

Knowledge-Based System Model to Support Diabetes Research and Clinical Process

Modelo de Sistema Basado en Conocimiento para Apoyo en la Investigación y Proceso Clínico de la Diabetes

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Abstract

Due to the great amount of information generated and supported by the explosive evolution of computer science systems since the end of the last century, the expansion and transference of scientific knowledge has caused a rapid transformation of scientific discoveries in products and applications that have positive effects in the life quality of societies. Today, a great amount of data in medicine is obtained by the application of biotechnological methods that constantly evolve. Thus, scientific research related to diabetes keeps improving. In this context, productivity and competitiveness must be sustained on knowledge which facilitates and encourages organizational innovation capacity. For this reason, knowledge based systems emerge as a useful tool to help organizations solve difficult assignments or improve their processes. In this work, derived from known diabetes group of symptoms and interactions that diabetes research maintains with the biotechnological processes, the authors carried out a brief analysis of the knowledge involved as well as the role that knowledge-based systems have played, and keep playing in support of them. Additionally, with the systemic perspective obtained by the authors regarding aspects like knowledge, practices and resources needed in clinical and laboratory practices, they propose a systemic model that can support diabetes research and clinical process.

Keywords: biotechnological process, computer science systems, diabetes, knowledge based systems, systemic.

Resumen

Debido a la gran cantidad de información generada y apoyada por la evolución explosiva de sistemas de la ciencia computacional, desde finales del siglo pasado, la expansión y transferencia de conocimiento científico ha provocado una rápida transformación de los descubrimientos científicos en productos y aplicaciones que afectan positivamente la calidad de vida de las sociedades. Actualmente, una gran cantidad de datos en medicina se obtiene por la aplicación de métodos biotecnológicos que constantemente evolucionan. De igual manera, la investigación científica sobre diabetes mantiene una mejora constante. En este contexto, tanto la productividad como la competitividad se deben apoyar con conocimiento que facilite y promueva la capacidad de innovación organizacional. Por esta razón, los sistemas basados en conocimiento emergen como una herramienta útil para coadyuvar con las organizaciones en la solución de situaciones difíciles o en la mejora de sus procesos. En este trabajo, derivado del conocido grupo de síntomas y de las interacciones que la investigación en diabetes mantiene con los procesos biotecnológicos, los autores realizan un breve análisis del conocimiento implicado y del rol que los sistemas basados en el conocimiento han desempeñado, -y continúan desempeñando, en apoyo a tales

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procesos. Adicionalmente, con la perspectiva sistémica obtenida por los autores respecto al conocimiento y recursos necesarios en prácticas clínicas y de laboratorio, proponen un modelo sistémico capaz de apoyar la investigación y el proceso clínico de la diabetes.

Palabras clave: diabetes, proceso biotecnológico, sistemas basados en conocimiento, sistemas de la ciencia computacional, sistémica.

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Introduction

Nowadays, information must be not only effective but efficient which would grants possibility to emerge as one of the key success factors using strategies and tactics to assure products or services quality that clients need. Therefore, the evolution of computer science has allowed the appearance and evolution of systems that facilitate the elicitation, classification, codification, storage, maintenance and update of the necessary information for the organizations. It leans more on the knowledge acquired and developed by its personnel than in the classic production factors, in order to generate a major productivity. The generation of value by means of knowledge application and the personnel's creativity allows generating strategies that affect the improvement of processes or products and, still more, in the establishment of innovation processes tending to support the establishment of competitive strategies.

In order to effectively support such intentions and with the purpose of diminishing risks, and preventing environmental impacts, as result of high production levels. Biotechnology takes advantage of Artificial intelligence techniques and tools, offered by knowledge-based systems to support its research processes. In the case of biomedical research, processes have already been carried out on-line. This facilitates simultaneity and participation between people located in different places, as well as security in the exchange of information in real-time. In the BVS 2007, it is mentioned that *"decision making processes, practices and policies, must be sufficiently informed by scientific evidences, such as variability in standards of information use, the capacity to get knowledge and the decision to react for getting new knowledge"*.

It is not omitted that web-blogs (or weblog) encourage writing and distribution of images and ideas. Ündey *et al.*, (2003), estimate that on-line process monitoring techniques could be extended to include predictions of end of batch quality measurements during the progress of a batch run. In the same way, process monitoring, quality estimation and fault diagnosis activities

could be automated and supervised by embedding them into a real-time knowledge-based system (RTKBS). Likewise, knowledge-based systems utilize acquired human expert knowledge in a computer, with the purpose of obtaining, storing and sharing this expertise (as well as knowledge extracted from databases or got from external sources) in order to be on hand for non experts.

Among different applications of knowledge-based systems, it is possible to find applications such as diagnosis, planning, designing, monitoring and control of processes, or training and consultation services. Therefore expert systems that focus onto support organizational making decisions are equipped with components denominated knowledge-based management subsystems. Thus, taking advantage of the characteristics of these systems and the contribution that can be obtained from them in a knowledge management system, with the systemic perspective obtained by the authors and regarding aspects like knowledge, practices and resources needed in clinical and laboratory practices, the authors design and propose a systemic model that can support diabetes research and clinical process.

Diabetes' aspects

Diabetes is recognized like syndrome because it combines a symptoms series. If diabetes does not stay down under control, it can generate very serious complications to human health. The U. S. A. National Institutes of Health classify diabetes as *" a condition characterized by hyperglycemia (high blood glucose) resulting from the body's inability to use blood glucose for energy"*, a disease that is characterized by alterations in the carbohydrates, fat and proteins metabolism, derivative from deficiencies in insulin secretion or its assimilation in the organism. With illustrative purpose and to obviate time, figure 1 shown the most known group of symptoms related with different aspects, such as age, genetics, cultural and individual habits, which involved a wide range of scientific and empiric knowledge.

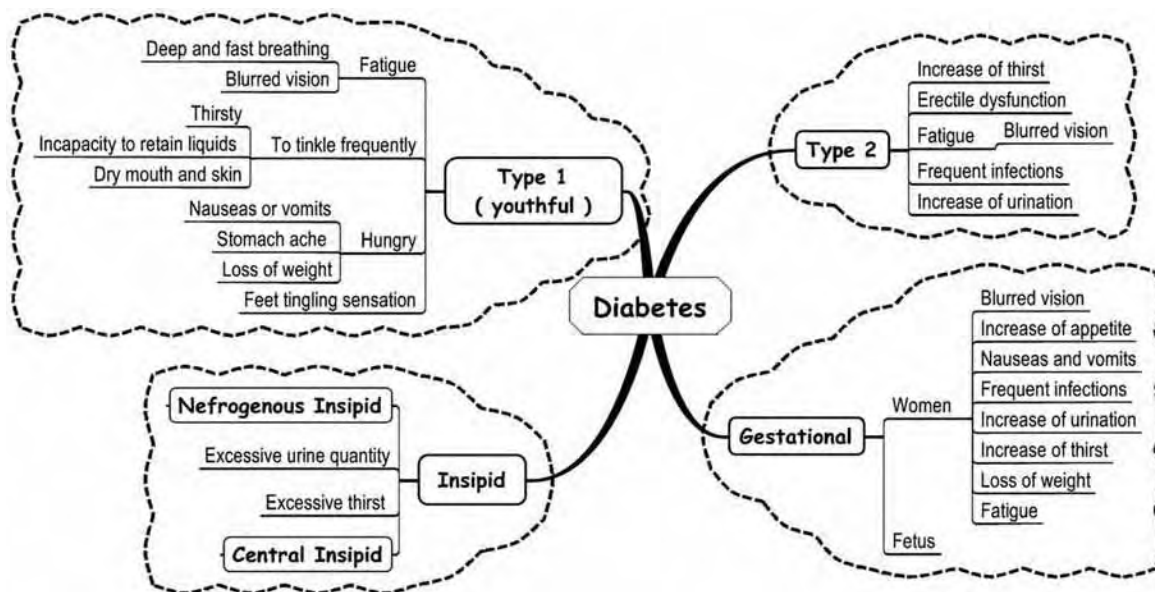


Figure 1. Diabetes types and symptoms (personal elaboration, according with information obtained from Medline Plus)

In Type-1 diabetes, known also as youthful because it is most frequently diagnosed in children or young people, pancreatic cells produce little or no insulin. Nevertheless, symptoms are detected, usually, when the glycemia levels are already low. According to Mexican Institute for Social Security, this type of diabetes provokes that the body unknowns own tissues and tries to destroy them; it attacks its insulin-producer cells (beta cells). So the metabolism of proteins, fat or carbohydrates cannot be carry out in an appropriate way because of the lack of insulin.

According to Koschorreck and Gilles (2008), Type-1 diabetes mellitus results from defective pancreatic insulin secretion; meanwhile, insulin resistance, obesity and type-2 diabetes mellitus may result from defects in the insulin signaling system and are often accompanied by abnormalities in insulin degradation. Although Type-1 diabetes is not curable, it can be under control; nonetheless, if patient has not adequate care of it, he could go into a cetoacidotic mortal coma. Besides an appropriate diet and exercising, it is necessary patients maintain control of both arterial pressure and cholesterol, trying to get glucose at non-diabetic levels.

Taking into account that common clinical experience has shown that multiple injections on the same subject often exhibit varying effects (between-day as well as within-day), possibly depending on the time of the day or

on the site of injection; Clausen *et al.*, (2006) studied the pharmacokinetics of biphasic insulin aspart administered by multiple subcutaneous injection, focusing into assess the magnitude of the inter-and intra-subject variation in the kinetics. He mentioned, in subjects with Type-1 diabetes, exogenous insulin is necessary for regulation of glycaemia. So, optimal control would reduce hyperglycaemia, which may cause long-term microvascular damage, blindness, renal impairment and peripheral neuropathy; it would also reduce the risk of life-threatening hypoglycaemia.

In Type-2 diabetes, organisms present the condition known as insulin resistance, causing that liver, muscle's cells or fats do not absorb sugar from blood to get energy; such that, this rejection increases blood sugar levels (hyperglycemia). Pancreas does not have enough capacity to produce the needed insulin. A most frequent issue in overweight people, without forgetting risks produced by age, genetic propensity or personal habits, such as feeding and sedentary lifestyle. Injectable medicines, as exenatide and pramlintide, can lower glycaemia levels. According to MedlinePlus (dependent on U. S. Medicine National Library), patients must try to maintain their arterial pressure at 130/80 mm/Hg, or less. Among cares patients must take of themselves, it is possible to mention some like get periodical checkups for kidneys, hemoglobin, cholesterol, triglycerides, feet or teeth. It should be noted that

in world death causes, an outstanding issue is that provoked by Type-2 diabetes derived from cardiovascular complications, which could be diminished if there existed an adequate resource that allowed diagnosing, treating and educating patients with respect to their clinical controls and personal habits. This condition was endorsed by Lincoln *et al.*, (2008) they developed a mathematical model to determine the effect of a foot care education programme in the secondary prevention of foot ulcers. Thus, they concluded that although they could not document a benefit from their particular intervention chosen for study, they consider that every effort should continue to be made to ensure that patients with healed ulcers reduce risk associated behaviour as much as possible. As mentioned before, diabetic patients should be conscious about lipids and arterial tension control as well as their exercising and nutritional habits.

On one hand, taking advantage that US Food and Drug Administration has approved exenatide for the treatment of Type-2 diabetes in adult patients who have not achieved adequate glycaemic control and who are taking metformin, or sulfonylurea, or a combination of both, Nauck *et al.*, (2007) found out that exenatide provides overall glycaemic control comparable to premixed insulin, and has the added benefit of weight reduction. It is convenient to mention that the participants in the case study were generally overweight. On the other hand, Dashora (2009), comparing blood glucose control when patients used biphasic insulin aspart (BIAsp) three times a day (using 70/30 high-mix before breakfast and lunch), with biphasic human insulin (BHI, 30/70) twice daily in adults with Type-2 diabetes already treated with insulin; he found out that an insulin regimen using high-mix BIAsp (BIAsp 70) before breakfast and lunch and BIAsp 30 before dinner can achieve lower blood glucose levels during the day through reduced mealtime glucose excursions, in particular at lunchtime than a twice-daily premix regimen.

In Gestational diabetes, though symptoms usually do not appear (or are slight) and are not potentially mortal for pregnant women, based on genetic and ethnic aspects (especially Latin or African) and the propensity to infections, and obesity, among others factors, this diabetes type can be detected during pregnancy. In order to control the glucose levels during pregnancy and to ensure health for her fetus and avoid potential problems during childbirth, mothers with this diabetes type have an increased risk in undergoing arterial hypertension during pregnancy. However, women with gestational diabetes can evolve diabetes 5 or 10 years after child birthing which is a risk that could increase in obese women. In MedlinePlus, it is recommended

that pregnant women who suffer gestational diabetes tend to get greater babies when being born. This can increase problems possibility at childbirthing. So these women have got an increased risk undergo arterial hypertension during pregnancy. Babies could be prone to get low sugar periods in blood (hypoglycaemia) during the first days of their lives. Women with gestational diabetes must be monitor carefully after the childbirth, in regular medical appointments, looking for diabetes signs. If women undergo to prenatal screening tests, between weeks 24 and 28 of pregnancy, this will support to detect gestational diabetes at just the right moment.

It is not omitted to mention that this type of diabetes can provoke in the fetus problems like are referred next:

- Among most serious cases, it is possible to mentioned baby's death, spontaneous abortion, red blood cells increase (policitemia), calcium reduction in blood (hipocalcemia), jaundice, breathing problems or pulmonary immaturity.
- Although less serious, if the baby receives more sugar than normal, by the placenta, his pancreas should produce additional insulin, which can cause that their organs and his body increase of size, elevating his weight (fetal macrosomia), being able to weigh more than 4kg when being born. Also, when being born, the baby can present a high insulin level; although he has not longer receives sugar derivative from the placenta, his sugar level (glucose) would decrease below the normal energy levels, generating neonatal hypoglycaemia.
- Also, the baby can be born with respiratory insufficiency or poor lungs development, which will require that he spends some time in some neonatal intensive cares unit.

According to the American Diabetes Association, babies with excessive insulin could be children with obesity risk and adults with the risk for developing Type-2 diabetes.

To Chu *et al.*, (2007) numerous studies in the U.S. and elsewhere have reported an increased risk of gestational diabetes mellitus (GDM) among women who are overweight or obese compared with lean or normal-weight women. So, it has been suggested that the relationship between decreased insulin sensitivity and excessive fetal growth in obese women and women with this type of diabetes may explain some of the increased incidence of obesity and glucose intolerance in their offspring. As an outcome of their study, these

authors concluded that high maternal weight is associated with a substantially higher risk of gestational diabetes mellitus, compared with normal-weight pregnant women. So, women with GDM are associated with a higher risk of developing Type-2 diabetes later in life in both the mother and child. In addition, Rowan *et al.*, (2008) mention that Gestational Diabetes is a complication in about 5% of pregnancies; also, they mentioned that Metformin is a logical treatment for women with gestational diabetes mellitus; besides women preferred Metformin to insulin treatment. Though Metformin is more acceptable to women with gestational diabetes mellitus than is insulin, Metformin crosses the placenta and could affect fetal physiology directly. As an outcome of their study, they found out that women receiving combined treatment required less insulin and gained less weight than those taking insulin alone. So, they concluded that in women with gestational diabetes mellitus, Metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin

Inspid diabetes appears when kidneys are no longer able to retain water while filtering blood. So, derivative of this affection it is possible to find the types listed next:

- Central Insipid, motivated by a small amount or lack of the anti-diuretic hormone known as vasopressin, which limits the urine amount produced by the organism, causing the individual to drink large amounts of water to compensate the loss of water in his or her body,
- Nephritic (nephrogenous) Insipid, caused when kidneys are not able to respond to the vasopressin action, triggering the kidneys to release excessive quantities of water in the urine and the individual tinkles very much. Although it can depend on congenital origins, this type of diabetes can be provoked by some drugs, urinary obstructions or low levels of calcium or potassium.

Engkilde, Menné and Johansen (2006) investigating whether environmental exposure to chemicals leading to contact allergy could influence the risk of Type-1 diabetes, they found an inverse relationship between contact allergy and Type-1 diabetes. However, Piątkiewicz, Czech and Tatoń (2007) stated that in diabetic patients, infections take a more severe course and complications occur more often because previous studies have shown that diabetes is a pathological state that influences immunity.

It is not omitted to highlight the importance of a nutritive diet and the necessity to exercise that patients with diabetes must implement in themselves, in order to prevent harms, such as depression which could lead patients to take poor care for themselves, as was analyzed by Paile-Hyvärinen, Wahlbeck and Eriksson (2007), who observed that Depression is prevalent in people with Type-2 diabetes and affects both glycaemic control and overall quality of life. This was confirmed by Chernyak *et al.*, (2009) they found out that depression and elevated depression symptoms are more prevalent in patients with Type-2 diabetes than in those without diabetes.

To Nielen, Schellevis and Verheij (2009), the prevalence rate of chronic diseases like hypertension and diabetes mellitus is rapidly increasing, particularly in industrialized countries. Hypertension and diabetes are major risk factors for the development of cardiovascular and renal diseases, and could result in premature death. Correspondingly, to O'Connor (2010), potential for the 30-aged Electronic Health Records technology to improve chronic disease care remains unrealized (especially, care for adults with Type-2 diabetes).

Biotechnological Considerations

The production of transgenic plants with nutritious, sanitary and industrial interest has managed to remarkably increase the quantity and rapid development of agricultural products, plus new varieties of plants able to tolerate adverse conditions and resist pesticides and plagues. Also, the search for less aggressive energy sources for the environment has led to the production of biofuels like ethanol, biodiesel and methane, from renewable sources such as agricultural debris. Falcon *et al.*, (2009) have worked with Microbial Fuel Cells (MFC), elucidating the mechanisms of electron transfer between microorganisms and electrodes in order to get better rates of electricity production.

DaSilva *et al.*, (2002) analyzed the way in which Biotechnology is considered as a technological advancement impulsor in both the developed and developing countries. They also analyzed how opportunities and constraints in agricultural biotechnology in developing countries are of significance in responding to poverty. Additionally, they review the establishment in several developing countries of biotechnology parks and showed them as examples of pro-poor biotechnology and pro-industrial programs for development. Bustamante and Bowra (2002) taking into account that knowledge-based industries have become major components of leading world economies visualize how in-

dustries in Latin American countries have to confront a lack of investment so that these countries are not achieving economic growth and competitiveness in these sectors. This is confirmed by a study developed by Cordero-Mata (2009), in which it is concluded that in Costa Rica there is practically no evidence of creation of companies based on technologic and this country is a technology receiver, with certain development on clusters of high-tech companies, such as manufacturing of medical devices, like electronic and automotive components. Nevertheless, university-industry relationships are weak, in spite of institutional changes, whereas more frequent technology transference is found through consultancy and researching contracts. Also, Gomez and Rodriguez (2008) found that in Mexico, although governmental programs state regulations to foster biotechnology, there are no strong links between industry and universities, such that, local researchers tend to pursue basic projects of general nature and do not focus on the specific needs of the Mexican market. In this context, taking advantage of that small and medium enterprises have a high impact in their local economies, they analyzed the way to boost the potential of the so called High-Technology Small and Medium Enterprises (High-TECH SME's), which include not only R&D based new products and services but also improved designs and processes and the adoption of new technologies. This allows both at national and global levels generating and accessing new technologies, especially Biotechnology. So, they give significant importance to clustering to gain access to new ideas and tacit knowledge, especially in young industries and governments commitment to project financing.

According to Saigí-Rubió and Lopez-Sevilla (2004), throughout history, science and technology have been key elements for human development, whereas today they are regarded by many people as the next great revolution of the knowledge economy. Thus, in the bio-security scope, it is no longer novel to hear about the use of cantilevers and the appearance of water and oil nanoemulsions to monitor and detect bacteria and virus in the environment, besides powerful tools for the manipulation of cellular behavior in the treatment of diseases and in the always new field of tissue engineering. In this sense, a work has been developed by Voronov *et al.*, (2009), modeling the flow behavior inside the space pore within scaffolds, using Poly-L-Lactic Acid (PLLA) and leaching salt with various grain size salt combinations. Therefore, within the research approaches like these it can be found:

- medicine effectiveness and security improvement,
- tumor detection nanocapsules' development,

- dendrimers for cancer treatment,
- nanometric biosensors to detect phenols, methane or carbon monoxide, to support environmental control,
- artificial cellular membranes for tissue restoration; so, better results can be obtained, by means of the robotic surgery support,
- better cut tools, since coal nanotubes are harder than steel,
- derivative products from petroleum used in diverse ways in mining operations, since certain natural enzymes, coming from microorganisms, plants and animals can be used to catalyze chemical reactions with high efficiency and specificity,
- biodegradable polymer development to diminish environmental pollution,
- biodegradable materials for use in surgery and implantation tissue (epithelial, bony),
- solar protectors, cosmetic products or food conservative containers,

Experimentally, Vanegas-Córdoba *et al.*, (2004), evaluate an economic alternative to produce xilitol, alternative sweetener (with similar characteristics to sucrose) that appears for diabetics' use. Also, Redi (2008) mentioned that staminal cells from human fatty tissue acquired cardiomyocit after its transitory exposure to a rat cardiomyocitic, which indicates the possibility of an efficient reprogramming of somatic cells between different species.

By injections of human bony staminal cells to diabetic mice, it has been repaired the mice producer insulin cells. It is important to mention that the Helsinki Declaration, written in 1964 by Worldwide Medical Association, in Finland, displays justification and principles to realize clinical investigations in humans. Saigí and Lopez (2004) mention that "*nowadays, modern biotechnology is meant like a multidisciplinary science that includes molecular genetics, chemical and process engineering, animal and vegetable anatomy, biochemistry, microbiology, immunology, cellular-biology, agriculture, electronic and computer science, among many other sciences* However, one of the problems biotechnology faces is rejection". Although therapies with antibodies represent one of the most promising sectors in the pharmaceutical industry, whose annual sales realize thousands of million dollars, commercialization of genetically-modified products causes great preoccupation. This is due to uncertainty about negative effects

on humans health and nature balance. People think that transgenic species would have more competitive advantages and, therefore, major possibilities of dominating natural communities, causing structural changes in natural ecosystems, injuring fauna or affect the health of humans which is unacceptable in the field of social ethics. In this context, Bioethics is meant in a special way where globalized ethics which involve great amounts of information (generated by international standards), brings about knowledge networks and the innovation clusters emergence, where computer science and knowledge-based systems play, again, an important role.

With the support of molecular biotechnology, knowledge handling, and control of staminal cells, it could be replaced bony marrow therapy in many cancers and other treatments, offering new alternatives for tissue and organ substitution to treat degenerative diseases. Also, cellular cloning technology allows producing embryos in a way that, Felmer (2004) establishes cattle farmers would increase their herd performance in only one generation, since cellular cloning allows producing embryos from an ovum, without spermatozoa. With such embryos staminal cells can be obtained (pluripotentials) from an individual, to develop human tissues able to cure diseases like diabetes, Parkinson and Alzheimer syndromes or certain medullar injuries, diminishing rejections that could be produced in transplants.

Taking advantage of the close relations at present maintained by Biotechnology with Nanotechnology, it has been possible to develop medicinal products and medical procedures that allow optimizing health and life quality of societies. Nanosensors and nanoparticles could help in disease diagnosis and treatment, such as cancer, diabetes or viral disease. So nanosensors could be implanted in humans to measure emissions. On one hand, Ozaydin-Ince *et al.*, (2011) have created particles, called microworms, with cylindrical shape coated with a biocompatible porous membrane to create fluorescent sodium sensors for use as in vivo sodium concentration detectors after subcutaneous injection. However, these hollow nanoparticles could be implanted under human skin and remain anchored at its original location to monitor levels of glucose. So people with diabetes could check their blood sugar by glancing at an area of their skin. On the other hand, Mann *et al.*, (2010) state that, genic therapy can be bear in mind to envisage a new approach or promising tool in the search of a treatment for diabetes, because advances in the genic therapy field allow to dispose of safer and effective vectors to transfer genes of interest to different cells or tissues of the organism. Recently,

the evolution of biotechnology and its interactions with nanotechnology has proved that medicine production by biotechnological methods (replacing traditional procedures) is a reality, as well as being safer and more economical. Multiple fuse sensors for detecting a wide rank of pathogens and indicating guests will be able to offer the highest detection capacity. Therefore, it is not strange that today people talk about biochips to determine correlation between gene expressions and different congenital diseases, at the moment without cure. It is possible that responsible genes for some diseases can be identified. Protein handling and control, in response to the necessity to obtain great amounts of deficit proteins for hospitals have channeled investigations towards the transgenic animal use as bio-reactors (live reactors). Animals produce in their cells the necessary proteins for humans, as it is the case of cows, sheep and goats in which human gene cells are introduced, into their milk producer cells to codify proteins of therapeutic interest. Thus, important amount of the desired protein are developed which can be very useful for both new born babies, old or sick people.

Beltrán-Fernández *et al.*, (2010) are working to optimize the actual surgical technique, analyzing the differences between the biomechanical effects on a bone graft, which replaces a damaged C4 vertebral body, a titanium alloy (Ti6A14V) cervical plate, used to isolate the C4 damaged vertebra, and the influence on the compressive loads on the complete and instrumented C3-C5 cervical model. In the same context, Merchán-Cruz *et al.*, (2007) published a work related to the development of an algorithm to improve the performance of manipulating robots which could support the development of a prosthesis as previously mentioned. Moreover, as coal nanotubes are much more resistant than steel, it is possible to design and build a prosthesis as seen in the research developed by Colombo and Vergani (2009), who experiment with a prosthesis to improve an athlete's performances.

Knowledge-Based Systems (KBS)

Among all the characteristics that identify knowledge-based systems, these systems support their performances over quality and quantity from specific domain knowledge rather than techniques to solve problems. Nonetheless, these systems provide useful applications when needed to solve very complex problems. Mostly, when organizations need to acquire and preserve specific expert knowledge, in order to share with non-experts the ability to explain reasoning processes applied in solving problems. Likewise, knowledge-based systems may maintain operative interactions

with other systems in a way that, eventually, they need information imported from other systems or, on the contrary, knowledge-based systems' results could be exported to other systems, in order to be treated.

Richards (2003) has stated that an explanation is important for knowledge-based systems as it satisfies users' necessities to decide whether to accept or reject a recommendation. Since it is not possible to know what goes on inside an expert's head, there is no way to accurately capture thought process and reason. So, using browsing tools to explore the knowledge of different views, the what-if analysis for case values and the display of rules and traces in a number of alternative formats give users control, linked to greater satisfaction and acceptance. Malhotra (2006) defines, "...Knowledge management systems engineering seeks model management solution to challenging problems involving the manipulation of complex metadata artifacts, or models...". Many systems that manage knowledge use several Artificial Intelligence methods and tools, such as neural networks, intelligent agents or fuzzy logic, in order to carry out activities related with knowledge identification, knowledge engineering, tacit-to-explicit knowledge transfer, and so on.

The evolution of decision support systems technology and its amalgamation with many other technologies such as knowledge-based techniques, object-oriented systems, intelligent agents, neural networks, genetic algorithms, as well as data warehousing and web-based technology, has led to many sophisticated knowledge-based systems (KBS) and modeling environments emerging. Farley *et al.*, (2008) defined artificial neural network as "a mathematical model aimed to function like the neural network in the human brain, and is able to map input data to the appropriate output data... often used as pattern classifiers or as function approximator". Also, among different applications of knowledge-based systems, it is possible to find applications such as diagnosis, planning, design, monitoring and process control, training and consultation services as is shown next. Boucher (2010) considers that technology is shifting knowledge; so, asking the question "how can we as providers embrace technology in our relationships with patients and use it to improve our communication with them?", he states that practitioners see the advantages of efficiency and accessibility but often feel concerned by how each tool may overwhelm them as patients seek or gain access to misleading information.

Applications of Knowledge-Based Systems (KBS)

Knowledge Management (KM), initiated after World War II and reinforced at the end of the last century, is characterized by focusing on intangible assets and knowledge value generation, known as intellectual capital, as well as taking advantage of other systems' utilities (mainly on information and communication technologies). These systems show great application in all organizational sectors, such as governmental, scientific, industrial, educational, and so on, in order to facilitate decision making processes. Also, it is recognized as one of the main factors for knowledge-based systems. Groot *et al.*, (2005), based on the idea of degradation studies, argue that KBS's abilities to deal with missing or invalid data is an essential dimension of KBS validation and the need for quantitative analysis of the KBS quality. Thus, in an expository but non limitative way, some applications are mentioned that are possible to find in the globalized world.

A. Management

In order to improve strategic, tactic or operative processes, these systems are advocated in retrieving, managing and sharing information stored in databases needed for:

- Minimizing or reducing operation costs, offering improvement in planning, coordination and control of complex activities,
- Homogenizing and clarifying specialized information, including that needed for training,
- Evaluating or explaining decision making.

Based on a business trip approval process, Lee *et al.*, (1999) proposed a knowledge-based approach for workflow modeling, concluded that Knowledge Workflow Management was useful because it proved a useful framework to implement fully automated workflow and to improve organizations that frequently change their business processes under turbulent organizational environments.

B. Consultancy

This knowledge-based systems activity includes disciplines such as medicine, jurisprudence, engineering, and so on, supporting organizations to use and control growing information volumes. They allow organizational workers to:

- Access information from experts, consultants or external sources,

- Modeling or simulating situations, problems or systems,
- Interpreting or explaining legal dispositions,
- Report elaboration, as well as updating operative information.

Brézillon and Brézillon (2008) state the lack of explicit context representation as one of the reasons for failures in many knowledge-based systems. So, they propose contextual graphs for uniform reasoning elements representation and contextual elements 356 at the level of links between contextualized reasoning elements that are organized in graphs like a nest of dolls, with no hierarchy. Thus, they infer that a contextual element may itself be a contextual knowledge piece (where more-basic contextual elements intervene) and consider that contextual graphs could facilitate representing good or bad practices, as a tool to identify and propose rational ways to improve human behaviors.

Many researches applied concept maps on knowledge management as a knowledge management tool. So that, concepts can be captured and queried, as well as connections among knowledge elements could be discovered. Thus, Wang *et al.*, (2008), present a self-associated concept mapping (SACM) in which they extend the use of mapping concept by proposing the idea of self-construction and automatic problem solving to traditional concept maps, in order to give the idea of concept maps with self-construction ability and automatic problem-solving ability.

C. Production

In order to improve activities related with production and manufacturing processes, such as machinery operation, quality control, stock inventories, and so on; knowledge-based systems sustain organizational performances by means of:

- Optimizing control and coordination of processes, as well as updating, communicating and distributing operative procedures,
- Forecasting objectives, goals or results related with production, including complex processes.

Csaszar *et al.*, (2000) presented a project conducted for the purpose of optimizing an automated modular, high-speed multi-station, in order to minimize the pulse rate (i.e. time elapsed between the completion of two consecutive boards) and the number of feeder mechanisms required. They conclude that using the knowledge-based system in conjunction with the simu-

lator, factory engineers were able to produce results that increased production considerably and decreased feeder slot usage.

Relating to the biochemical industry field, Régis *et al.*, (2008) proposed a non-model based method of physiological state identification, based on segmentation of bioreactor sensors signals, in which the method is supported by the detection of signal singularities by the Maximum of Modulus of Wavelets Transform and the characterization by the Hölder exponent evaluation. Meanwhile, physiological states characterization was based on the correlation product between biochemical signals and, according to the results confirmed by microbiology experts. The authors deduce that their method could help to automatically control and optimize the analyzed bioprocess.

D. Financial Management

Perhaps one of the most demanding applications is involved in the financial world, because of the importance and complexity of this process, related to bank loans, financial accounting or auditing, stock exchange, and so on. In this context, it is necessary to hold intelligent tools that allow organization planning, controlling and evaluating different and complex existent systems, as well as the operational and financial effects derived from this process.

Sun and Li (2006) saw neural networks as a black-box whose structure weight values is the hidden knowledge for classification, which is difficult for ordinary investors and finance majors to understand. However, with the development of information technology, machine learning, and artificial intelligence, data mining appears and grows, in order to support detailed researchers to depend on reliable methods for financial distress prediction, because data mining dynamically mine out valuable hidden knowledge, which could be applied to predict listed companies' financial distress. In this context, the authors conclude that the decision tree can overcome lack of dynamic learning ability and understanding, in order to effectively predict listed companies' financial distress.

E. User's behavior

Nowadays, it is a common practice for people to get different types of information from the Internet; so, in a similar way, activities related with the use of Internet, such as entertainment, publicity, sales, and so on, are supported by knowledge-based systems with efficient and adequate tools, in order to know, evaluate, and update information related with their market position.

Likewise, organizations could evaluate and control their programs related with assistance or customer services and control and evaluate their virtual environments or user's behavior when they are connected.

Taking advantage of the convergence of fuzzy logic techniques and Internet, Sedbrook (1998) described architecture and a prototype for developing, delivering, and maintaining expert systems on the World Wide Web. On the other hand, looking for reduction of data needed for conclusions, Ghalwash (1998) developed an inference engine supported by a connectionist knowledge base, so, he concluded that knowledge-based neural networks (KBNN) could be used as expert system knowledge bases.

Huang and Hsu (2006) designed a prediction-based proxy server used to improve hit ratios of accessed documents. The architecture of which consists of three functional components such as a log file filter, an access sequence miner, and a prediction-based buffer manager. They present a development to take appropriate actions such as document caching, document pre-fetching, and even cache/prefetch buffer size, adjusting to achieve better buffer utilization. Finally, the authors report that, through simulation, they found that their approach had a better performance than others in quantitative measures, such as hit ratios and byte hit ratios of accessed documents.

F. Health Care

Taking into account that the number of available Web-services increases and there is a growing demand to realize complex business processes by combining and reusing available Web-services, Argüello and Des (2007) concentrate one study about a services-based application for diagnosis and clinical management of Diabetic Retinopathy, where the end-users are health professionals who are not familiarized with Semantic Web technologies. Thus, they used the Ontology Web Language to encode domain ontology fragments and SWRL rule fragments as the inputs and outputs of Web services; focusing on Clinical Practice Guidelines (GL) related to the biomedical field. Their study highlights the benefits and drawbacks found when applying this approach to obtain Web services intended to be used in clinical decision-making and rely on clinical practice guidelines.

Akter, Uddin and Haque (2009) showed in the 13th International Conference of Biomedical Engineering a knowledge-based system, developed with 26 rules implemented using Prolog language, in order to support patients and practitioners in the diagnosis and management of diabetes mellitus.

Applications of Knowledge-Based Systems in Biotechnological Processes

As will be notice, the use of knowledge-based systems as a support for Biotechnology is not recent. However, it takes into account the challenges that Globalization impose on organizations. Next is mentioned some works related with 449 the use of knowledge-based systems in biotechnological processes.

Due to availability problems shown by some key parameters involved in bioprocesses assessment; Glassey *et al.*, (1996) analyzed how knowledge-based systems, making an integration of software sensors with fundamental knowledge process could offer improvement in bioprocess optimization by reducing overall process variability and the contribution of human operator error. Guthke *et al.*, (1998) considered knowledge acquisition as a major bottleneck with respect to efficient computer control design of knowledge-based systems in bioprocess engineering and presented their work related with the automatic generation of fuzzy rules applied to data of an industrial antibiotic fermentation. Likewise, due to the growing importance of the bioprocess monitoring capabilities both in bioprocess development and physiological studies, Olsson *et al.*, (1998) focusing on on-line analytical systems, analyzed advantages and drawbacks of various of the most frequently used analytical techniques and components.

By trying knowledge engineering methods for chemical and biochemical process modeling and control, Peres *et al.*, (2001) published their experience with an application into a baker's yeast production process. They concluded that it was possible to obtain a more accurate process description when all available sources of knowledge were incorporated in the process model. Also, Schügerl (2001) made a review about the development of bioprocess engineering in the past 20 years. He took into account advanced control, and used structured and hybrid models, expert systems and pattern recognition for process optimization, in order to give a report relating to the existing state of the art of metabolic flux analysis and metabolic engineering. He concluded that Artificial Intelligence and knowledge-based systems were tools that made possible an organized use of schematic information and logical descriptions.

In simulation case studies with a bioreactor dynamical hybrid model that combines first principles modeling with artificial neural networks, Oliveira (2004) states that hybrid modeling through knowledge integration can be employed when processes are complex and poorly understood in a mechanistic sense, because the model

accuracy can be increased by the incorporation of alternative and complementary sources of knowledge.

Taking into account that unidimensional electrophoresis gel analysis methods need continuous improvement, Santiesteban-Toca *et al.*, (2007), proposed a new algorithm to improve the performance in band detection and the automatic selection of lanes; concluding that their procedure could be a low cost alternative with a good performance for the researchers in use of the unidimensional electrophoresis techniques. Likewise, to provide efficiency and productivity to the powder industry, Alarkan, EsSaheb and Kamal (2009) presented a work in the 3rd International Conference on Advanced Computational Engineering and Experimenting, ACEX-2009, related to the building of an expert system prototype which, using forward and backward searching techniques, acquired knowledge for the user to give, subsequently, recommendations on powder production method, satisfying the powder requirements for a specific application, taking advantage of a rule-based representation model.

Knowledge Management System Model Proposed to Support Diabetic Treatment and Clinical Research

Nelson *et al.*, (2006) trying to review the performance and effectiveness of methods for the diagnosis, management and treatment of infected diabetic foot ulcers in sources like MEDLINE, PREMEDLINE, EMBASE, AMED, British Nursing Index and CINAHL, as well as internet registers like Controlled Clinical Trials and the National Research Register, in addition to nine internet sources for clinical guidelines or reviews and the journal "The Diabetic Foot"; they concluded that there was insufficient evidence on which to base any conclusions. So, they proposed some recommendations for further research. Moreover, Aragón-Sánchez *et al.*, (2008) taking into account that Osteomyelitis is one of the most frequent complications of diabetic foot ulcers, they analyzed 185 diabetic patients with foot osteomyelitis and histopathological confirmation of bone involvement until healing, amputation or death. Thus, they found that osteomyelitis has different characteristics and prognosis if combined with a soft tissue infection. So, they consider that the endpoint in diabetic foot ulcers complicated by osteomyelitis must be complete healing of the ulcer or surgical wound performed to treat the bone infection.

In order to obtain improvement abilities, organizations can take advantage of knowledge management whose structure allows them to systematize knowledge pre-

viously got to innovate or to solve problems. Martínez-Aldanondo (2004) declares: "*learning demands to remember*"; a condition that traditional information systems cannot fulfill, because only human mind stores cases and experiences. If expertise is shared with others, it can provide knowledge which, integrated in an adapted process of qualification and development, supported with suitable technologies of information, will promote an effective forecast culture and an effective capacity response to environment changes.

Technology would not be worthwhile for organizations if they did not have capable people for its use because they have the capacity to learn, understand and, modify methods or procedures contributed by technology. In this context, Artificial Intelligence has facilitated the appearance of systems for managing, catching, storing, distributing and sharing information, taking advantage of the specialization reached by their workers, as well as in the solution of either emergent or extraordinary events. This avoids distracting the attention of specialists to routine tasks so that they can take care of major relevance tasks, thus improving expert personnel productivity.

Figure 2 shows the authors' proposal for the integration of a research and clinical structure in a knowledge management system, using a qualitative representation in which relations between the diverse factors have been considered. This proposal regards aspects like knowledge and practices, as well as resources that clinical and laboratory practices must utilize, taking into account that they can define and document the specific and necessary knowledge for their key activities.

Diabetes' research and treatments generate a lot of information related with symptoms, diagnosis procedures, treatments' results and progress, new discoveries about medicines, methods, techniques, procedures and interactions with other disciplines (such as Biotechnology and Nanotechnology advances). The proposed model integrates interactions between human capital and structural capital. Such as use, maintenance or improvement of methodologies, data repositories and information technologies that are generated in the daily work, in order to support the organizational productivity and competitiveness.

It is not omitted to mention that this model, independently of the knowledge-based system utilized (illustrated in figure 2 as expert system), it involves the main processes related with an organizational knowledge management system, such as:

- Knowledge necessities identification,

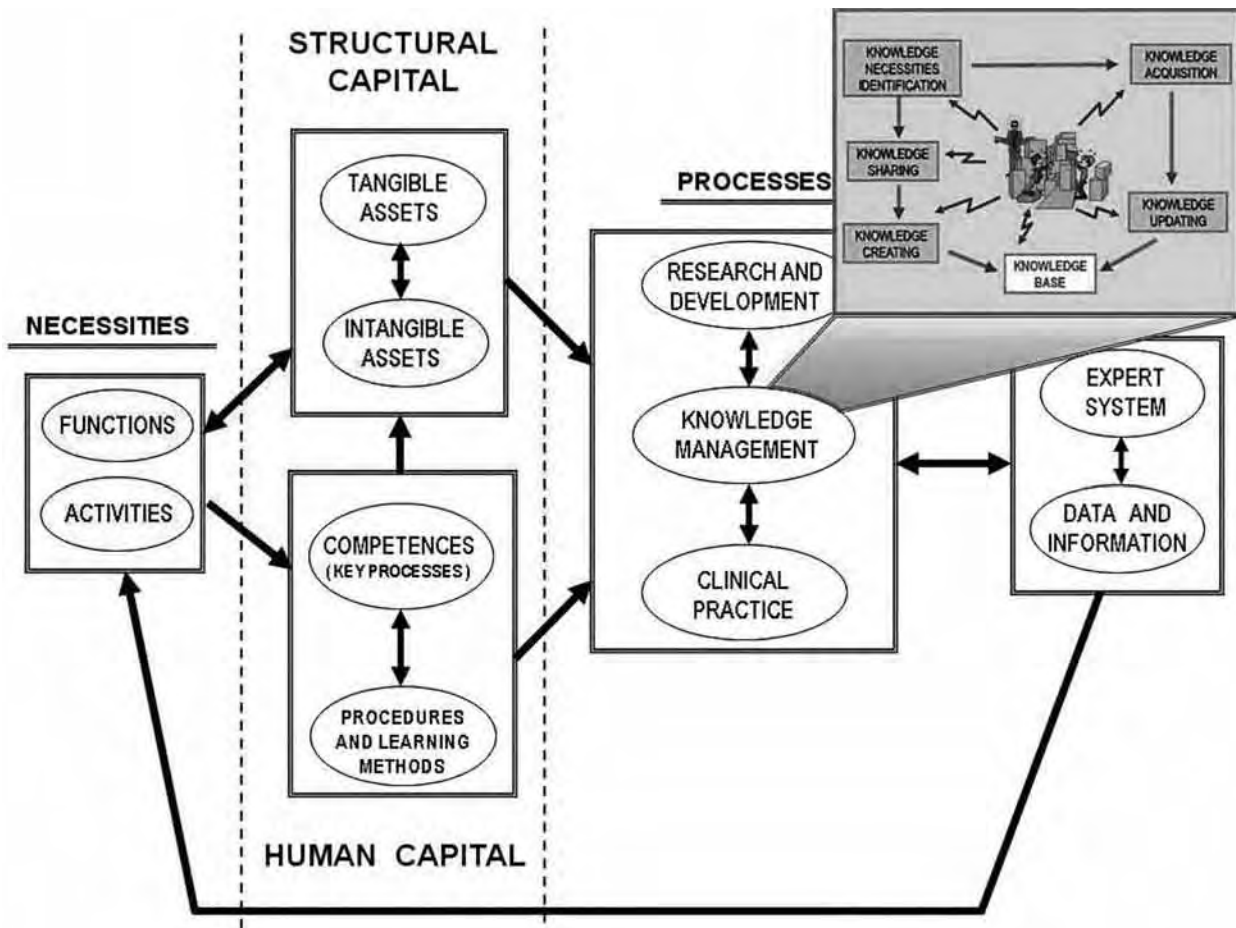


Figure 2. Knowledge management process inserted in the proposed model (personal elaboration)

- Knowledge acquisition,
- Knowledge updating,
- Knowledge sharing,
- Knowledge creating,
- Knowledge base maintenance.

Furthermore, the knowledge management process, showed as a nuclear process, takes advantage and updates the information generated (or acquired) from external sources (concerning to clinical practice or the research and development activities) as well as the data treatment from the organizational data repositories. Thus, the generated information could be used to support the organizational strategies related with its human or structural capital. Because it is not the purpose of this work analyzing or treating about organizational development, the authors avoid go into this topic in any depth). Nonetheless, figure 2 shows the way in which the above mentioned processes can be

integrated to suitably increase efficiency and operative effectiveness, as well as leading intellectual capital (or organizational knowledge) to a measurable and sustainable competitive advantage for supporting the desired successes.

Because globalized activities oblige organizations to be alert to changes in the environment, to get an holistic (or systemic) visualization, figure 3 shows interactions that organizations would maintain with the relational capital. Remembering that such interactions are fundamental for the organizational performance and, in consequence, these interactions must be considered in the organizational strategic planning. As it can be observed, besides integrating relational capital in the processes and results (taking advantage of the integration of computational, technical, and administrative systems), the proposed model would adapt properly with the organizational intentions, achieving a suitable leverage for the organizational performance. Hence,

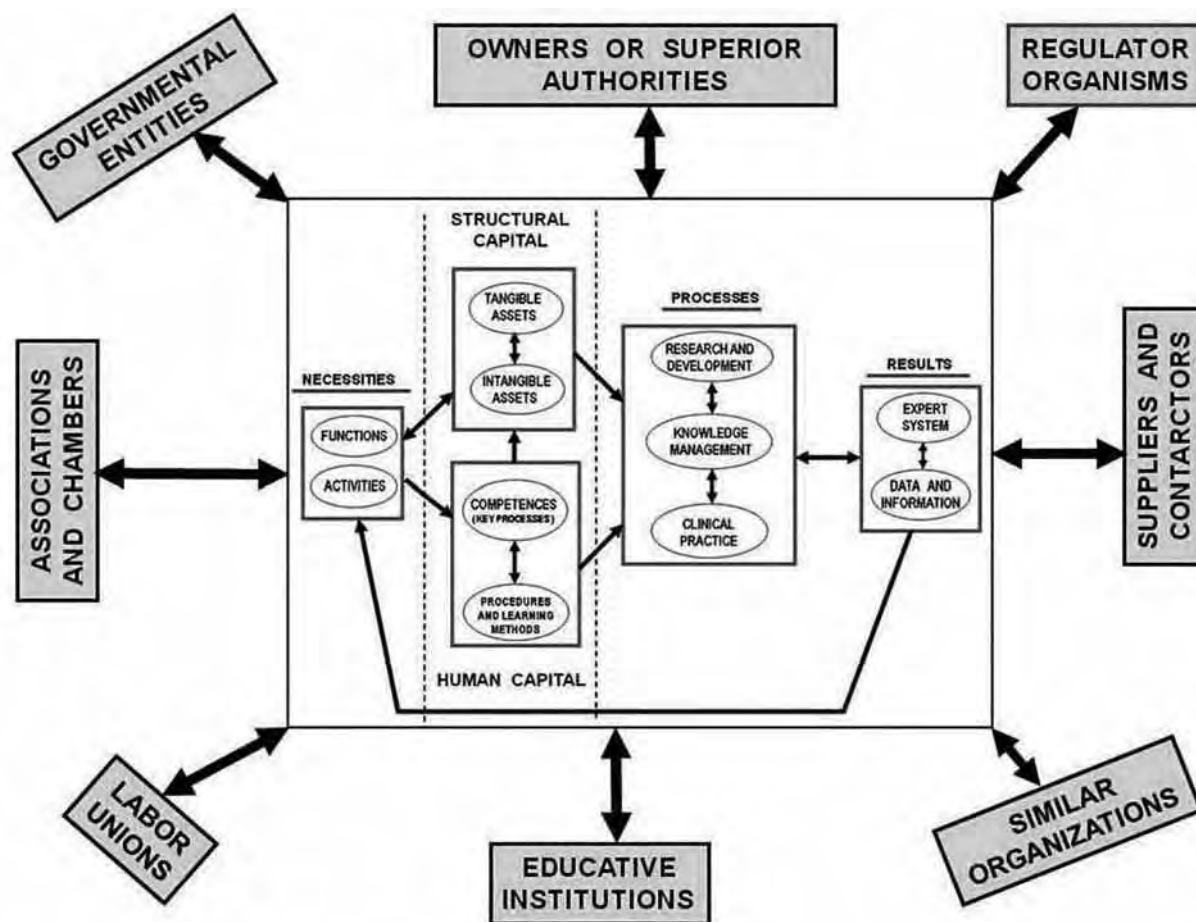


Figure 3. A holistic vision of the Knowledge Management System Model Proposed (personal elaboration)

Thus, it is convenient, and necessary, to develop a knowledge management system that takes advantage of information systems owned by the organization, in order to effectively support the decision making for Diabetes' research and clinical processes related with both internal and external knowledge, as well as acquired experiences from either experts or external sources related with the organization.

Conclusions

Though technology transference from industrialized countries to developing countries can be a fundamental condition for the technological development and businesses impulse for the developing countries interests created by transnational companies and the lack of systemic vision of governors, have caused disinterest in establishing mechanisms adapted for suitable in-sourcing and operation of external knowledge. Also, conditions are needed to encourage creation of new knowledge through knowled-

ge-bodies and knowledge-networks, developing constructive collaborations within knowledge limits, in order to optimize results and focus the efforts of scientific researchers in the development of systems and products adapted to the culture and necessities of their communities. In spite of this, Globalization puts in reach of regional scientific communities great volumes of information, which should be used and disseminated in an effective way to facilitate the suitable use of this specific knowledge and to manage the accumulated organizational experience. Nowadays, it is possible to get methodologies, techniques, models and robust tools that facilitate integration of information and knowledge into data repositories which could support strategic decision making, offering more advanced research fields corresponding to superior levels, such as fuzzy logic, data mining, neural and Bayesian networks, computational vision, and so on, as well as continuing the research and development in disciplines such as bioengineering, medicine, nanotechnology, accounting, and so on.

It is convenient to mention that long-term economic growth is linked with innovation capacity and technological productivity. Thanks to the social, economic and environmental benefits obtained by means of Biotechnology, new possibilities emerge to direct worldwide economy to a more sustainable development and a better life quality. Soon, artificial organs will be used (since genetic engineering involves a significant advance in the Science objectives and life-sciences). Thus Biotechnology, thanks to their social, economic and environmental potential, is going to be economically more important, setting up along with information and communication technologies, the base of a new economy based on the “*know and the know what to do*” (know-how), such that conversion of know-how to competitive and sustainable processes, combined with R&D investments will be key success factors for the Knowledge Society. The systemic persistence of gaps between what is known and what practices impact on the quality of services is one of the iniquity causes in health. So, access to information and to up-to-date scientific knowledge constitutes a social determinant for public health, leading scientific knowledge transference in research, education, promotion or health attention systems as one of the critic problems for the global public health (BVS, 2009).

Therefore, with suitable management of knowledge-based organizations (or communities), specific knowledge is meant as the suitable use of organizational experience to increase and generate new knowledge on the basis of the generated information at its interior (or by means of the interchanges that these communities maintain with their surroundings), transforming it into measurable and sustainable competitive advantages, that can be transformed into the awaited successes. Camisón *et al.*, (2006) mention that rapidity in the extension of enterprise knowledge is a fundamental issue in creating competitive advantages, besides the recognizing that most valuable knowledge for the company is that one which is characterized like tacit, condition that hinder its transmission outside the company limits. In this context, knowledge-based systems provide users with a set of robust tools for getting and describing metadata contents and their applications, besides to make easier the formal integration and retrieval of that data, for an adequate use of expertise or specific knowledge.

Taking into account the so-called scientific-communication’s globalization (Gevers, 2009), as well as the maturity of artificial intelligence in medicine (following the thought of Patel *et al.*, 2008) and the developed work over clinical aspects for increasing flexibility to related tasks, such as Kumar and

Smith (2003) as well as Moser and Miksch (2005), or Groot *et al.*, (2009) or Grando, Peleg and Glasspool (2010); this work proposes a model that takes advantage of the knowledge-based system’s characteristics in order to support the clinical and research processes with either ripe decisions or up-to-the-minute scientific reports which lead the organizational strategies to maintain and establish improvement conditions for the specialized knowledge, including both the organizational and the external expertise, such as is referred by Dormandy *et al.*, (2005), or McGarry and Chambers and Oatley (2007), or Jenssen *et al.*, (2008); besides the management of either technical or regulatory information, as is treated by Steiness (2009).

As described in this work, knowledge-based systems are utilized for supporting biotechnological research processes as well as supporting tactical and strategic decisions. In spite of political or cultural rejections, thanks to Artificial Intelligence techniques and tools that knowledge-based systems exploit, and the evolution of nanotechnical materials, Biotechnology can view the future with optimism. Thus, scientific communities from developing countries should only have to worry about getting economical conditions to develop their activities and projects, such as is suggested by Slingerland (2006) in her study about monogenic diabetes in children and young adults.

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References

- Alharkan, I., EsSaheb, M. and Kamal R. 2009. Developing an Expert System for Powder Technology, 3rd International Conference on Advanced Computational Engineering and Experimenting, Rome: ACEX-2009 Proceedings: 174-175,
- Akter, M., Uddins, MS. and Haque, A. 2009. Diagnosis and Management of Diabetes Mellitus through a Knowledge-Based System, Proceedings of the 13th International Conference on Biomedical Engineering, 23 (3): 1000-1003,
- American Diabetes Association, Diabetes Gestacional, consulted at www.diabetes.org/espanol/todo-sobre-la-diabetes/diabetes-gestacional/ in February 2011,
- Aragón-Sánchez, FJ., Cabrera-Galván, JJ., Quintana-Marrero, Y., et al. 2008. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement, *Diabetologia*, 51(11):1962-1970,

- Argüello-Casteleiro, M. and Des-Diz, J.J. 2007. Clinical practice guidelines: A case study of combining OWL-S, OWL, and SWRL, *Knowledge-Based Systems*, 21(3): 247-255,
- Beltrán-Fernández, J.A., Hernández-Gómez, L.H., Urriolagoitia-Calderón, G., et al. 2010. Biomechanics and numerical evaluation of cervical porcine models considering compressive loads using 2D classic computer tomography CT, 3D scanner and 3 D Computed Tomography, *Applied Mechanics and Materials*, 24-25: 287-295,
- Boucher, J.L. 2010. Technology and Patient-Provider Interactions: Improving Quality of Care, But Is It Improving Communication and Collaboration?, *Diabetes Spectrum, American Diabetes Association*, 23(3): 142-144,
- Brézillon, P. and Brézillon, J. 2008. Context-Sensitive Decision Support Systems in Road Safety, Paris, France: *International Handbooks on Information Systems*, Handbook on Decision Support Systems 2, Chapter 42, pp 107-123,
- Bustamante P.I. and Bowra S. 2002. Biotechnology in developing countries: harnessing the potential of high-TECH SMES in the face of global competition, *Electronic Journal of Biotechnology*, 5(3): 197-202,
- BVS, 2007. La OPS realza el papel de la información y del conocimiento científico para el desarrollo de la salud, *Newsletter 076 31*, Biblioteca Virtual en Salud, Centro Latinoamericano y del Caribe de Información en Ciencias de la Salud, Organización Panamericana de la Salud, Organización Mundial de la Salud,
- BVS, 2009. Ambientes aprendices e informados para la transferencia de conocimiento, *Newsletter 089 27*, Biblioteca Virtual en Salud, Centro Latinoamericano y del Caribe de Información en Ciencias de la Salud, Organización Panamericana de la Salud, Organización Mundial de la Salud,
- Camisón-Zornoza, C., Boronta-Navarro, M. and Villar-López, A. 2006. Innovando a través del establecimiento de alianzas estratégicas: La generación de competencias distintivas en conocimiento y su efecto en el desempeño organizativo, *Cooperación, Innovación y Conocimiento I - Tribuna de debate*, N° 36, consulted at www.madrimasd.org/revista/revista36/tribuna/tribuna1.asp in August 2010,
- Chernyak, N., Petrak, F., Plack, K., et al. 2009. Cost-effectiveness analysis of cognitive behaviour therapy for treatment of minor or mild-major depression in elderly patients with type 2 diabetes: study protocol for the economic evaluation alongside the MIND-DIA randomized controlled trial (MIND-DIA CEA), *BMC Geriatrics*, 9(25): 1-8,
- Chu, S.Y., Callaghan, W.M., Kim, S.Y., et al. 2007. Maternal Obesity and Risk of Gestational Diabetes Mellitus, *American Diabetes Association*, 30(8): 2070-2076,
- Clausen, WHO., De Gaetano, A. and Vølund, A. 2006. Within-patient variation of the pharmacokinetics of subcutaneously injected biphasic insulin aspart as assessed by compartmental modeling, *Diabetologia*, 49(9): 2030-2038,
- Colombo, C. and Vergani, L. 2009. Numerical Models of a Carbon Fibre Prosthesis for Athletes, Rome, Italy: 3rd International Conference on Advanced Computational Engineering and Experimenting, ACEX-2009 Proceedings, ACEX 082: 98,
- Cordero-Mata, O. 2009. ¿Es Posible la Creación de Empresas de Base Tecnológica en Costa Rica? Un Análisis desde el Enfoque de La Tercera Misión, *Ciencias Económicas* 27(1): 303-316,
- Csaszar, P., Nelson, P.C., Rajbhandari, R.R. and Tirpak, T.M. 2000. Optimization of Automated High-Speed Modular Placement Machines Using Knowledge-Based, *IEEE Transactions on Systems, Man, and Cybernetics – Part C: Applications and Reviews*, 30(4): 408-417,
- Dashora, U., Ashwell, S.G., and Home, P.D. 2009. An exploratory study of the effect of using high-mix biphasic insulin aspart in people with type-2 diabetes, *Diabetes, Obesity and Metabolism, Journal of Pharmacology and Therapeutics*, 11(7): 680-687,
- DaSilva, E.J., Baydoun, E. and Badran, A. 2002. Biotechnology and the developing world, *EJB Electronic Journal of Biotechnology*, 5(1): 64-92,
- Dormandy, J.A., Charbonnel, B., Eckland, D.J.A., et al. 2005. Secondary prevention of macrovascular events in patients with type-2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial, *The Lancet*, 366(9493): 1279-1289,
- Engkilde, K., Menné T. and Johansen, J.D. 2006. Inverse relationship between allergic contact dermatitis and type-1 diabetes mellitus: a retrospective clinic-based study, *Diabetologia*, 49(4): 644-647,
- Falcón, A., Lozano J.E. and Juárez, K. 2009. Bioelectricidad, *BioTecnología*, 13 (3): 62-78,
- Farley, S.J., Durodola, J.F., Fellows, N.A. and Hernández-Gómez, L.H. 2008. A Neural Network Approach for Locating Multiple defects, *Trans Tech Publications, Applied Mechanics and Materials*, 13-14 : 125-131,
- Felmer, R. 2004. Animales transgénicos: pasado, presente y futuro, *Archivo de Medicina Veterinaria*, XXXVI (2): 105-117,
- Gevers, W. 2009. La globalización de la publicación científica, *Newsletter 092 08*, Biblioteca Virtual en Salud, Centro Latinoamericano y del Caribe de Información en Ciencias de la Salud, Organización Panamericana de la Salud, Organización Mundial de la Salud,
- Ghalwash, A.Z. 1998. A Recency Inference Engine for Connectionist Knowledge Bases, *Applied Intelligence*, 9(3): 201-215,
- Glassey, J., Ignova, M., Ward, A.C., et al. 1997. Bioprocess supervision: neural networks and knowledge based systems, *Journal of Biotechnology*, 52(3): 201-205,
- Gómez, M. and Rodríguez, J.C. 2008. The Emergence of Biotechnology Related Industries in Mexico, *Revista Nicolaita de Estudios Económicos*, III(2): 37-55,
- Grando, A., Peleg, M. and Glasspool, D. 2010. A goal-oriented framework for specifying clinical guidelines and handling medical errors, *Journal of Biomedical Informatics*, 43(2): 287-299,
- Groot, P., Hommersom, A., Lucas, P.J.F., et al. 2009. Using model checking for critiquing based on clinical guidelines, *Journal of Artificial Intelligence in Medicine*, 46(1): 19-36,
- Groot, P., ten Teije, A. and van Harmelen, F. 2005. A quantitative analysis of the robustness knowledge-based systems through

- degradation studies, *Knowledge and Information Systems*, 7(2): 224-245,
- Guthke, R., Schmidt-Heck, W. and Pfaff, M. 1998. Knowledge acquisition and knowledge based control in bioprocess engineering, *Journal of Biotechnology*, 65(1): 37-46,
- Huang, YF. and Hsu, JM. 2006. Mining web logs to improve hit ratios of pre-fetching and caching, *Knowledge-Based Systems*, 21(1): 62-69,
- Instituto Mexicano del Seguro Social, consulted at www.imss.gob.mx/salud/Diabetes/Diabetes_tipo_1.htm in February 2011,
- Jenssen, TG., Tonstad, S., Claudi, T., et al. 2008. The gap between guidelines and practice in the treatment of type-2 diabetes: A nationwide survey in Norway, *Diabetes Research and Clinical Practice*, 80(2): 314-320,
- Koschorreck, M. and Gilles, ED. 2008. Mathematical modeling and analysis of insulin clearance in vivo, *MBC Systems Biology*, 2(43): 1-18,
- Kumar, A. and Smith, B. 2003. Ontology for Task-Based Clinical Guidelines and the Theory of Granular Partitions, *Artificial Intelligence in Medicine*, 9th Conference on Artificial Intelligence in Medicine in Europe, AIME 2003: 71-75,
- Lee, HB., Kim, JW. and Park, SJ. 1999. KWM: Knowledge-based Workflow Model for Agile Organization, *Journal of Intelligent Information Systems*, 13: 261-278,
- Lincoln, NB., Radford, KA., Game, FL. and Jeffcoate, WJ. 2008. Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial, *Diabetologia*, 51(11): 1954-1961,
- Malhotra, R. 2008. Metamodeling framework: A new approach to manage meta-model base and modeling knowledge, *Knowledge Based Systems*, 21(1): 6-37,
- Mann, C., Ayuso, F., Bosch, F. and Anguela, X. 2010. Aproximaciones de terapia génica para la diabetes tipo 1, *Avances en Diabetología*, 26(4): 6-12,
- Martínez-Aldanondo, J. 2004. e-learning y los 7 pecados capitales (2), consulted at www.gestiondelconocimiento.com/leer.php?colaborador=javitomar&id=341 in September 2010,
- Medline Plus, Biblioteca Nacional de Medicina de EE. UU., Institutos Nacionales de la salud, consulted at www.nlm.nih.gov/medlineplus/spanish/ency/article/000305.htm in February 2011,
- McGarry, K., Chambers, J. and Oatley, G. 2007. A multi-layered approach to protein data integration for diabetes research, *Journal of Artificial Intelligence in Medicine*, 41(2): 129-143,
- MedlinePlus, Biblioteca Nacional de Medicina de EE. UU., Institutos Nacionales de la Salud, consulted at www.nlm.nih.gov/medlineplus/spanish/ency/article/000313.htm in August 2010,
- Merchán-Cruz EA., Hernández-Gómez LH., Velázquez-Sánchez AT. et al, Exploiting Monotony on a Genetic Algorithm based Trajectory Planner (GABTP) for Robot Manipulators, *Proceedings of the Applied Simulation and Modeling (ASM2007)*, Track 581:051,
- Moser, M. and Miksch, S. 2005. Improving Clinical Guideline Implementation Through Prototypical Design Patterns, *Artificial Intelligence in Medicine*, 10th Conference on Artificial Intelligence in Medicine in Europe, AIME 2005: 126-130,
- Nauck, MA., Duran, S., Kim D., et al. 2007. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type-2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study, *Diabetologia*, 50(2): 259-267,
- Nelson, E. A., O'Meara, S., Craig, D., et al. 2006. A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers, Centre for Reviews and Dissemination, International Network of Agencies for Health Technology Assessment, Global Networking for Effective Healthcare, HTA Database, consulted at www.crd.york.ac.uk/CRDWeb/search.aspx?SessionID=3019695&SearchID=301969&SearchFor=diabet&RPP=10&DB=&DefaultOr=No&D=8&E=29&H=0 in February 2011,
- Nielen, MMJ., Schellevis, FG. and Verheij, RA. 2009. Inter-practice variation in diagnosing hypertension and diabetes mellitus: a cross-sectional study in general practice, *BMC Family Practice*, 10(6): 1-6,
- O'Connor, PJ. 2010. Using Electronic Health Records to Improve Outpatient Diabetes Care, *Diabetes Spectrum*, American Diabetes Association, 23(3): 146-148,
- Oliveira, R. 2004. Combining first principles modeling and artificial neural networks: a general framework, *Computers & Chemical Engineering*, 28(5): 755-766,
- Olsson, L., Schulze, U. and Nielsen, J. 1998. Online bioprocess monitoring – an academic discipline or an industrial tool?, *TrAC Trends in Analytical Chemistry*, 17(2): 88-95,
- Ozaydin-Ince, G., Dubach, JM., Gleason, KK. and Clark, HA. 2011. Microworm optode sensors limit particle diffusion to enable in vivo measurements, *Proceedings of the National Academy of Sciences*, 107(1): 2656-2661,
- Paiile-Hyvärinen, M., Wahlbeck, K. and Eriksson, JG. 2007. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomized placebo controlled 6-month trial, *BMC Family Practice*, 8(34): 1-7,
- Patel, VL., Shortliffe, EH., Staefanelli, M., et al. 2009. The coming of age of artificial intelligence in medicine, *Journal of Artificial Intelligence in Medicine*, 46(1): 5-17,
- Peres, J., Oliveira, R. and de-Azevedo, SF. 2001. Knowledge based modular networks for process modeling and control, *Computers & Chemical Engineering*, 25(4-6): 783-791,
- Piątkiewicz, P., Czech, A. and Tatoń, J. 2007. Glucose transport in human peripheral blood lymphocytes influenced by type 2 diabetes mellitus, *Archivum Immunologiae et Therapiae Experimentalis*, SpringerLink, 55(2): 119-126,
- Redi, CA. 2008. Reprogramación genética a través del citoplasma del huevo, *Ciencia Conocimiento Tecnología*, 83: 53-55,
- Régis, S., Doncescu, A. and Desachy, J. 2008. Detection and characterization of physiological states in bioprocesses based on Hölder exponent, *Knowledge-Based Systems*, 21(1): 70-79,

- Richards, D. 2003. Knowledge-Based System Explanation: The Ripple-Down Rules Alternative, *Knowledge and Information Systems*: 2-25,
- Rowan, JA., Hague, WM., Gao, W., et al. 2008. Metformin versus Insulin for the Treatment of Gestational Diabetes, *The New England Journal of Medicine*: 2003-2015,
- Saigí, F. and López, A. 2004. Las ciencias de la vida y la biotecnología en la nueva sociedad del conocimiento. La base de la nueva economía, Universidad Oberta de Catalunya, consulted at www.itescham.com/Syllabus/Doctos/r570.PDF, in July 2010,
- Saigí-Rubió, F. and López-Sevilla, A. 2004. Ciencias de la vida y Biotecnología en la nueva sociedad del conocimiento, *Revista Quark*: 14-23,
- Santiesteban-Toca, CE., García-Borroto, G., Villuendas-Rey, Y. and Báez-Pérez, E. 2007. Algoritmo de detección de carriles y bandas en imágenes de geles de electroforesis de una dimensión, *Revista Cubana de Ciencias Informáticas*, 1(3): 72-82,
- Schügerl, K. 2001. Progress in monitoring, modeling and control of bioprocesses during the last 20 years, *Journal of Biotechnology*: 149-173,
- Sedbrook, TA. 1998. A collaborative fuzzy expert system for the Web, *Association for Computing Machinery*, 29(3): 19-30,
- Slingerland, AS. 2006. Monogenic diabetes in children and young adults: Challenges for researcher, clinician and patient, *Reviews in Endocrine and Metabolic Disorders*, 7(3): 171-185,
- Steiness, E. 2009. GLP-1 (glucagon like peptide) and Methods for Treating Diabetes, European Patent Specification, International Application Number: PCT/DK2003/000463, International Publication Number: WO 2004/005342 (15.01.2004 Gazette 2004/03),
- Sun, J. and Li, H. 2006. Data mining method for listed companies' financial distress prediction, *Knowledge-Based Systems*, 21(1): 1-5,
- Ündey, C., Tatar, E. and Çinar, A. 2004. Intelligent real-time performance monitoring and quality prediction for batch/fedbatch cultivations, *Journal of Biotechnology*, 108(1): 61-77,
- U. S. A. National Institutes of Health, consulted at <http://diabetes.niddk.nih.gov/dm/pubs/dictionary/pages/ad.htm#D> in February 2011,
- Vanegas-Córdoba, IA., Yopez-Pérez, MS. and Ruiz-Villadiego, OS. 2004. Producción de xilitol a partir de levaduras nativas colombianas, *Revista Colombiana de Biotecnología*, 2: 31-36,
- Voronov, R., VanGordon, S., Sikavitsas, VI. and Papavassiliou, DV. 2009. *Tissue Engineering*, Rome, Italy: 3rd International Conference on Advanced Computational Engineering and Experimenting, ACEX-2009 Proceedings: 99,
- Wang, WM., Cheung, CF., Lee, WB. and Kwok, SK. 2008. Self-associated concept mapping for representation, elicitation and inference of knowledge, *Knowledge-Based Systems*, 21(1): 52-61.,