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Identification of Relevant Genes with a Multi-Agent System using Gene Expression Data

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1. Introduction

In recent years, technology for information extraction from gene activity in cells, has made an important breakthrough with the DNA microarrays. With this technology it is possible for researchers to know which genes are active in a particular cell in particular situation. The comparison of gene expression patterns (which genes are active) of two cells of the same type, one normal and the other belonging to a tumor, can be of great help in understanding what are the genes that might be involved in the tumor formation.

Microarray technology is a high throughput information extraction technology; with a single microarray it is possible to extract, at once, information about the expression of thousand of genes. A typical experiment might involve the study of several microarrays and the comparison of the information extracted from them with standardized microarray gene expression databases.

From a computing point of view, microarray technology, opens interesting research issues at different levels, like data analysis and statistical information processing, information standardization, and automation of the whole information processes involved in each experiment.

This chapter addresses this latter issue. We present a multi-agent platform automating information processing of experimental microarray samples and its comparison with publicly accessible microarray databases.

A complete system for gene expression analysis can be based on different agents to solve parts of the problem, and due the diversity of paths that knowledge discovery could find, a system based on coordinated multiple agents can improve performance.

Here we describe a multi-agent system that was used for gene expression analysis in samples of cervical cancer for obtaining specific knowledge about the genetic basis of the cancer. Cervical cancer is one of the most common in Females. Its incidence in Mexico (50 per 100,000 inhabitants per year) is among the highest in the world (Lazcano-Ponce, 2009).

Section 2 presents an introduction to microarray for gene expression analysis; in section 3 there is information about multi-agent system technology related with gene expression

analysis; in section 4 we discuss the architecture of a multi-agent system proposed, in section 5 we present the outcome reached and finally the conclusions.

2. Background gene expression analysis with microarrays technology

Microarrays are a molecular biology technique that appeared in 90's which display the expression of thousands of genes in a matrix.
One kind of probes that can be used for the design of microarrays is transcriptome others can detect loss or gain of genes and other mutations can be detected in DNA. The difference between each of them is the type of DNA that is fixed on the plates of the microarray.

2.1 Microarrays that detect changes in gene expression

When one wants to determine a change in the level of expression of a gene, this may be detected by expression analysis of microarray called chips or biochips. The DNA to be studied is immobilized by hybridization of mRNA, a known gene product by cDNA. This comes from healthy tissue cells (control) and patients (study samples). If a gene is over expressed in a certain disease, a greater amount of cDNA hybridizes at a point (spot) representing the affected gene and therefore the fluorescence intensities are dissimilar between the study group and the control group. Once characterized the genes involved in certain diseases, the cDNA of human cells may be hybridized to determine whether the person has the pattern of gene expression related to disease and to optimize diagnosis and treatment.
The chips of gene expression can also be used to determine changes in the expression over time, such as during the cell cycle. This represents an important tool in cancer research, that could identify new cancer markers for diagnostic purposes.

2.2 Microarray data analysis

The true potential of microarrays is realized when they are used for global approaches to gene expression patterns. There have been large-scale analyses of gene expression changes in bacteria, yeast and in animals to identify genes with similar expression pattern. To this end we have developed computer programs that may interest the researcher because they facilitate this type of global analysis. In this type of analysis one first identifies genes with significant changes during the experiment.. This is achieved by filtration of genes and identification of active genes. After obtaining purified data on a reduced number of genes grouping or clustering methods are applied. Several methods have been described (hierarchical clustering, self-organizing maps, k-means), each with tradeoffs.
Currently we recommend using more than one technique for each data set. The idea of identifying clusters or partitions of genes is that genes that have expression patterns contain near the same regulatory mechanisms, and eventually could create maps for precise control of transcription.
Microarray analysis provides quantitative information about the complete transcription profile of cells that could facilitate drug and therapeutics development, disease diagnosis, and better understanding basic cell biology. One of the challenges in microarray analysis, especially in cancerous gene expression profiles, is to identify genes or groups of genes that are highly expressed in tumor cells but not in normal cells and vice versa.

After reading the microarrays and creating the numerical matrix with gene expression intensities the analysis process continues with data normalization, filtering of genes and clustering samples and/or genes.

2.3 Normalization of data

The signal obtained from microarrays must be standardized or normalized because its difference expressed in the genes among the samples could differ a lot, so that data from different microarrays can be reliably compared. These methods are applied in the pre-processing of datasets.

The normalization is applied to expression data to adjust the individual hybridization intensities of genes in the microarrays.

The oligonucleotide microarrays are normalized using the two algorithms more reported, Affymetrix Microarray Suite *(*MAS*)* and Robust Multichip Average (RMA) (Irizarry, 2003), which remove the variation in overall chip intensities.

And finally in the preprocessing phase the transformation of level expression of genes to an equal rank in all chips permits a continuous spectrum of values. Generally the Log2 transformation is used with the clustering methods.

2.4 Statistical analysis

In order to reduce the initial amount of genes included in the microarray analysis it is recommended by specialists to use statistical methods, like T-test and significant analysis of microarrays (SAM) (Tusher, 2001). With these statistical tests experimental results are compared to standard samples for differences in gene expression according their signal values in nature (molecular biology).

With SAM differentially expressed genes are chosen using the false discovered rate (FDR), which represents the ratio of false positives to all positives according to a determined threshold.. The T-test uses the p-value of the fold change value (FC) that express the difference of genes between two groups of samples. In the case of SAM this value is expressed with delta value (Δ-value). The amount of filtered genes depends on the chosen threshold for those parameters. Also, the FC and d-value could show if the differentially expressed genes are up or down regulated.

When there are two experimental conditions, the most basic statistical test used for the two-sample comparision are differential expression tests within genes like SAM and T-test.

2.5 Genes differentially expressed

A key goal of microarray experiments is to identify genes that are differentially expressed while keeping the probability of false discoveries acceptably low. From a statistical perspective, it involves minimizing false negatives or maximizing power of the statistical test (sensitivity), and minimizing false positives (specificity). Microarray data are often assessed as fold-changes between experimental conditions. While this scale has interpretive value, inference based solely on fold-change is misleading because error variability for each gene is heterogeneous under different biological conditions and intensity ranges.

The main application of biochips is the comparison between genes expressed in diseased tissue and normal tissue to find those genes that change significantly their level of expression and thus related to the disease.

This finding could help to identify genes or groups of genes as targets for potential therapeutic intervention or prevention of diseases, like a cancer or diabetes.
The expression level could increase, this case exists when the gene is up regulated, or decrease, gene is down regulated, in the experiment. With this information researchers create sets of genes in order to find the minimal number of marker genes identifying potential points for therapeutic intervention, understanding tumor behavior and for facilitating drug development.

2.6 Machine learning and gene expression analysis

Machine learning is a computer area with a very important application in Bioinformatics. It has methods for knowledge discovery of molecular biology to identify genes or to find gene patterns.
Some reasons to apply machine learning in Bioinformatics are (Bergeron, 2003):

- New experimental approaches based on biochips, which can obtain huge genetic data from individual genomes (mutations, polymorphisms) or cellular approaches (gene expression).
- The huge volume of data generated by various genome projects (human and other organisms).
- Universal access to databases of biological information.

Machine learning approaches perform well in domains with a large amount of data, this is the situation in gene expression analysis. There are two types of learning: supervised learning, where the learner has some prior knowledge of the data and the output has been given a priori to the learner, and unsupervised learning, where no prior information of the output is given to the learner.
Machine learning supervised and unsupervised methods have been used in applications of gene expression analysis like Gepas (www.gepas.org), Dchip (sites.google.com/sites/dchipsoft/), Weka (www.cs.waikato.ac.nz/weka), and works like (Tamayo, 1999; Dembelé , 2003, Wang 2003; Márquez 2008)

3. Gene expression analysis through agents technology

3.1 Microarrays and multi-agent systems

The use of microarrays in genetic studies is a very dynamic field, new applications, new procedures and new microarrays with more gene capacity are appearing all the time. These are not the only changes in this field. A whole area of active research and new findings is emerging, related to the generation and management of all the related data, as well as the statistical studies of it, including machine learning techniques for better test selection procedures.
Such an information-intensive, dynamic field demands a flexible approach for information system design. It is clear that a traditional approach of solving the basic information processing issues of one particular application as a single fixed process will not survive long due to rapidly changing procedures and related technology. This rapid change introduces extra complexity to the information processing involved in the general problem of the information exploitation of microarray applications.
Now, agent technology offers an advantageous alternate option for building software in bioinformatics. The complexity of required systems offers an advantage to an architecture

that can distribute tasks to specialized agents. Recently, there has been some agent-based systems to tackle the complexity of bioinformatics systems (Karasavvas, 2004; Keele, 2005; Lam, 2006; Luck, 2005; Merelli, 2005; Moreau, 2003; Štiglic, 2004).
We distinguish the following basic processes in the microarray analyisis system, that would be better handled by specialized agents:

1. Pre-processing, application of a set of techniques and methods of analysis prior to data mining, to work with different algorithms whose nature will be assessed at processing time.
2. Mining, in this step there is advantage to using different machine learning algorithms for finding patterns and relationships of genes and tumors.
3. Representation, a simple representation of the information and findings with diagrams, graphs and tables to make the results easy to understand.
4. Interaction with external databases, , the use of databases that exist on the Internet, as well as for the handling of knowledge generated and control their access.

3.2 Current situation

Today, the process of gene expression analysis to identify genes involved in diseases. It is in many cases quite troublesome for researchers since they need to go through different tricky stages of the process: a) There is no single package solution; they need to use several software programs to complete the analysis. This implies the user must provide the data format required by the program and the user must understand the software performance, this is not easy; b) the user must have some experience or he must make many experiments with the parameters of the programs to solve his problems, and make many experiments and, c) with the result of their experiments they must search information for characterization of genes using external databases. The previous process is more difficult if you consider that the researchers, in most cases, are biologists or medical scientists with only basic knowledge in computer systems and they have to do almost manually. With a view toward helping or solving those problems we present a multi-agent system.
The aim of our research is to automate the whole gene expression analysis process. To do that we organize our system architecture in a 2-layer structure. The upper layer is where the different agents interact. Each agent is a specialist in a well-defined component of the process and has the skills to se different types of mathematical and computing tools. The lower layer corresponds to the specific tools needed in each component of the process. The general strategy to solve a specific type of gene expression analysis is defined at the upper layer where multi-agent technology can look for the best procedure through the multi-agent interaction protocols facilities. The decisions of which specific tools need to be used for each task are taken by each agent who is a problem solver specialist.
Our multi-agent system has been developed as a bioinformatics tool to help researchers in two main tasks, 1) gene selection through an expression analysis process, and 2) tumor classification. This tool must be conceived as part of the toolset available to the human researchers in order to assist them during the diagnosis process.

4. Multi-agent system for gene expression analysis (MAS-GEN)

In order to accomplish the process of gene expression analysis using a multi-agent system architecture, we identify four operational agents coordinated and organized by one

manager. The gene identification process can be distributed among a few operational agents, each one in charge of a specific subprocess. And some tasks can be solve in parallel.
We decompose the gene specification process in the following subprocesses: preprocessing data, gene identification, tumor classification and use of external databases, as showing in figure 1. Each subprocess is assigned to a specialized agent to carry out the current tasks and to make the right decisions that allow reliable and useful knowledge.
The MAS-GEN system is in fact a new layer inserted between the user and the specialized problem solving toolsets used currently in the semiautomatic setting. The multi-agent system for gene expression analysis involves the completion of different tasks that can be distributed among autonomous agents.
In addition to the four operational agents, a manager agent is in charge of the coordination and the planning of the overall process and mediates the communication between the agents. These agents are rule based problem solving systems programmed in Clips, a well-known expert system shell.

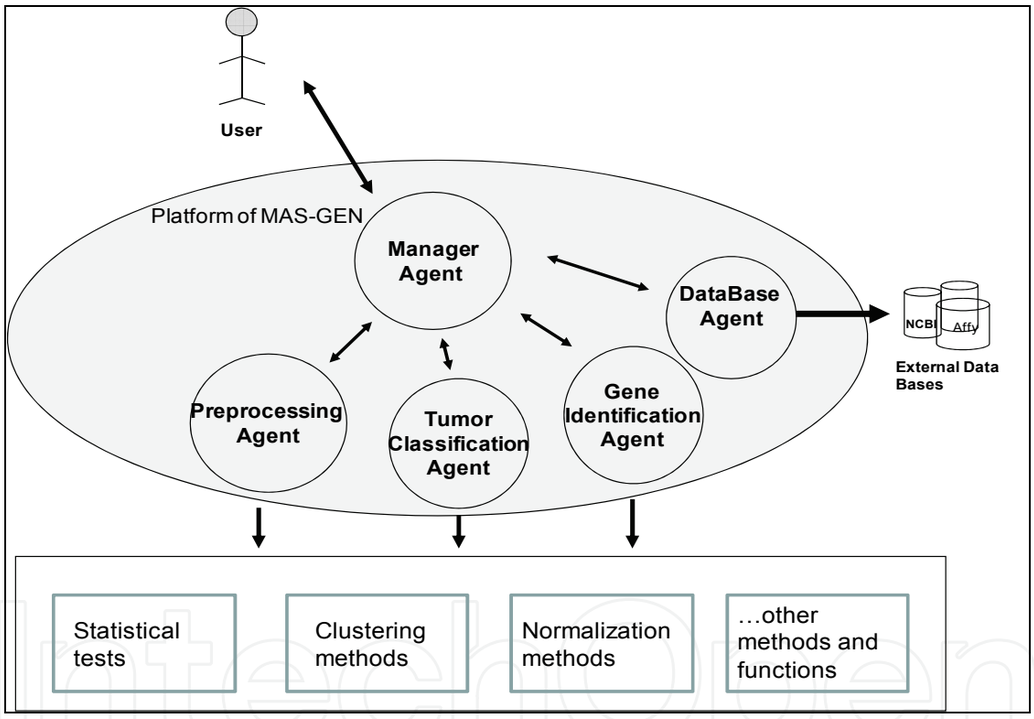


Fig. 1. MAS-GEN architecture for gene expression analysis. The platform of agents includes four operational agents and one manager agent. The specialized methods for solving their task are independent of agents. The external databases are used through database agent

Our agent platform has been tested for gene expression analysis using microarray samples of tumor cells of cervical cancer. However, its architecture is flexible enough to incorporate other functions or procedures to work with other type of diseases and other Affymetrix GeneChips. This is due to its layer architecture that separates the agent's process logic from its toolset layer where can coexist different concurrent tools in such different programming languages such as Java, C or R. This layer independence allows our platform to incorporate or modify new functions for the processing, analysis and data presentation tasks, causing no problem in performance.

4.1 Platform of agents

4.1.1 Preprocessing agent

The preprocessing agent get the data of intensity of expressed genes, it could use functions already implemented in the R language for microarray of Affymetyrix by Bioconductor (http://www.bioconductor.org/). Intensities may come from a single microarray or several at once, according to the user request. This agent must normalize the data, the algorithm RMA (Robust Multi-Averaging) (Irizarry, 2003), or MAS (Normalization of Affymetrix), (http://www.affymetrix.com/support/technical/manual/) which are currently the most widely used directly on data from Affymetrix microarrays and/or apply log or log2 on data already read. According to the task to be executed with the data, identification of genes or the classification of tumors, this agent decides what must be the data format in the matrix. The normalized data are assigned to an expression matrix. If the expression data of one gene in the matrix are incomplete the agent obtains the values or removes the raw data to avoid noise in data.

4.1.2 Gene identification agent

The gene identification agent's goal is to extract a list with the most important genes and reducing the initial amount of genes. If the agent has enough data it will apply the most used statistical filters, t-test and SAM (significant analysis of microarrays) (Tusher, 2001). Through the filters the agent reduces the number of genes from thousands to hundreds or less. According to the user request, the agent obtained the final list with the most relevant genes. The agent uses clustering methods to create the lists of genes, from the formated data that it gets from pre-processing agent. It could interact with the classification agent to test the capacity of lists of genes to classify the samples, controls and cases, and with the agent of external data bases to characterize the genes. With the knowledge provided by the others agents this agent decide what genes could be more important in the experiment.

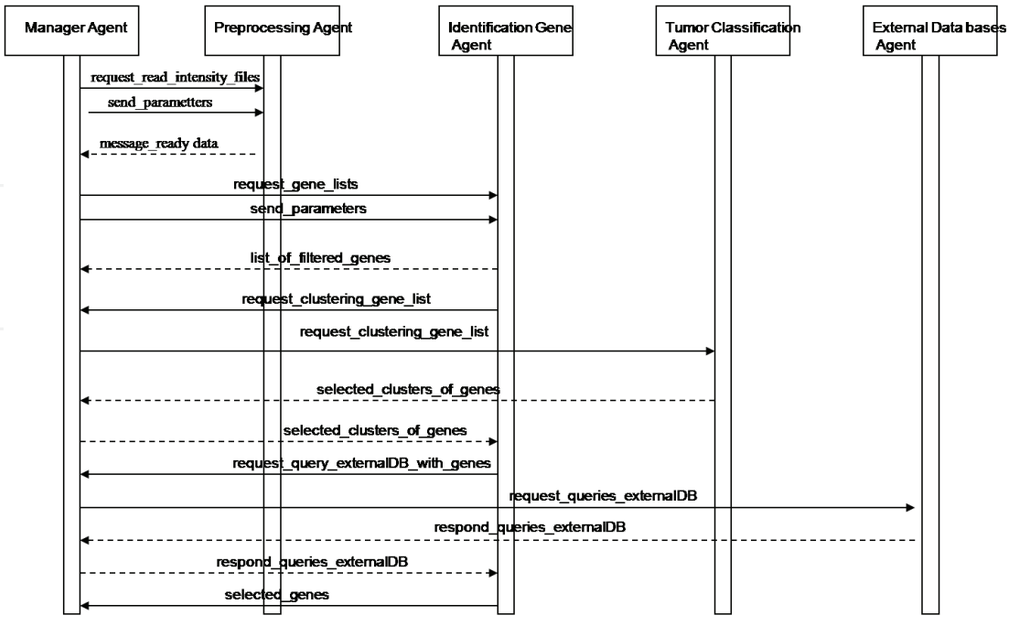


Fig. 2. An example of the sequence of messages to identification of genes. The agents send and receive messages with the manager agent when other requires something to another agent

4.1.3 Tumor classification agent

The goal of this agent is grouping the microarray samples, i.e. control and cases, as well as the identification of cancer type and tumor variants. For creation of groups in the samples, the agent uses machine learning, clustering methods like self-organizing maps (SOM) (Tamayo. 1999), vector quantization (VQ) , fuzzy k-means (c-means) (Dembelé , 2003; Wang 2003) and principal component analysis (PCA) (Price, 2006).

If the request for classification of samples comes from the gene identification agent, the tumor classification agent must review if the list of selected genes could classify in control and cases the samples. In this case the agent uses clustering methods and should select the lists of genes with less misclassification samples.

If the request of classification samples is the main goal of the user of MAS-GEN, the agent must find the clusters with the patters of samples, which could represent variants of cancer type. Once one has groups of tumors, another task of this agent should be to indicate what kind of tumor represents a new sample, which helps to determine accurate treatment.

4.1.4 Database agent

The goal of this agent is gathering knowledge about the identified genes. There are several databases that give access to genomical information through the Internet that will help in the characterization of genes to identify the relation between a gene and diseases. This agent will execute the queries to the external databases, and will standardize the results.

With the knowledge of the genes that this agent gets, the gene identification agent should verify the relevance of the genes, i.e. in a biological process, in a biological function, about the disease of the study

4.1.5 Manager agent

The manager agent coordinates all activities of the multi-agent system. It does the planning for the overall solution and distributes tasks among all agents, according to their specialization. The communication that is required between the agents is through this agent, since it is responsible for sending and receiving messages among the agents, the other agents can not interchange messages directly. Each operational agent only has permissions to send and receive messages with the manager agent, they can not access directly any other agents in the system.

At the request of the user the manager agent plans the general task that each must do. The manager agent organizes and coordinates the cooperation of all agents.

The other agents plan and execute their tasks in an autonomous fashion. The manager agent waits for queries or results of other agents and the user.

We had decided on a centralized architecture for MAS-GEN due to the small number of processes that may be involved all our agents; rather than an architecture where different actors could negotiate among themselves solutions.

4.1.6 Agent ontology

The agents have an ontology about their domain, they need to use the same language to interchange knowledge about genes, diseases or genomic words. The ontology defines the structure of messages that indicate the request to another agent and the answer, also defines the concepts about the problem domain.

For the database agent the ontology is very important because it has to communicate via Web to genomical databases and gets the knowledge about genes, searches and gathers relevant information to make decisions by other agent like the gene identification agent. Actually most genes do not have a unique name or identification, according to the database then it is important to have an ontology to find information in different sources in the Internet.
Example of ontology:
Concept Gene:

Their attributes or fields of its structures are: ID, symbol, source_information, chromosome, pahways, disease relation and more.

4.2 Responsibilities of the agents

The reponsibilities assigned to each agent of MAS-GEN are in table 1.

Agent	**Responsibilities**
Preprocessing Agent	Read data files Data normalization Statistical tests Data format Local planning Send/receive messages
Gene Identification Agent	Create lists of genes Filter of genes Clustering of genes Request information of genes Characterization of genes Send/receive messages
Tumor Classification Agent	Find patterns of samples Clustering of samples Evaluate clusters of genes Classification of new samples Local planning Send/receive messages
External Data Base Agent	Communicate with external databases of genes Get information of genes from databases of genes Local planning Send/receive messages
Manager Agent	Coordinate other agents Global planning Communication with the user Show the results Send/receive messages

Table 1. Responsibilities of agents in MAS-GEN

5. A case study

5.1 Data set

The multi-agent system for gene expression analysis has been used to help identification of relevant genes related to cervical cancer.

Data of gene expression was generated using the Affymetrix HGFocus GenChip of mRNA that contains ~8600 genes. The sample taken from 41 Mexican women with diagnostic of cervical cancer and from 12 controls (from women without cervical cancer). All tumors correspond to Human Papillomavirus 16 (HPV16) infection that represents the most important risk factor for the development of cervical cancer and are linked to a high incidence of cervical cancer in Mexico and HPV16 is the most frequently detected (50%) worldwide (Sanjosé, 2007).

The experiments to identify the involved genes in the process of cervical cancer using the multi-agent system, requires the cooperation of all agents of the system. In the sequential graph of figure 2. there are interchange requests among the operational agents via manager agent. MAS-GEN can perform various experiments with the data with minimal user intervention.

The manager agent does the overall planning with different configurations of methods or tasks to be executed by operational agents. That is the overall planning is composed of sub-plans in which combines the types of normalization of data, statistical tests for filtering, clustering methods to group genes, and/or samples and databases for characterization of genes.

The user can obtain results with different lists of genes found as relevant by all these sub-plans. MAS-GEN helps to identify the genes that occurred more relevance easily.

This does not mean that the user can not interact in the process. The user could also select the processes that are considered appropriate for analysing gene expression. Also MAS-GEN can help those researchers unexperted.

Here are some results obtained for gene expression analysis using data from samples of cervical cancer with MAS-GEN.

5.2 Results

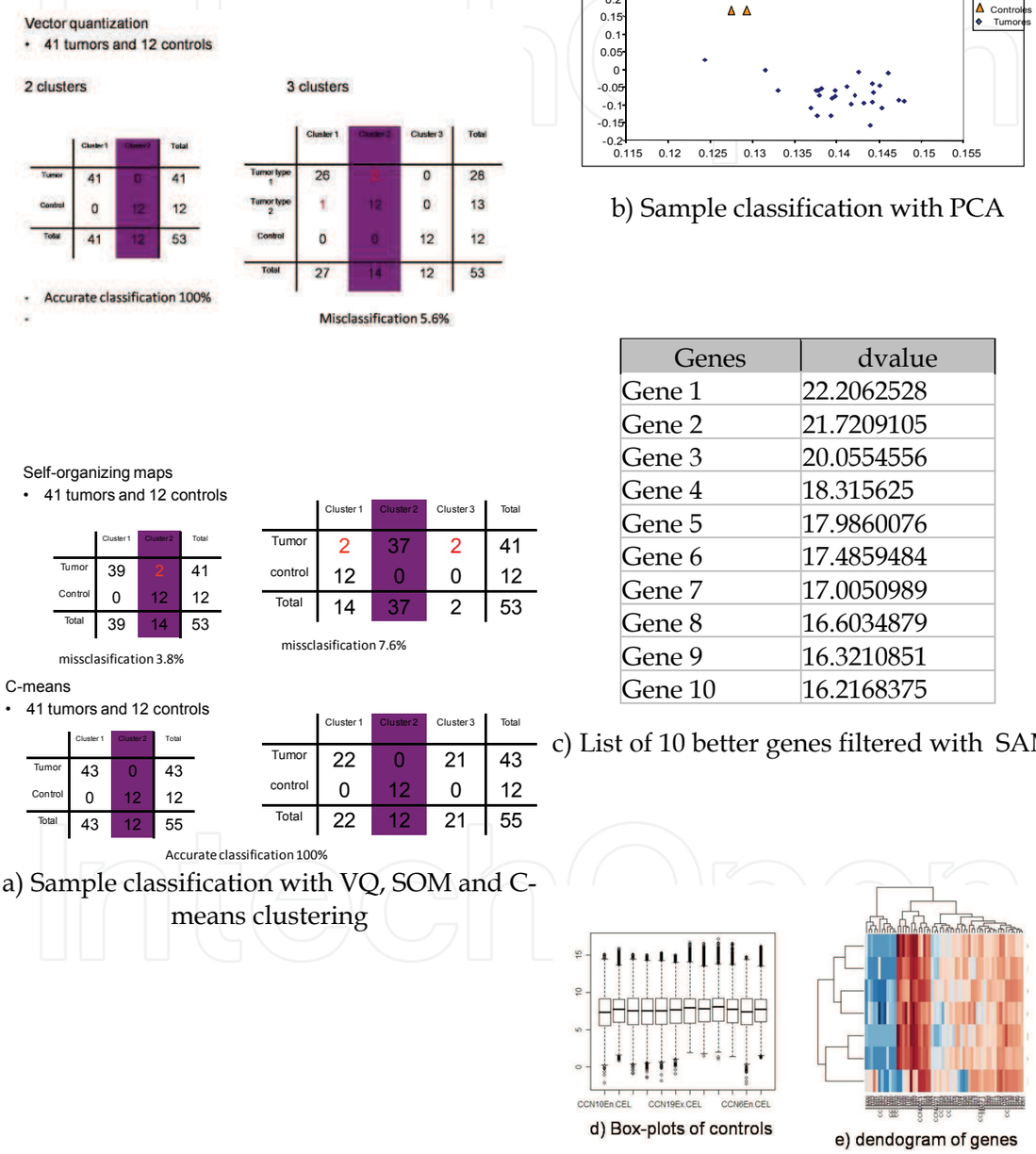
In figure 3 there are some tables that present to the user the results of gene expression analysis with MAS-GEN. The presentation of results is through the manager agent, according the information could use tables and charts.

The results presented in tables seen as 3a, show the clusters created with a selected list of genes. The gene identification agent selects the lists of genes and checks on collaboration with the tumor classification agent the capacity of genes to divide the samples in the basic groups: control and cases. In 3a, there are 3 tables of this way, one for each cluster method: SOM, VQ and c-means. In this case can see VQ and c-means are the better methods to classify the samples with fewer mistakes.

In 3b, we reduced the number of dimenssions of the samples, to 2dim, in order to create a graphic to visualize the separation of samples. We used the 2 principal components generated by PCA method. In the graphic it is clear the separation between this 2 basic kinds of samples:tumor and controls.

The table 3c shows the user see the results given by the SAM statistical method, to find the differentially expressed genes.

Finally, the system can create graphics like boxplot and histogram to see the distribution of data and also a specific normality graph.



b) Sample classification with PCA

Genes	dvalue
Gene 1	22.2062528
Gene 2	21.7209105
Gene 3	20.0554556
Gene 4	18.315625
Gene 5	17.9860076
Gene 6	17.4859484
Gene 7	17.0050989
Gene 8	16.6034879
Gene 9	16.3210851
Gene 10	16.2168375

c) List of 10 better genes filtered with SAM

a) Sample classification with VQ, SOM and C-means clustering

d) Box-plots of controls

e) dendogram of genes

Fig. 3. Examples of result presentation to user from MAS-GEN

Another clustering method, the hierarchical dendogram to join up samples or genes.

The user could see the results of the better lists of genes, with the information about the capacity of sample classification, characterization of genes with queries of DB agent. The knowledge given by MAS-GEN allows to the user to support the decision of selected genes.

6. Acknowledgments

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7. Conclusions

The multi-agent system is a tool that helps biologists and medical teams responsible for the analysis of gene expression to better understand the genetic details of disease. MAS-GEN provides a comprehensive and flexible tool for performing various procedures instead of using several different software applications representing an investment of users time and adaptation of their data to those applications. In addition, with MAS the decision-making and analysis flows in an automated fashion via the manager agent.

Distributing the analysis into pre-processing methods, data filtering, machine learning, and presentation and display of results provide a versatile system that can be conveniently adapted to the rapidly changing area of genomic bioinformatics. The modular architecture of independent multi-agent software allows for straight forward implementation of procedural changes without troublesome dependency-related software conflicts. This flexibility also insures that software development effort will not become obsolete.

The analysis of gene expression is feasible through a multi-agent collaboration with the operational agents specializing in distributed tasks of data preprocessing, gene identification, classification of tumors, and database management. A single management agent assigns tasks and controls data flow, simplying the human interaction with the system. Some of the operational agent work can be executed in parallel because the agents have sufficient independence.

This system further facilitates and simplifies the completion of the analysis of gene expression because it automates the steps the researcher performs for the complete task of identification of genes and classification of samples. Transparent to the user are the tasks to be performed and the decisions taken to find genes that may differ in certain samples or to create pools of data to be used later. Having already defined filter parameters and types of tests to apply, the user only has to provide the files containing the microarray data obtained from the Affymetrix platform and identify the samples as cases or controls. The system uses the knowledge from expert analyses of gene expression so that others can perform these tasks at the same level of expertise..

With this type of multi-agent system for the analysis of gene expression it is like using a single software tool to complete the expert analysis of genes without user intervention. The system will make decisions in a similar way as do the genomics specialists.

The implementation of the agents using Java and CLIPS gives flexibility to their development and provides simplicity compared with existing software tools that require

deployment of more staff to administer the system. MAS-GEN offers an effective expert and simplified solution that focuses only on administering the single managing agent for complete gene expression analysis.

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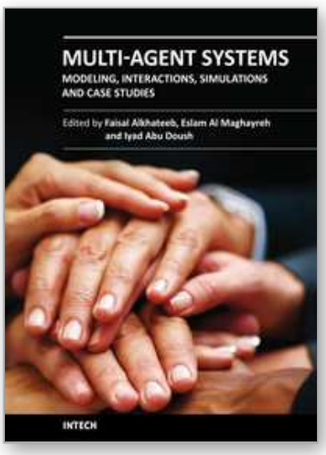

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A multi-agent system (MAS) is a system composed of multiple interacting intelligent agents. Multi-agent systems can be used to solve problems which are difficult or impossible for an individual agent or monolithic system to solve. Agent systems are open and extensible systems that allow for the deployment of autonomous and proactive software components. Multi-agent systems have been brought up and used in several application domains.

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