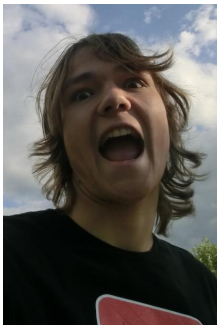
Contextproject Programming Life
Group 2 - GEVATT
Final Report

TU Delft



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Abstract

This is the final report for the Programming Life Contextproject, a second year course from Computer Science at TU Delft. The Contextproject course is about applying all learned skills in a particular context at developing an piece of software. In this case the context was bioinformatics and we worked 10 weeks with a team of five people.

This document contains the main information about development, implementation and validation of the product. Main features of the product will be presented and it will be discussed how they satisfy the user needs. Furthermore, this document will contain an HCI module about the interaction of users with the product. Finally, an outlook will be given to show what possible improvements could be implemented if this project will continue in the future.

Besides this document several other documents are made covering other parts of the project. This is the final document consisting of the most information about the project.

Contents

1 Introduction

The application developed is called GEVATT, which stands for GEnetic Variations Analyzer Through Triodata, which is an application used by doctors to browse genetic information of patients. Such applications are also called genome browsers. It is a secured web application based on the Play Framework. Doctors need to login from any device with a browser in order to use the application.

The application makes it possible for a doctor to upload a VCF file and let the application analyse it. A VCF (Variant Call Format) file is a file used in bioinformatics for storing gene sequence variations. This storing of genetic information of patients is based on variations between de patient and a reference genome. This is done because storing al information would be taking too much space. The

After uploading the file the user of the application, a doctor waits till the file is processed. In the meanwhile the doctor could browse other patients he uploaded information about earlier. After uploading, the first important part of the applications is executed: analysing the data. The outcome of the analysation consists of mutations found in the genome of the patient and the relations between these mutations.

Secondly, the main focus of the application is about visualising the found mutations. This is firstly done by giving a main overview of the whole patient. An overview of all chromosomes is given and per chromosome is indicated if and how many mutations it contains. Besides a visual overview of the chromosomes there's a tabular overview given with all mutations and some extra information per mutation. This makes it easier to estimate which mutations are more harmful than others.

Most information is shown on the overview pages per mutation. The pages with these visualisations have two visualisations which both give another insight in the mutation. The first part shows the position of the mutation relatively to a gene. The second visualisation is a graph based interactive visualisation showing proteins related to the mutation and the connections between these proteins. Here we also have a tabular overview per protein with per protein information about which deceases they could cause and to which other mutations of the patient they are related.

2 Overview

The developed product, a secured web application, is built on de Play Framework. It contains several parts that work together to deliver a user friendly environment for the users to explore genetic information.

2.1 Authentication

Starting with the basis, it's a secured web application where a user needs to login. After logging in some secured pages become accessible. Some other pages already are accessible before loggin in, e.g. the documentation and about pages. We distinguish the following parts:

- A login page

- Securing pages that aren't publicly accessible
- Redirect if secured page is unauthenticated requested
- Prevent doctors from accessing patients data of other doctors

2.2 Context specific

The web framework and it's builtin securing module isn't developed by ourselves so we could focus on developing the context specific parts. This was mainly separable in three parts: analysing data, retrieval of relevant data of databases and visualising data.

2.2.1 Data analysation

Analysing the data is done by processing the VCF file and detecting mutations. The outcomes of the processing is used in the visualisation. At both of these parts there's information used given by some databases. The information was used the get more information about mutations and find relations between several mutations. The application does the following:

- Read the VCF file and find mutations of two types: de novo's and recessive homozygous
- Save metadata about the uploaded file
- Find relations between found mutations

2.2.2 Data retrieval

Information from multiple databases is used for both visualisation and finding relations between mutations. This includes:

- Manage connections to multiple databases
- Querying databases to get relevant information from mutations and proteins

2.2.3 Visualisation

The most important part of the application: visualisation. Multiple views at the same found mutations are taken to give as most insights as possible. This includes the following visualisations:

- An overview of all found mutations in a patients VCF file with a view per chromosome
- Per separate mutation a distinct page with:
-
  - The position of the mutations relative to nearby genes
  - A graph with a protein related to the mutations and related proteins to that protein

3 Description

This chapter covers a detailed description of the developed functionalities in the product. The description is based on the overview of functionalities given in the previous chapter.

4 Human Computer Interaction (HCI)

As described before, we developed an application for doctors to browse through genetic information. A big challenge in this assignment was to make our product intuitive for the end users: people that have a complete other background then we all have. We couldn't just deliver a product, and hope it was good, we had to have some feedback from a person that was not involved in the project (but still had biological background).

4.1 Our action plan

After meeting with Willem-Paul Brinkman, we decided that we were going to organise an empirical evaluation. This evaluation should be of the type experiment, the experiment would make use of the **think aloud protocol**. As testing person, we had a fellow student at the TU Delft that studied nanobiologie named Max. We were going to give him a computer with our application on it, and give the following assignment:

> *You want to browse through the genome of patient John Doe, he is sick. He has the symptoms of Marfan's syndrome, can you look if you can find any traces of this sickness?*

We deliberately added the patient to the application, because adding a new patient and unploading his SNPs aren't the main concern in our project.

4.2 The realisation of our experiment

As expected, our test person didn't have any trouble to find his way through our dashboard (See Figure 1), this dashboard has a clear "Getting started" instruction that easily helps the user to navigate to the Patients page. Also when at the Patients page (See Figure 2), Max was able to directly navigate to John Doe.
When clicking on the patient John Doe, the patient overview page appeared (See Figure 3) . Here are a couple of quotes that our testing person made:

1. *"I see browse mutations, and a lot of vertical red lines. I suppose these lines represent the mutations that are found in the patient".*

2. After hovering over these so called mutations (they represent chromosomes), a new block with the title Mutations in chromosome X appeared, it became clear that Max was wrong. *"Ah, I see, these vertical lines represent chromosomes. Not that obvious since the header says: Browse mutations".*

Initially, our testing person was a bit confused by all the information that appeared. What is a rsID, what is a frequency and what is the CADD score? After some explanation (we basically told that the CADD score is an indication about how harmful a mutation could be), Max immediately sorted the column with mutations by the CADD score, and clicked on the mutation with the highest value. Our tester saw the mutation view (See Figure 4 and Figure 5). Here are a couple of useful quotes that the tester made:

3. *"I see a big vertical red line with a id on it, and a couple of horizontal lines next to it. I can imagine that the red line symbolizes the mutation, and that the black lines symbolize the proteins around it".*

4. *"So I guess that this central green bulb symbolizes the protein that has a mutation, but I'm not really sure how I can get more information to confirm that this is the mutation that causes the Marfan syndrome".*

Our tester was clearly not going to come further, we explained that the green bulb was clickable and useful information appeared. We stopped the experiment and started with the debriefing.

4.3 Debriefing

The first thing we asked Max was: "So what did you think of our application?" He was quite positive, most parts were quite intuitive. The main problem in our experiment was that Max wasn't exactly the end user. A couple of terms (like CADD score) were terms that he never heard of. We asked if there were any observations that Max had, and if he wanted to share them with us. Max answered that he didn't have a lot, he did think that the navigation in a mutation view could be more intuitive.

4.4 Conclusion

The numbered quotes that Max made and are included in this report are all quotes that we used in making our product better. Quote number one for example made us realise that the heading "Browse Mutations" is inappropriate when it is placed above 23 pairs of chromosomes, this was confusing an is renamed. Quote number three was a confirmation that our mutation overview is quite intuitive, quote number four however still gave us an improvement: we should make it clear that the round Proteins are clickable. We implemented this with a tooltip that pops up when hoovering over the protein.

5 Evaluation

This section describes the evaluation of the functional modules and how they are tested to guarantee that each module performs as required. Furthermore the failure analysis is discussed to show where the product does not perform as needed.

5.1 Evaluation of functional models

asdf.

5.2 Failure analysis

We rely a lot on data coming from other systems. First of all we have to read VCF-files to load the data of a patient. This is done by a doctor which could load a corrupted file to our server. This causes the system to stop processing the current file and the error will be written to the log. At the moment there is no notification to warn the user of this error, however this could be simply added in a future release.

Second we need access to external databases to retrieve relevant data. As these databases are too large to host them on the same webserver as the application, we cannot expect to always have a connection to the remote server. However we also store basic information in a small database on the webserver which stores the basic information such as authentication, user data and patient data. This helps us to always have a basic running system. If for some reason the connection to the database is dropped the application will continue to function, but now information is loaded. In the future we could added useful notifications to the user about database problems.

Thirdly a user could direct his webbrowser to an invalid URL, in this case a "Not found" page will show, to prevent retrieving private information from the webapplication. Also when something goes wrong in the application the user will be sent to an "Error" page, which will only show a basic error and not the full error trace, which could expose our application logic.

6 Outlook

GEVATT is developed in quite a short time. The course Contextproject lasts about ten weeks and in this ten weeks the team had to become skilled in the context, make accompanying documents and present the final product. So only a limited part of the time is actually used to develop the application. This means there's focussed on the main parts of the application and there are more functionalities that could be added later if development would continue. This chapter is about what functionalities could be added.

One thing is exporting; this is currently not possible in the application. The found mutations and information from the VCF files are only visible in the application itself and require logging in. For a doctor, it might be handy to export some data and visualisations to make it easier to present them. E.g. it's easier for a doctor to show a print of visualisations to his patients than showing a screenshot of the application. It also might be handy to have the data exported to a spreadsheet format.

The application is web based and therefor in principal platform independent: each device with a modern browser and an internet connection could open the application. Something that is limited to the use of the application now is the minimum screen width. When a device with a resolution of lower than 1024px is used, the user need to scroll to see all information. The application could be modified so that the layout adopts to smaller screens and become thereby usable on tablets and phones. A nice feature, but is questionable if a doctor would use the application on such devices.

Currently the application is mainly focused on individual mutations found in the uploaded data, and less on the relations between these mutations. When

development of this application would continue, it will probably make sense to focus on implementing/extending visualisations that show these relations.

Testing is only done on a low scale. If GEVATT would be used in production, there should be some testing be done based on heavy use. Furthermore, if the application would be used in producten, some managing features should be added. For example, creating accounts en revoking access to specific doctors. Due to time considerations this is left out in this project so far.

7 Apendix A: Screenshot

Here are a couple of screenshots of our application.

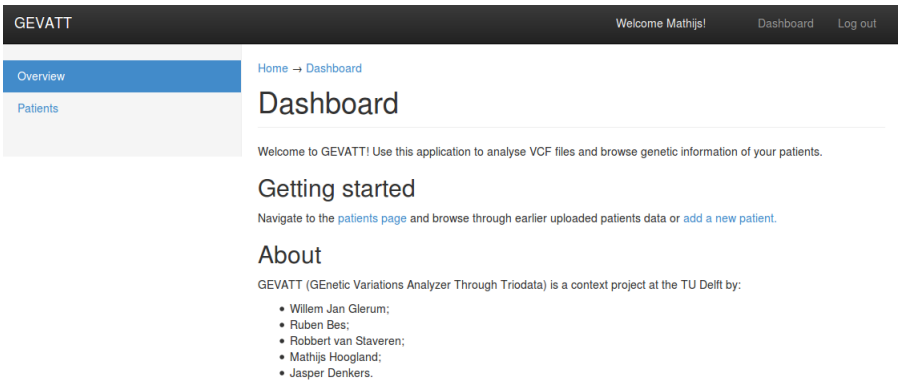

Figure 1: A screenshot of the dashboard

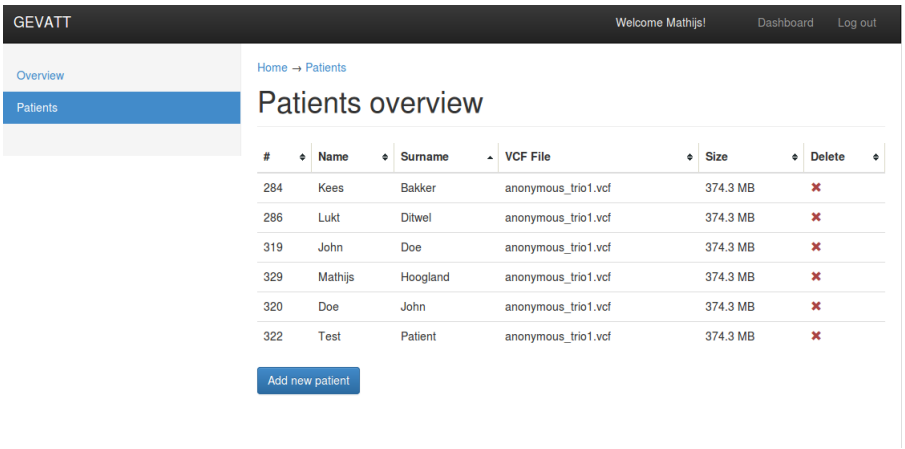

Figure 2: A screenshot of the patients view

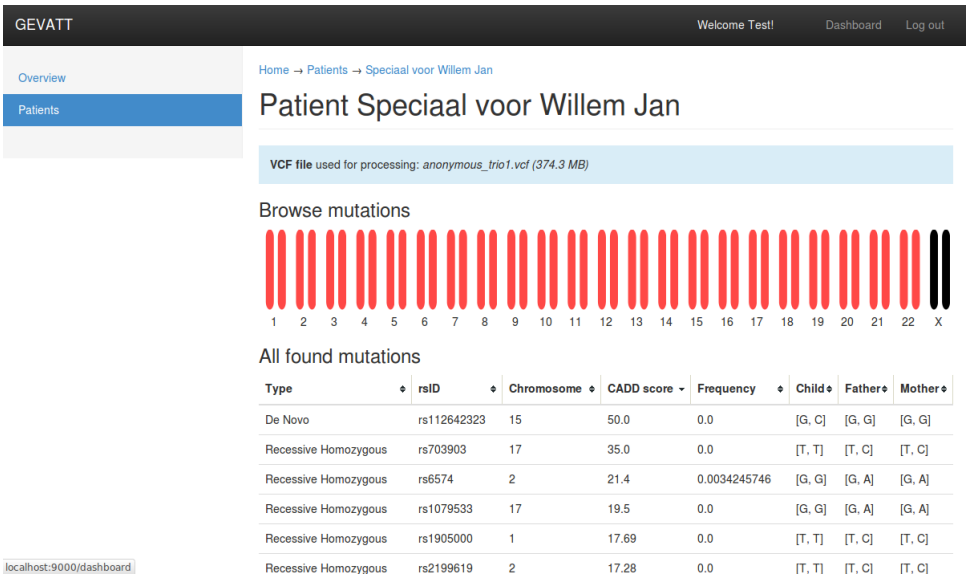

Figure 3: A screenshot of the patient view

Figure 4: A screenshot of the mutation view

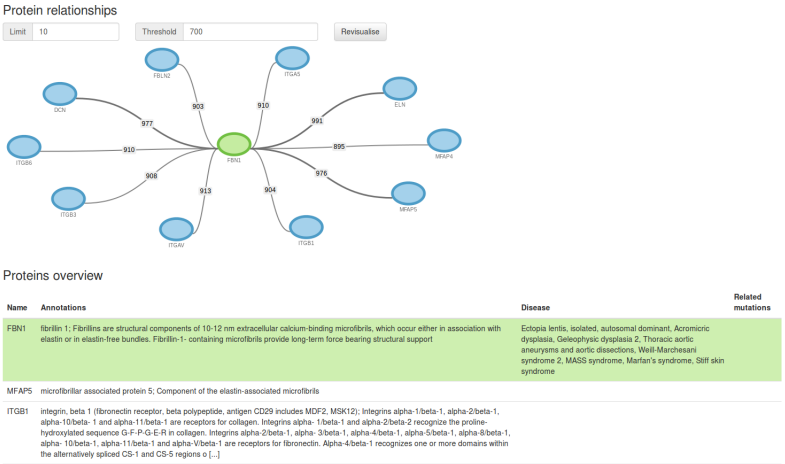

Figure 5: A second screenshot of the mutation view