

MutationDetector[®]. Software tool for detecting amino acid substitutions

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Introduction

Motivation

Proteins play an essential role in our lives, because they are regulating sub-cellular processes^[1]. If any disruption occurs, a protein will cease acting properly and may cause severe diseases. Many factors can result in such disruptions. We consider the most important of those – a single nucleotide polymorphism (SNP). Having learned to find positions in protein sequence where the substitution might occur, we would get a possibility to identify the so-called variant proteins, which can be biomarkers for a variety of hard diseases^[2].

Single nucleotide polymorphism (SNP)

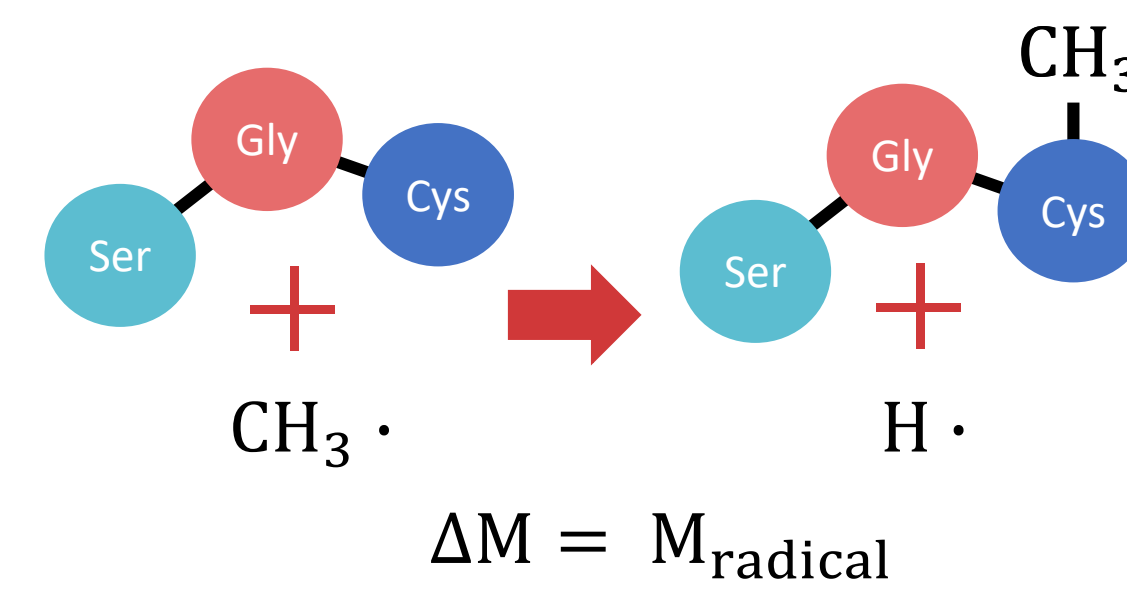
SNP is a substitution of nucleotide in a DNA strand. Since codons encode amino acid, SNP can lead to substitution of amino acid

	Wild type	Variant type (A->T)
DNA strand	ACC AAA CCG AGT	ACC ATA CCG AGT
mRNA	UGG UUU GGC UCA	UGG UAU GGC UCA
Protein	-Trp-Phe-Gly-Ser-	-Trp-Tyr-Gly-Ser-

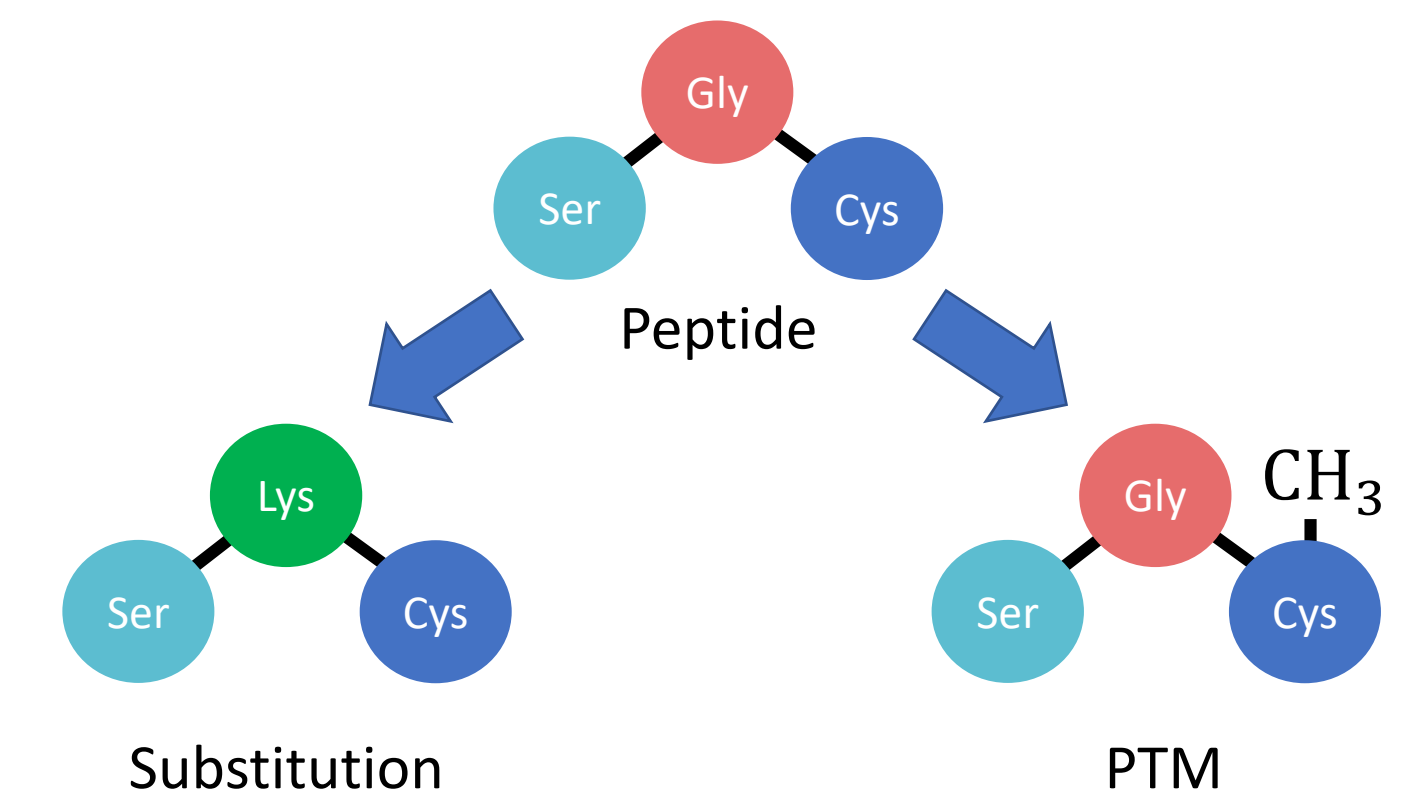
$$\Delta M = M_{\text{variant type}} - M_{\text{wild type}} = M_{\text{Tyr}} - M_{\text{Phe}}$$

Post translational modifications (PTMs)

PTM is a change of amino acid's chemical composition through adherence of some chemical radicals. (ex. the mass of methionine increases by approximately 14Da upon methylation)

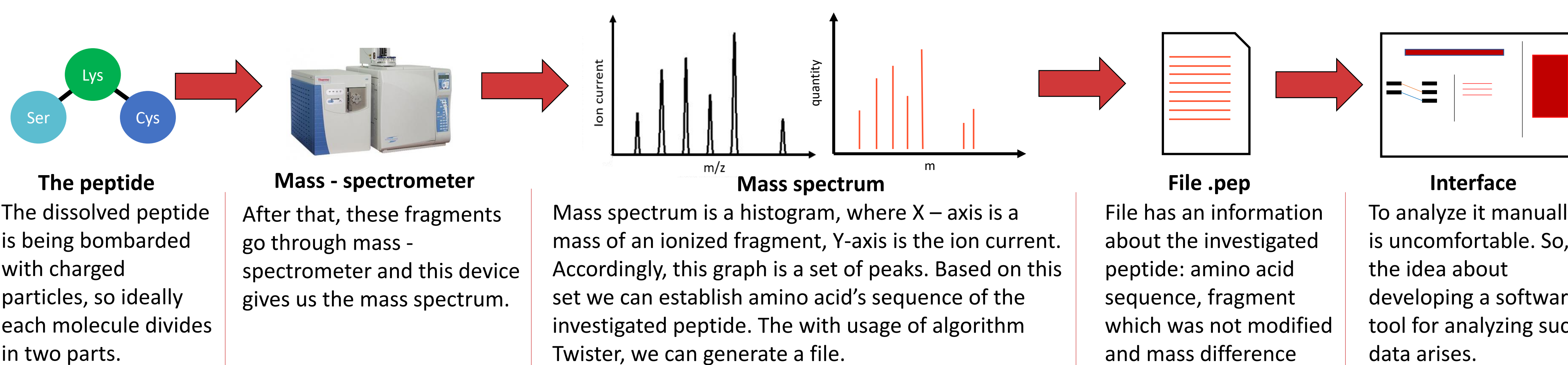


Possible modifications



Problem statement

There are two different methods for analyzing such peptides. First is qualitative and second is quantitative. Our work was concentrated on qualitative analyze. Here is the scheme of such analyze



The Goal

To develop a software tool for analysing data, obtained from modified peptide

The sub-tasks

- Learn how to read file .pep
- Learn how to find positions in the peptide where a substitution or a PTM could occur
- Learn how to generate a result file

Methodology

Programming tools

For developing this interface I used Java for a basic programming language. And an additional library for creating graphical interfaces, named, Swing



Input

Structure of .pep file

General	Example
<peptide>	...LTASMLAA...
<fragment which has not been modified>	SMLA
<Prefix/Suffix>	Prefix
<experimental mass of this peptide>	4653.40152 Da

Output

The developed program gives to user as an output: the peptide with highlighted positions and a .pepout file.

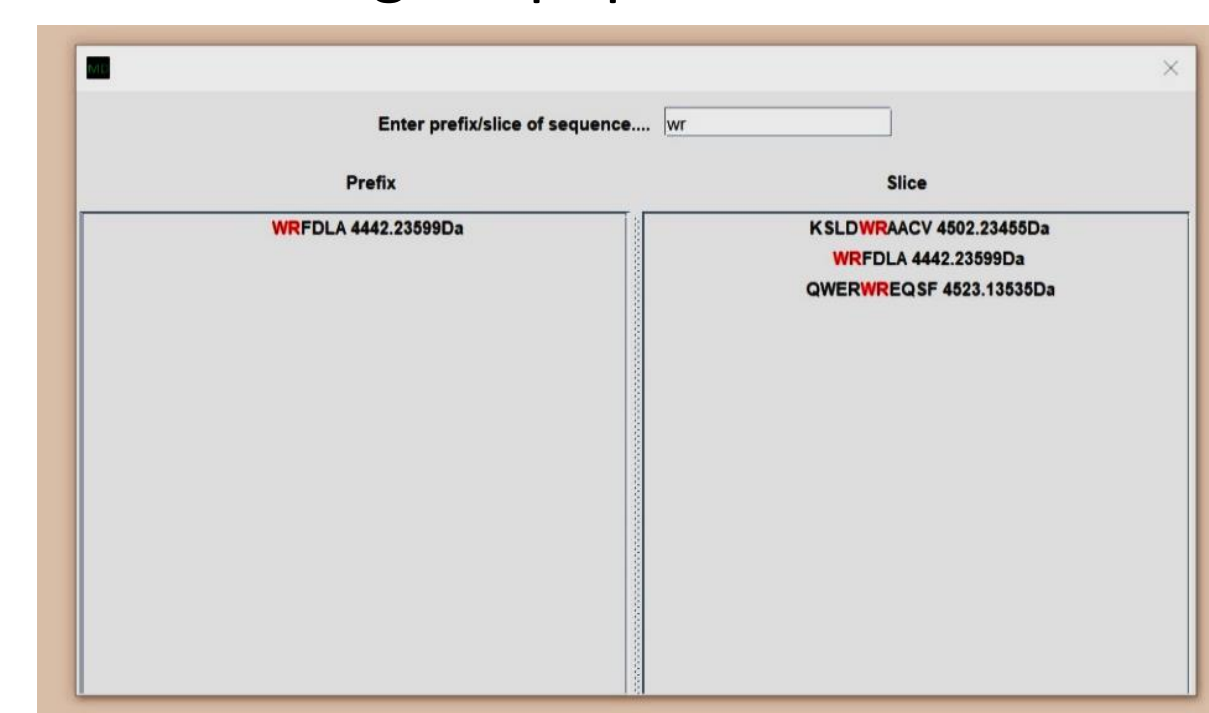
V	Q	S	S	A	R	C	V	N	G	N
				PTM						
				both						
				substitution						

Structure of .pepout file

General	Example
<peptide>	YASSV ⁵ RSPHP ¹⁰ AIQPL ¹⁵ QAP...
<Prefix/Suffix> Selected	Prefix selected
at position(s)	at positions 11, 17: A>>V
<numbers>: <sub/PTM>	at positions 13, 16: Q>>R
...	

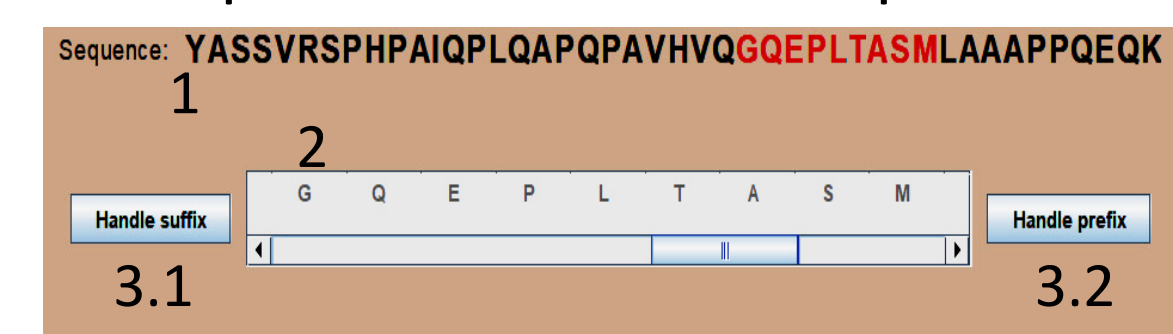
Interface

1. Searching for peptides



A user can search through the program's database with help of this dialog window to find peptides which are interest him

2. Sequence and scrollable panel

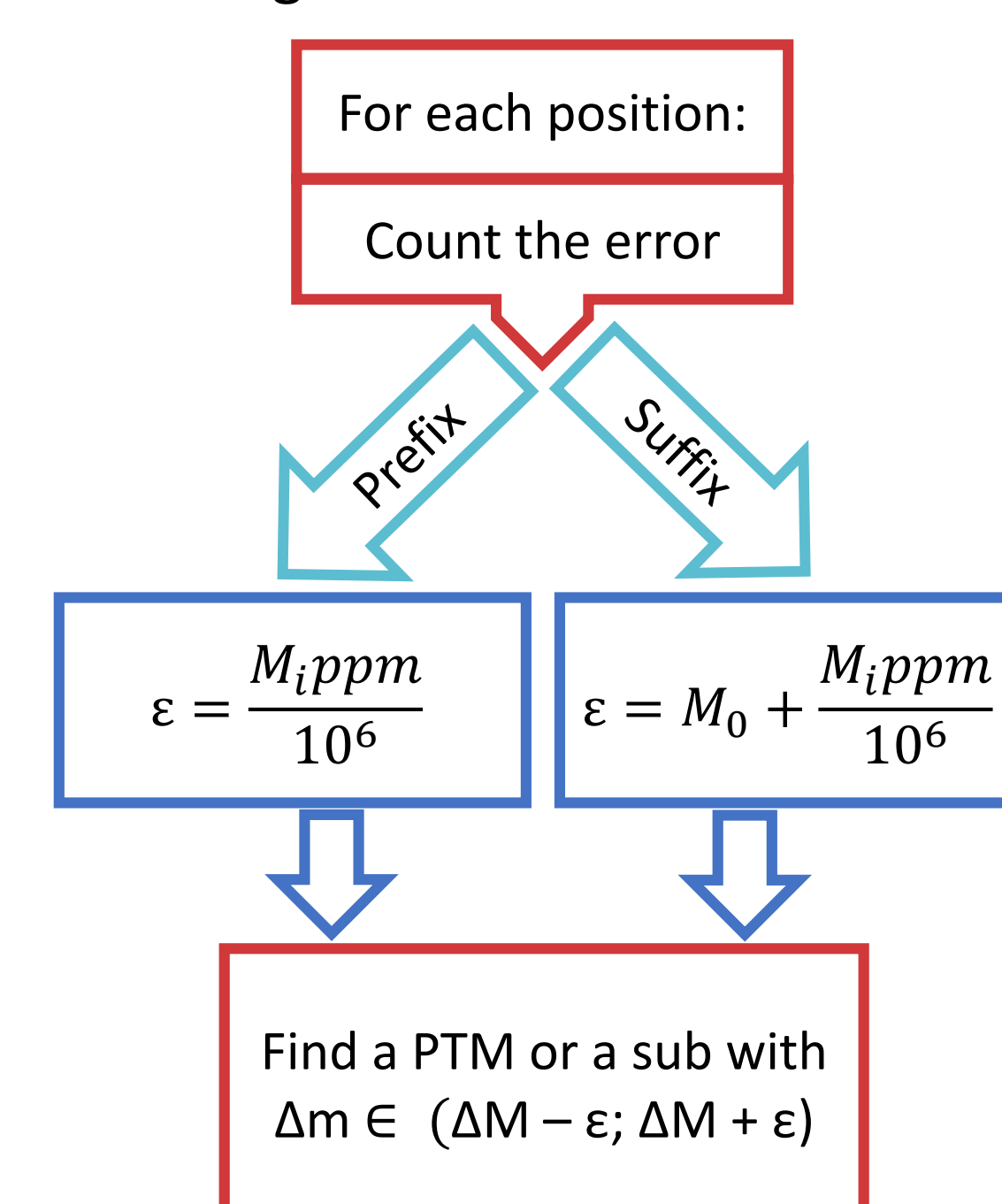


When a user clicks on some of the peptides, the main frame appears.

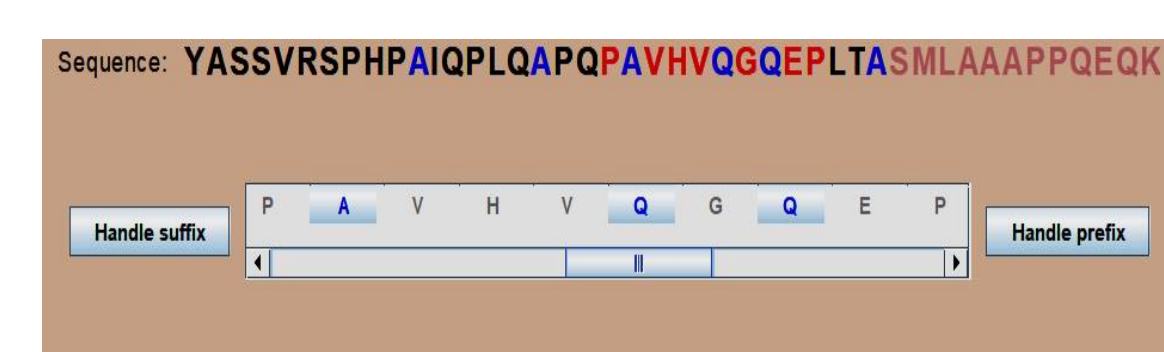
- 1 – the chosen amino acid sequence
- 2 – scrollable panel with zoomed amino acids
- 3.1 – button “handle suffix”
- 3.2 – button “handle prefix”

These buttons allows to choose the prefix or suffix, where the algorithm will search for PTMs and substitutions.

3. The algorithm



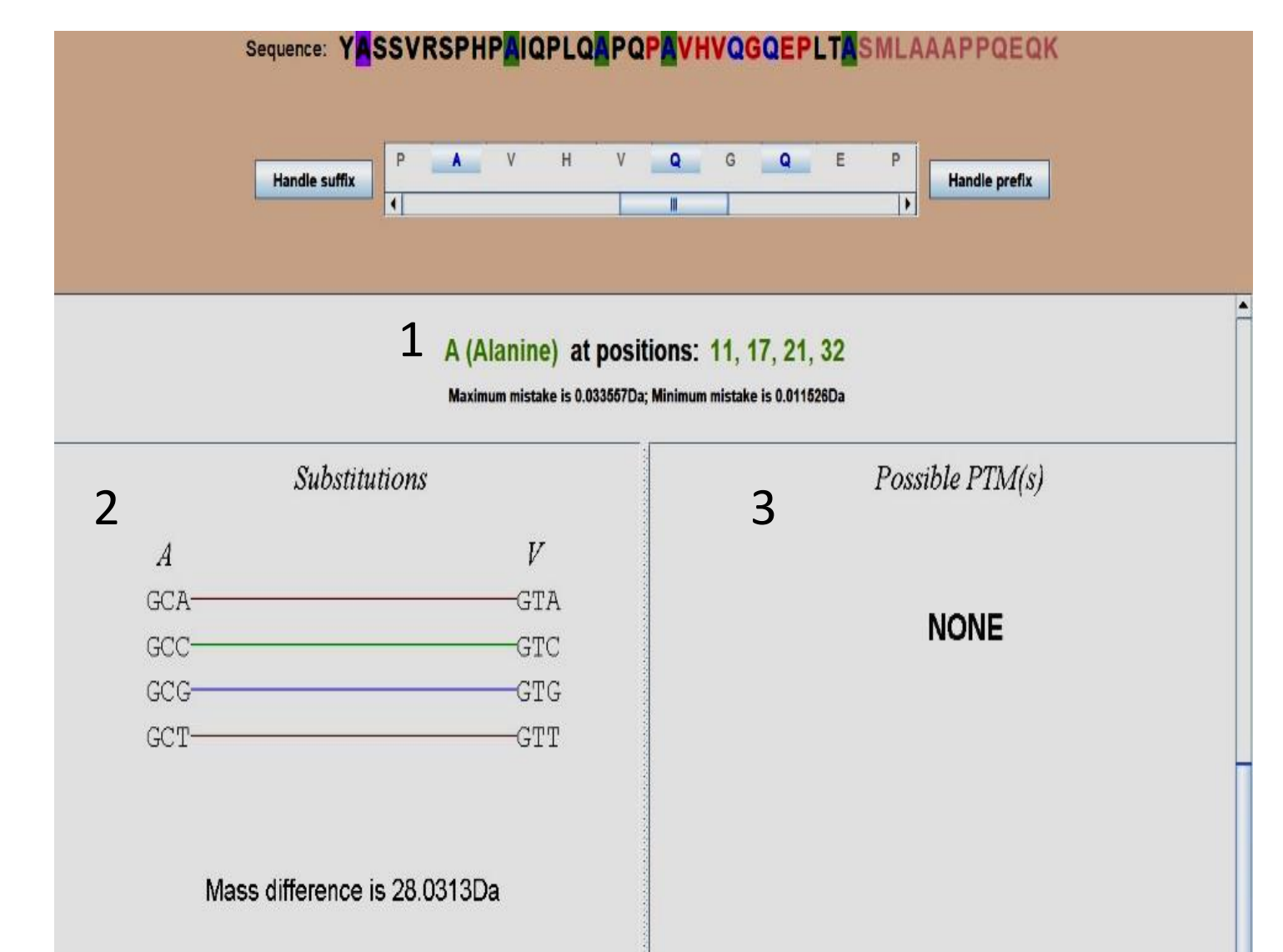
4. Highlighted positions



After this operation some of the positions appears highlighted. But not all of “A”s (and “Q”s) appears highlighted with blue color,

because closer is position to the beginning of sequence smaller the error. So, in the beginning the error is not big enough.

6. Information about substitutions

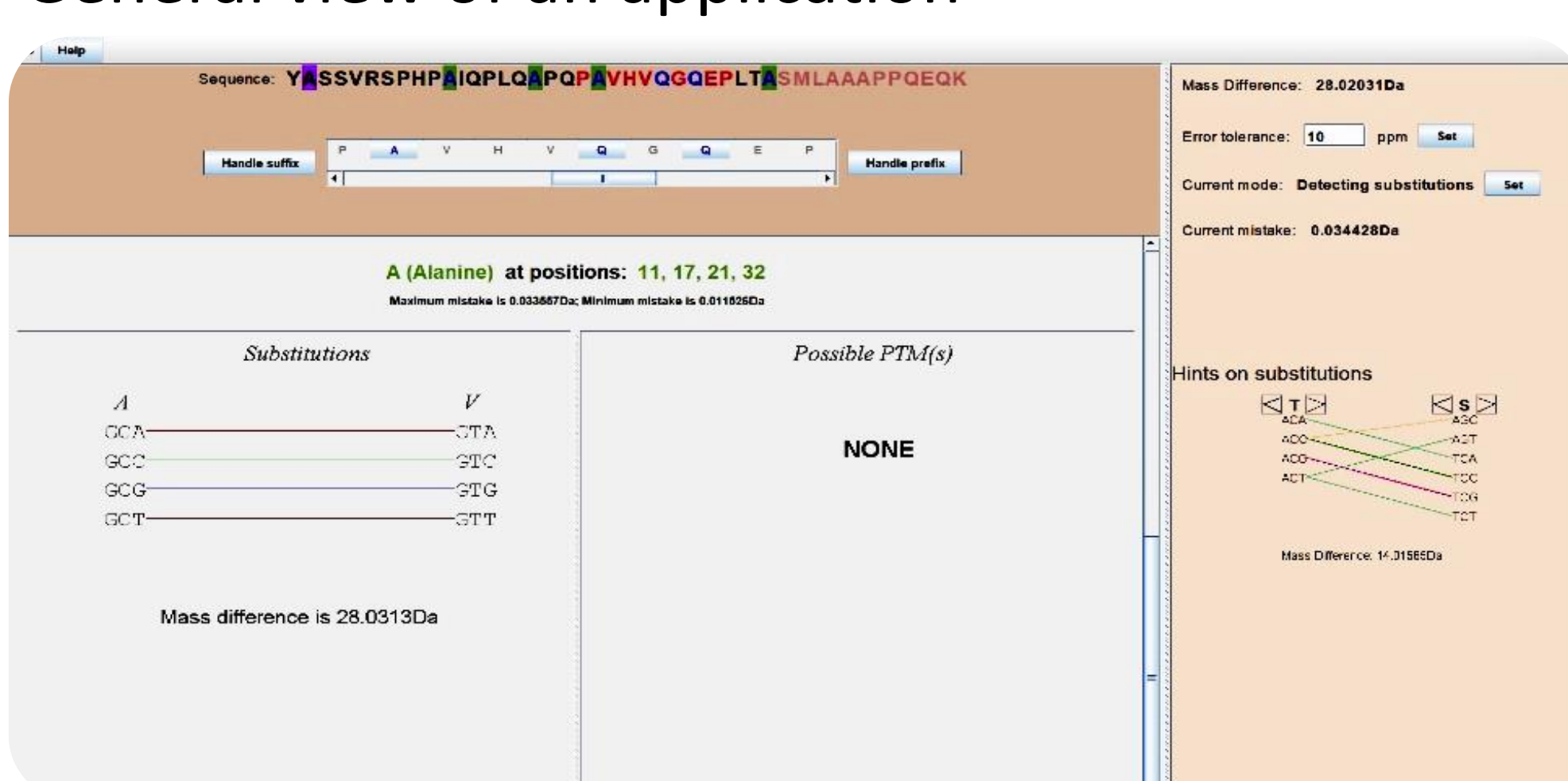


When a user clicks on some of the enabled buttons, the information about subs and PTMs appears.

- 1 – name of the amino acid under observation
 - 2 – information about substitutions
 - 3 – information about PTMs
- Some of the codons are connected with colorful lines because they can to get into each other by SNP.

Results and conclusions

General view of an application



Additional functionality

1. Tab help
2. Hot keys
3. Hints on substitutions

Testing

To test our software tool we took some peptides, which were analyzed earlier.

.pep file:

YASSVSRSPHPAIQPLQAPQPAVHVQGGQEPLTASMLAA
APPQEQQ SMLA prefix 4653.40152

Right result is

At positions 11, 17, 24: A>>V

At positions 13, 16, 22, 28, 30: Q>>R

Conclusion

The developed interface deals with high-resolution data, the algorithm which gives such data is new^[3], so there is no a lot of applications that using such data. Also, there is no a lot of graphical applications concerned with this subject

References

1. B. Lewin. *Cells*. BINOM Russia, 2011. 951 c.
2. S. Nie, H. Yin, Z. Tan, M. A. Anderson, M. T. Ruffin, D. M. Simeone, D. M. Lubman. *Quantitative Analysis of Single Amino Acid Variant Peptides Associated with Pancreatic Cancer in Serum by an Isobaric Labeling Quantitative Method*. J Proteome Res. 2014, 13(12):6058–6066.
3. K. Vyatkina, S. Wu, L. J. M. Dekker, M. M. VanDuijn, X. Liu, N. Tolic, M. Dvorkin, S. Alexandrova, T. M. Luidier, L. Pasa-Tolic, P. A. Pevzner. *De Novo Sequencing of Peptides from Top-Down Tandem Mass Spectra*. J Proteome Res. 2015, 14(11):4450–4462.
4. Qisheng Peng, Zijian Wang, Donglin Wu, Xiaou Li, Xiaofeng Liu, Wanchun Sun, Ning Liu. *Identification of single amino acid substitutions (SAAS) in neuraminidase from influenza a virus (H1N1) via mass spectrometry analysis coupled with de novo peptide sequencing*. Rapid Commun. Mass Spectrom. 2016