32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

E-Health towards Ecumenical Framework for Personalized Medicine via Decision Support System

Ioannis Kouris, Charalampos Tsirmpas , Stavroula G. Mougiakakou, *Member, IEEE* , Dimitra Iliopoulou, and Dimitris Koutsouris, *Senior Member, IEEE*

***Abstract*— The purpose of the present manuscript is to present the advances performed in medicine using a Personalized Decision Support System (PDSS). The models used in Decision Support Systems (DSS) are examined in combination with Genome Information and Biomarkers to produce personalized result for each individual. The concept of personalize medicine is described in depth and application of PDSS for Cardiovascular Diseases (CVD) and Type-1 Diabetes Mellitus (T1DM) are analyzed. Parameters extracted from genes, biomarkers, nutrition habits, lifestyle and biological measurements feed DSSs, incorporating Artificial Intelligence Modules (AIM), to provide personalized advice, medication and treatment.**

I. Introduction

THE concept of PDSSs has evolved from the idea to improve and enhance the decision being taken. The output derived from the process of the input data in a PDSS may be used in numerous fields such as marketing, health, economics etc. A PDSS may be an information system that performs a specific task or may be any other activity that is designed to receive an input of raw or categorized information and result to a specialized output. Usually, when examining a PDSS, it is composed of three main parts: a pool that stores the data to be processed, a model to extract the decision and finally an interface through which the data is being imported or exported [1]. The inputs require manual analysis by the user, the criteria on which the results will be based, have to be well defined and described so that the results produce the desired output. Enhancing the results produced by a PDSS, Intelligent Decision Support Systems have been proposed that are based on artificial intelligence, intelligent agents and cognitive systems [2]. The PDSS incorporates a logic module that uses intelligent techniques to classify and process the input data. The applications of a PDSS are widely used, but maybe the most promising ones are Clinical Decision Support Systems for medical diagnosis and the PDSS for personalized medicine.

Manuscript received April 23, 2010.

Ioannis Kouris is with the School of Electrical and Computer Engineering, National Technical University of Athens, 9 Heroon Polytechneiou Str., 15780 Zografou, Athens, Greece (email: ikouris@biomed.ntua.gr)

Charalampos Tsirmpas is with the School of Electrical and Computer Engineering, National Technical University of Athens, 9 Heroon Polytechneiou Str., 15780 Zografou, Athens, Greece (email: htsirbas@biomed.ntua.gr)

Dimitra Iliopoulou is with the School of Electrical and Computer Engineering, National Technical University of Athens, 9 Heroon Polytechneiou Str., 15780 Zografou, Athens, Greece (email:dilio@biomed.ntua.gr)

Stavroula G. Mougiakakou is with ARTORG Diabetes Technology Research Group, University of Bern, Stauffacherstrasse 78, 3014 Bern, Switzerland (e-mail: stavroula.mougiakakou@artorg.unibe.ch)

Dimitris Koutsouris is with the School of Electrical and Computer Engineering, National Technical University of Athens, 9 Heroon Polytechneiou Str., 15780 Zografou, Athens, Greece (email: dkoutsou@biomed.ntua.gr)

II. Decision support systems in personalized medicine

A. Decision Support Systems

A DDS is a way to model data and make quality decisions based upon it. Making the right decision is usually based on the quality of the data and the ability to choose and analyze the data in order to find trends in which a solution can be created. DSS are usually computer applications along with human components that can dig through large amounts of data and choose between many results.

Many think of DDS specialized only for business, but this system is integrated into various daily operating activities. For example, sales data analysis, budgets and market forecasts in order to update a company's strategies, is a very common application field of DSS. In reality, the data that are used as inputs are constantly changing, so the main concept of DSS is to be able to adapt to the varying conditions. Despite the fact that computer equipped with artificial intelligence algorithm interpret with the data, it is up to the user to provide the appropriate strategies so that the result to be useful.

There are many ways to classify the DSS. One model uses relationships and is divided in three categories (passive, active and cooperative). Passive models are used to collect data and organize them, without suggestion a specific decision [3]. Active DSS process data and propose solutions based upon the data provided, while cooperative DSS collect data, analyze them and then wait for an extra input by the user. Taking into consideration the mode of assistance provided by the user, more categories may be defined, such as Model Driven DSS, Communications Driven DSS, Data Driven DSS, Document Driven DSS, and Knowledge Driven DSS [4].

Model Driven DSS uses statistics, simulations or financial models to come up with a solution or strategy. Communications Driven DSS models apply when many collaborators work together to come up with a decision or to set in motion a solution or strategy. Data Driven DSS model emphasize on collected data that is manipulated to fit the decision maker's needs. Usually, data is collected and categorized as a time series which is a collection of data that forms a sequence (daily, yearly, etc). Document Driven DSS model uses text documents, spreadsheets and database records to come up with decisions and further manipulate the information to refine strategies. Knowledge Driven DSS model takes advantage of algorithms stored in a computer, or used by the user, to determine whether a decision should be made [5].

B. Personalized medicine

Personalized medicine is a rapidly growing field of healthcare. The advantage of a personalized medicine is the availability of each person's unique clinical, genetic, genomic, and environmental information. The healthcare that incorporates personalized medicine provides coordinated, continuous and based on the data of the patient. The goal of personalized medicine is to promote health wellness, satisfaction, sense of security and to increase the possibility of a successful disease prevention, detection and treatment. This form of medicine, apart from patient's personal data and medicine-biological measurements, uses genomic information data to understand the molecular structure of the disease and to optimize health care strategies and drug therapies [6].

Patients of the same age group, with similar duration of disease and Body Mass Index (BMI) will not respond in the same way to a given treatment. Treatments are effective for some patients while not for others. A possible reason is that every patient has different genetic predisposition to respond or not to a drug [7]. The personalized medicine gives the ability to the physicians to give the most appropriate treatment to each patient, based on their personalized data, such as their genetic makeup, biological measurements and physical characteristics (age, height, weight, etc.).

Until now the physicians had to give patients preferential treatment based on the effectiveness. However, one treatment may be effective to cure 100% of patients while other treatment may reach 0% of its effectiveness for a certain patients' group. In this case the problem stems from the fact that it is not clear which treatment is likely to be effective for a given patient, so the treatment that works for the most is primarily selected first [8]. This tactic has caused loss in healthcare quality, since there are groups of patients in which a treatment will not be effective. On the other hand, the personalized approach in the field of healthcare leads to better and more effective therapies. It shifts the emphasis from reaction to prevention, predicts susceptibility to disease, improves disease detection and preempts disease progression [9].

Personalized Clinical Decision Support System

Decision support is part of the basic medicine. In proportion, a personalized decision support system is part of the personalized medicine. The purpose of the personalized medicine is to improve the quality and the effectiveness of patient's healthcare. That, requires genetic information to be incorporated into a Clinical Decision Support System (CDSS), in order new perspective to be provided to the physicians on diagnosis and treatment [10].

A Personalized CDSS (PCDSS) provides computationally simple but high importance tasks, such as identifying possible drug-to-drug interactions or allergy-to-drug interactions [11]. However, as the tasks become more and more complex and critical such as identifying predisposition of a patient to a particular disease, the PCDSS needs to integrate as many personal data of the patient as possible and blend knowledge deriving from genomic' s research on disease and health. Although genetic tests provide new opportunities to the PCDSS, the available medical tests, technologies and personalized medicine feed the DSS with significant personalized information of each patient.

Meanwhile, there has been great progress in developing personalized genetic tests. Currently, at the DNA level, 598 genetic labs perform tests for 1729 diseases, which 1449 of the focus on clinical care and 280 on research [12]. There have been many studies to find genetic markers predisposing for simple and for complex diseases. When these genetic markers and other personalized data are loaded in and processed by a PCDSS, the results assist physicians and other health professionals to make a better decision for each patient undergoing a certain disease.

C. Genome Information and Biomarkers

Every human has different genome sequence. The variation in genome sequence is also found on healthy and sick persons. Although, the common variants of the genome sequence are estimated to several millions, there are countless rare ones which are discovered on very few people or even on a single person [13]. A fact of great significance in the context of the personalized medicine is whether and how a genome affects the probability and the extension of a disease. It is also important, how a change in healthy genome would affect the expression of genes, and moreover the effect of this change on the occurrence of the disease.

An effective and early prediction is the base for an effective health care. Physicians have used variations in biological fluids to estimate the best treatment and the effects on the patient. In the past, marker based prediction to identify of phenylketonuria from tryptophan metabolism, led the research to deal with identification and prediction of diseases at molecular, genetic and protein level [14]. Nowadays, it is possible to unravel the human proteomes, which are the collection of proteins expressed in a particular cell type or tissue. Almost all useful markers have been peptides or proteins. A plethora of biomarkers exist for the diagnosis of nutritional status [15], metabolic diseases (carbohydrate, amino acid and fatty acid metabolism), inflammation (CRP, haptoglobin, orosomucoid, anti-trypsin) [16-20], hormonal imbalance (insulin, thyroxine, adrenaline, pituitary hormones), tissue damage (SGOT and SGPT for liver and heart, collagen for joints) [21-23], cancer (CA15.3, CA27.29, CEA, PSA, S100- beta, hCG) [24-25], neurodegeneration (amyloid plaques, beta-amyloid peptide) [26-27] and autoimmune diseases (autoantibodies) [28-33].

As noted above, diseases such as diabetes, hypertension, cancer and cardiovascular diseases have genetic basis, which means that genes could be useful in their prediction [34]. Furthermore, there are environmental factors which affect common diseases. As a result, in order to enable a DSS to advise a physician about disease outcome, we have to take into account of interactions between genes and determinant environmental factors.

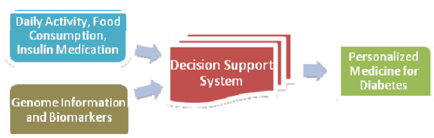

Fig. 1 Design of a Personalized Decision Support System for Diabetes

III. Applications in Personalized Medicine

A. *Personalized Clinical Decision Support System for Cardiovascular Diseases*

Cardiovascular Disease (CVD) is a group of diseases that engage heart or blood vessels. Genes, environment, exercise, nutrition habits as well as their combination are the most important factors which influence CVD. Such a disease can be treated by early prevention. To obtain an effective treatment, the relationship between genomic and personal data should be defined. Thus, the recent research aims to personalize environmental information on individual's genetic makeup in order to prevent, to treat or even to detect diseases [35].

A PCDSS is able to assess a person's risk to develop a CVD, using genetic information, patient's clinical data and lifestyle-diet data. It also proposes to the physician a personalized treatment which involves advice for nutritional habits, exercise and a personalized medication, whether it is necessary. The architecture of these PCDSS is based on two models one for interaction between factors and risk assessment and one for the personalized advice.

The first model uses one or more biomarkers like (BMI) for CVD risk factor [36]. The input data for this model will be taken from separate sources. Nutrient intake measurements and lifestyle-exercise habits are determined from the responses to the diet questionnaire and are depicted by their average diet habits. Furthermore, genotype data are acquired using genetic tests while clinical data are available from electronic health records. The necessary data analysis is processed by an Artificial Intelligence (AI) based model, which is an Artificial Neural Network (ANN) [37]. The latter has been optimally designed and trained via a hybrid method based on Genetic Algorithms (GAs) [38]. The method is able to select the most optimal feature subset of variables (number of input neurons) starting from an initial set of variables and simultaneously determine the number of hidden neurons, estimate the initial weights, initial learning rate and momentum term.

The second model generates rules and advices to the physicians. The rules are created by an intelligent mechanism based on first model's results, personal gene, clinical data and diet-lifestyle habits. The most important thing is that the personal data are combined with preexisting knowledge, found in literature on the effects of genes and habits on a person's health. Finally, personalized advice is produced by relevant rules, which involve personal data, gene data (Single Nucleotide Polymorphisms values), answers to a questionnaires and biomarkers.

To sum up, the core of the above PCDSS is the risk assessment (first model) and the personalized advice model (second model). The first is based on the combined use of ANN and GA aiming to identify a person's risk to develop CVD using a biomarker as independent risk factor and personal information as input data. The second, based on first model's results, produces rules and advises for the physicians for a personalized treatment in order to reduce the CVD risks.

B. *Personalized Medicine – Diabetes*

Type-1 Diabetes Mellitus (T1DM) is a chronic metabolic disease characterized by absence of insulin secretion due to destruction of pancreatic beta-cells. A person incapable to produce the appropriate insulin levels may suffer, in short term from hypoglycemia or hyperglycemia and in the long-term by heart diseases, neuropathies, nephropathies or retinopathies [39]. In order the stability of the insulin levels to be preserved, frequent insulin injections must be performed by the patient. Blood glucose measurements, either using invasive or non-invasive techniques should be made and the insulin dosage should be modified appropriately.

Miniaturization techniques used in digital circuits, have enable the industry to produce and distribute small, portable devices that can be used by diabetics. Continuous Glucose Monitors (CGMs) [40] that provide high frequency measurements of glucose levels and Continuous Subcutaneous Insulin Infusion Pumps (CSIIPs) [41] and Physical Activity Monitoring Modules (PAMM) interconnected with a Personalized Decision Support Logic, construct a complete system supporting T1DM patients [42]. In that way, the term Personalized Medicine for Diabetes (PMD) can be defined. A PDM uses the inputs aforementioned and also uses information about the genome to extract personalized results. Apart from predicting only the body needs in insulin during the day, strategies for preventing, treating or monitoring T1DM are also provided. Genome analysis and biomarkers lead to the identification of the genes which are related to obesity and predisposition for diabetes, based on the genotype. Combining all of them, individualized therapies are composed, involving which drug to use and which dosage is the best and also what type of diet should be followed [43].

Examining in depth the methodologies followed for the creation of PMD, a personalized model for the simulation of insulin metabolism and a non-linear predictive controller can be used to satisfy the creation of a real time DSS [44]. The inputs that feed a closed-loop control system that will derive the PMD include blood glucose levels measurements, insulin infusion rates, information related to the consumed food (especially interested in carbohydrates) and physical activity (energy expenditure, carbohydrate's metabolism, etc)[45]. Following, a Real Time Artificial Neural Network (RT-ANN) combined with the usage of a Compartmental Model (CM) simulate the glucose absorption into the blood and based on previous glucose measurements and individual's activity, calculate the current needs in insulin resulting to modify the infusion rates.

IV. Conclusion

Personalized medicine, especially a PCDSS will provide great benefits in the future, as DNA analysis improves. Personalized medication based on genetic profiles, biomarkers and habits of each individual will become the basic tool for healthcare professionals on the appropriate medication selection.

The physicians will be able to predict susceptibility to disease, improve disease detection and preempt disease progression. An PCDSS based on personal data, environmental information, biomarkers and genome sequence, will enable the medicine to create more effective drugs and to avoid drugs intakes with unpredictable side effects.

References

[1] Haettenschwiler, P. (1999). Neues anwenderfreundliches Konzept der Entscheidungsunterstützung. Gutes Entscheiden in Wirtschaft, Politik und Gesellschaft. Zurich, vdf Hochschulverlag AG: 189-208

[2] Gadomski A.M. et al. (1998). Integrated Parallel Bottom-up and Top-down Approach to the Development of Agent-based Intelligent DSSs for Emergency Management,TIEMS98, Washington

[3] Frada Burstein, "Handbook on Decision Support Systems 2: Variations", Springer; 1 edition (August 31, 2007), ASIN: B001BTBNV4

[4] Li Niu, Jie Lu, Guangquan Zhang, "Cognition-Driven Decision Support for Business Intelligence: Models, Techniques, Systems and Applications", Springer; 1 edition (September 2, 2009), ISBN: 3642032079

[5] Daniel Power, "Decision Support Systems: Concepts and Resources for Managers", Praeger (March 30, 2002), ISBN: 156720497X

[6] Woodcock J. The prospects for "personalized medicine" in drug evelopment and drug therapy. Clin Pharmacol Ther. 2007;81:164-9.

[7] Willard H, Ginsburg GS. Genomic and personalized medicine. 1st ed. Philadelphia, PA: Elsevier, 2009.426–7.

[8] Obama B. Genomics and personalized medicine act of 2007. U.S. Congress, Washington, DC, 2007.

[9] Geoffrey S. Ginsburg, Huntington F. Willard, Genomic and personalized medicine: foundations and applications, Translational Research, Volume 154, Issue 6, Special Issue on Personalized Medicine, December 2009, Pages 277-287, ISSN 1931-5244, DOI: 10.1016/j.trsl.2009.

[10] Jenkin MA, Cheezum L, Essick V, et al. Clinical patient management and the integrated health information system. Med lnstrum. 1978;12(4):217–21.

[11] Ginsburg GS, McCarthy JJ. Personalized medicine: revolutionizing drug discovery and patient care. Trends Biotechnol. 2001;19(12):491–6.

[12] Guttmacher AE, Porteous ME, Mclnerney JD. Educating healthcare professionals about genetics and genomics. Nat Rev Genet. 2007;8(2):151–7.

[13] Willard H. Organization, variation and expression of the human genome as a foundation of genomic and personalized medicine. In: Willard H, Ginsburg GS, eds. Genomic and personalized medicine. 1st ed. Durham, NC: Elsevier, 2009.

[14] West M, Ginsburg GS, Huang A, Nevins J. Embracing the complexity of genomic data for personalized medicine. Genome Res 2006;16:559–66.

[15] Frederick, K., Beck, M.D., Rosenthal, M.D., 2002. Prealbumin: A marker for nutritional evaluation. Am. Fam. Physician 65, 1575–1578.

[16] Agrawal, A., 2005. CRP after 2004. Mol. Immunol. 42, 927–930.

[17] Sadrzadeh, S.M., Bozorgmehr, J., 2004. Haptoglobin phenotypes in health and disorders. Am. J. Clin. Pathol. 121 (Suppl:S97-104), S97–S104.

[18] Kanikowska, D., Grzymislawski, M.,Wiktorowicz, K., 2005. Seasonal rhythms of "acute phase proteins" in humans. Chronobiol. Int. 22, 591–596.

[19] Lomas, D.A., 2005. Molecular mousetraps, alpha1-antitrypsin deficiency and the serpinopathies. Clin. Med. 5, 249–257.

[20] Fournier, T., Medjoubi, N., Porquet, D., 2000. Alpha-1-acid glycoprotein. Biochim. Biophys. Acta 1482, 157–171.

[21] Conigrave, K.M., Davies, P., Haber, P., Whitfield, J.B., 2003. Traditional markers of excessive alcohol use. Addiction 98 (Suppl. 2), 31–43.

[22] Collier, J., Bassendine, M., 2002. How to respond to abnormal liver function tests. Clin. Med. 2, 406–409.

[23] Poole, A.R., Nelson, F., Dahlberg, L., Tchetina, E., Kobayashi, M., Yasuda, T., Laverty, S., Squires, G., Kojima, T., Wu, W., Billinghurst, R.C., 2003. Proteolysis of the collagen fibril in osteoarthritis. Biochem. Soc. Symp. 115–123.

[24] Rosai, J., 2003. Immunohistochemical markers of thyroid tumors: significance and diagnostic applications. Tumori 89, 517–519.

[25] Shitrit, D., Zingerman, B., Shitrit, A.B., Shlomi, D., Kramer, M.R., 2005.Diagnostic Value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125Assays in Pleural Effusions: Analysis of 116 Cases and Review of the Literature. Oncologist 10, 501–507.

[26] Bossy-Wetzel, E., Schwarzenbacher, R., Lipton, S.A., 2004. Molecular pathways to neurodegeneration. Nat. Med. 10 (Suppl: S2-9), S2–S9.

[27] Teunissen, C.E., de Vente, J., Steinbusch, H.W., De Bruijn, C., 2002. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiol. Aging 23, 485–508.

[28] Pender,M.P., 2000. Neurology. 4:Multiple sclerosis.Med. J. Aust. 172, 556–562.

[29] Weetman, A.P., 2004. Autoimmune thyroid disease. Autoimmunity 37, 337–340.

[30] Masaki, Y., Sugai, S., 2004. Lymphoproliferative disorders in Sjogren's syndrome. Autoimmun. Rev. 3, 175–182.

[31] Dorner, T., Egerer, K., Feist, E., Burmester, G.R., 2004. Rheumatoid factor revisited. Curr. Opin. Rheumatol. 16, 246–253.

[32] Atkinson, M.A., 2005. ADA Outstanding Scientific Achievement Lecture 2004. Thirty years of investigating the autoimmune basis for type 1 diabetes: why can't we prevent or reverse this disease? Diabetes 54, 1253–1263.

[33] Notkins, A.L., 2004. Type 1 diabetes as a model for autoantibodies as predictors of autoimmune diseases. Autoimmun. Rev. 3 (Suppl. 1), S7–S9.

[34] C.D. Collins, S. Purohit, R.H. Podolsky, H.S. Zhao, D. Schatz, S.E. Eckenrode, P. Yang, D. Hopkins, A. Muir, M. Hoffman, R.A. McIndoe, M. Rewers, J.X. She, The application of genomic and proteomic technologies in predictive, preventive and personalized medicine, Vascular Pharmacology, Volume 45, Issue 5, The 8th International Conference on the Vascular Endothelium: Translating Discoveries into Public Health Practice - Part I, November 2006, Pages 258-267, ISSN 1537-1891, DOI: 10.1016/j.vph.2006

[35] Stavroula Mougiakakou, Ioannis Valavanis1, George Karkalis1, Stathis Marinos1, Keith Grimaldi1 and Konstantina Nikita1, " An Integrated Web-based Platform for the Provision of Personalized Advice in People at High Risk for CVD", ITAB, 2009

[36] A. J. Frint, and E. B. Rimm, “Commentary: Obesity and cardiovascular disease risk among the young and old-is BMI the wrong benchmark?,” Int. J. Epidiom., vol. 35, pp. 187–189, 2006.
[37] D. Goldberg, Genetic algorithms in search, optimization and machine learning, Addison-Wesley Publishing Company, Boston MA USA,1989
[38] D. Goldberg, Genetic algorithms in search, optimization and machine learning, Addison-Wesley Publishing Company, Boston MA USA,1989
[39] The Diabetes Control and Complications Trial Research Group, “The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-term Complications in Insulin-Dependent Diabetes Mellitus,” New England Journal of Medicine, vol. 329, no. 14, pp. 977-986, 1993
[40] O. Lyandres, J. M. Yuen, N. C. Shah, R. P. VanDuyne, J. T. Walsh, M. R. Glucksberg, “Progress Toward an In Vivo Surface-Enhanced Raman Spectroscopy Glucose Sensor,” Diabetes Technology & Therapeutics, vol. 10, no. 4, pp. 257-265, 2008.
[41] C. M. Girardin, C. Huot, M. Gonthier, E. Delvin, “Continuous Glucose Monitoring: A Review of Biochemical Perspectives and Clinical use in Type 1 Diabetes,” Clinical Biochemistry, vol. 42, pp. 136–142, 2009
[42] S.G. Mougiakakou, C. Bartsocas, E. Bozas, N. Chaniotakis, D. Iliopoulou, I. Kouris, S. Pavlopoulos, A. Prountzou, M. Skevofylakas, A. Tsoukalis, K. Varotsis, A. Vazeou, K. Zarkogianni and K. S. Nikita, "SMARTDIAB: A Communication and Information Technology Approach for the Intelligent Monitoring, Management and Follow-up of Type 1 Diabetes Patients", IEEE Transactions on Information Technology in Biomedicine, Special Issue: New and Emerging Trends in Bioinformatics and Bioengineering , 2010.
[43] D. Klonoff, “Personalized Medicine for Diabetes”, Journal of Diabetes Science and Technology, Volume 2, Issue 3, May 2008
[44] K. Zarkogianni, S.G. Mougiakakou, A. Prountzou, A. Vazeou, C. S. Bartsocas, K. S. Nikita, "An Insulin Infusion Advisory System for Type 1 Diabetes Patient based on Non-Linear Model Predictive Control Meyhods", Engineering in Medicine and Biology Conference 2007 (EMBC'06), IEEE, Lyon, France, August 2007
[45] J. Staudenmayer, D. Pober, S. Crouter, D. Bassett, P. Freedson, “An artificial neural network to estimate physical activity energy expenditure and identify physical activity type from an accelerometer”, J Appl Physiol (July 30, 2009)