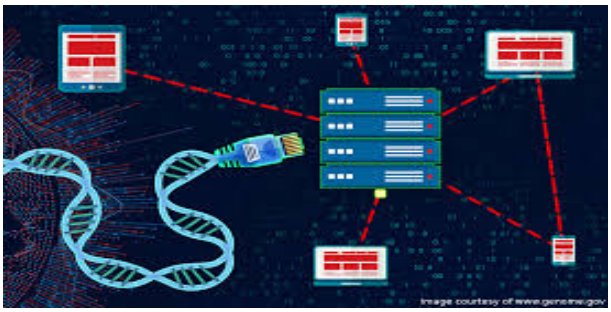
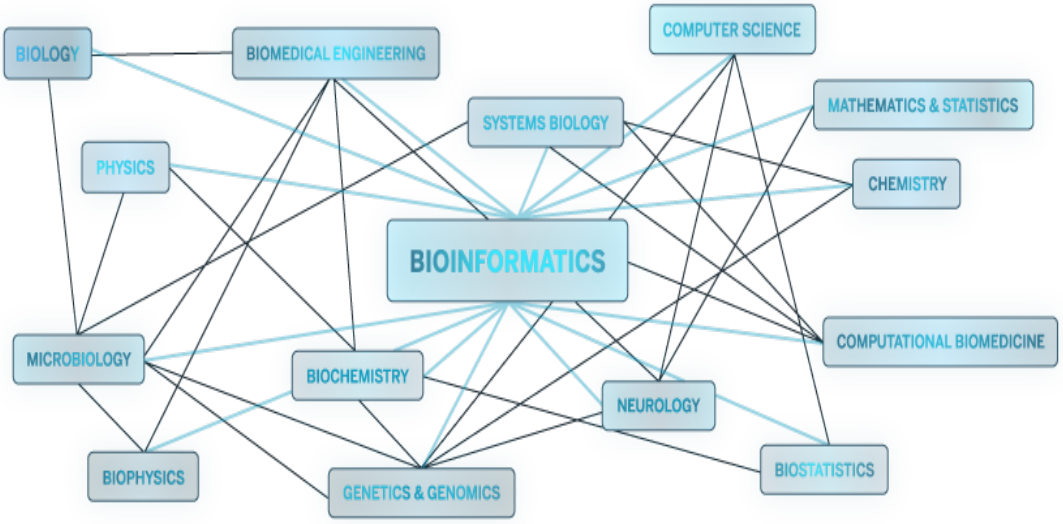


Image courtesy of www.genome.gov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