Type-2 Fuzzy Control for Bioinformatics – A Systems Approach

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Summary

Life is governed by high-precision perfectly engineered control processes, from the simplest cell to the most sophisticated ecosystem - and beyond. Biological control systems are at the heart of life. This paper reports the study of regulation and the applicability of type-2 fuzzy control systems in bioinformatics. The framework of study is systems biology. In addition to two previously-described levels of bioinformatics discipline, characterized by intelligence-free programs, and artificial intelligence-based programs, respectively, another level is now proposed that incorporates intelligent control action exemplified by type-2 fuzzy control. As such, the new level reported here is the most complex as it is dedicated to offering a scientific and developmental framework for enhancing bioinformatics through the determination of optimal therapeutic strategies or tissue engineering. The resulting framework is a contribution towards practical innovations in engineering, medicine, and pharmacy.

Key words:
Bioinformatics, biological regulation, intelligent control , type-2 fuzzzy control.

1. Introduction

Our aim is to integrate type-2 fuzzy control and regulation in bioinformatics, under one unified systems-oriented perspective within the framework of systems biology. The field of bioinformatics has naturally evolved with the primary task that involves the development of computational tools enabling efficient access, management, storing, retrieval, and interpretation of various types of biological data, including nucleotide and amino acid sequences, protein domains, and protein structures. Another major task is the development of enhanced algorithms and advanced statistical methods with which to assess relationships among members of large data sets, such as finding location of a gene within a sequence, predicting protein structure and/or function, and clustering protein sequences families of related sequences. The biological data must be compiled to form a comprehensive picture of normal cellular activities. Tools are developed to show the way these data are altered in different disease states [1]. It has been proposed that the field of bioinformatics went through two main historical phases,

during which standard heuristics-free programs were used such as database management systems (DBMSs), followed by limited artificial intelligence-based programs [2]. How can the fuzzy control systems paradigm enhance bioinformatics? First of all, a control system for a physical system is an arrangement of hardware components designed to alter, to regulate, or to command, through a *control action*, that physical system so that it exhibits certain desired characteristics or behavior. Physical control systems are typically of two types: open-loop control systems, in which the control action is independent of the physical system output, and closed-loop control systems, also known as *feedback control systems*, in which the control action depends on the physical system actual output. Intelligent control uses methods and techniques from artificial intelligence (AI), such as fuzzy inference, and machine learning methods (ML), such as neural networks, among others. The integration of control methodology within biology and principally within metabolic processes has been on the way but is still in its infancy [3]. As a complement to a previous work, concentrating on the integration, within bioinformatics, of machine learning characteristics [4], and control systems paradigm [5], emphasis is now made on type-2 fuzzy control methods. The main aim is to contribute to the development of future enhanced bioinformatics platforms through the integration of these theories within a coherent framework.

The paper is organized as follows. Section 2 deals with the problem formulation. This section poses the fundamental question: "Why do we need a third level involving type-2 fuzzy control in bioinformatics on top of the two purporting levels?" Section 3 describes some relevant biological issues. Section 4 describes the main components of the proposed solution. Section 5 describes methods from intelligent control relevant to bioinformatics, namely type-2 fuzzy control. A conclusion sums up the main results and points towards some potential future developments.

2. Problem Formulation

The discovery of the structure of deoxyribonucleic acid (DNA), as a building bloc of living species, was a turning point in the history of science, culture and society. Its visible impacts on medicine, agriculture, energy production, social issues, ethics, and others, continues to create an intensive debate and interesting challenges in all human endeavors. To address these multidisciplinary issues, society requires scientists who are able to cross boundaries between many disciplines and who can make a valuable contribution to science and society at large. Awareness of the wholeness of this task as well as its implications, not only for science but for humanity, requires a sense of responsibility that is equally whole [6]. As far as the study of bioinformatics is concerned, we suggest using the traditional entry points available to computer and control scientists. Specifically, the aim is to extend earlier works on control and give directions of application to bioinformatics [7] and especially to contribute to the enhancements of the previously-described two levels of bioinformatics by the emphasis on type-2 fuzzy control. It is a challenging task owing to it is multidisciplinary. What are the main building-blocks of the proposed multidisciplinary framework? Before answering this central question, we need some basic definitions related to relevant biological issues.

3. Biological relevant issues

In this section, we concisely present the main concepts from biology relevant to our discussion. These concepts concern structure of genes, transcription, and transcription factors.

3.1 From Genes to DNA

3.1.1 DNA and Intelligence

First of all, let us have a look at DNA and make an important introductory philosophical digression. DNA is not merely a molecule with a pattern. It is a code. It is a language, and a very sophisticated information storage mechanism. All codes of known origin are the product of a conscious mind. DNA, as a code is no exception to this rule. DNA is therefore not the result of blind natural operations; otherwise there would remain no sense to the code and no useful language to be conveyed. DNA must have been designed and engineered by a conscious, intelligent mind. The complex language and information embodied within DNA are proofs of the intelligent action of this mind. Randomness is a belief that consists in supposing that DNA developed by chance alone. In fact randomness alone is a noise-like component. Adding noise to a noisy signal will not make it better. It simply generates the opposite result.

3.1.2 Genes as Pieces of DNA

Genes are pieces of DNA that encode for proteins through the intermediate action of messenger RNA (mRNA). Proteins are made of amino acids arranged in a linear chain and joined together by peptide bonds. A gene and the genomic region surrounding it consists of a transcribed sequence, which is converted into an mRNA transcript, and of various *untranscribed* sequences. The mRNA is transcribed from a DNA template, and carries coding information to the sites of protein synthesis called the ribosome. The mRNA consists of a coding sequence that is translated into a protein and of several *untranslated* regions (UTRs). The untranscribed sequences and the UTRs play a major role in the regulation of expression. Notably, the *promoter region* in front of the transcribed sequence contains the *binding sites* for the *transcription factor* proteins that start up transcription. Moreover, the region upstream of the transcription start contains many binding sites for transcription factors that act as *activators* and *repressors* of gene expression, although some transcription factors can bind outside this region [8].

3.2 Transcription

Transcription means the assembly of ribonucleotides into a single strand of mRNA whose sequence is dictated by the order of the nucleotides in the transcribed part of the gene. The transcription process is initiated by the binding of several transcription factors to regulatory sites in the DNA, usually located in the promoter region of the gene. The transcription factor proteins bind each other to form a complex that associates with an enzyme called RNA polymerase. This association enables the binding of RNA polymerase to a specific site in the promoter. Together, the complex of transcription factors and the RNA polymerase loosen the DNA and separate both strands. As a result, the polymerase proceeds down on one strand while it builds up a strand of mRNA complementary to the DNA, until it reaches the terminator sequence. In this way, an mRNA is produced that is complementary to the transcribed part of the gene. Then, the mRNA transcript leaves the RNA polymerase, and the polymerase breaks its contact with the DNA. In a later stage, the mRNA is processed, transported out of the nucleus, and translated into a protein [8].

3.3. Transcription Factors

Transcription factors are proteins that bind to regulatory sequences on eukaryotic chromosomes thereby modifying the rate of transcription of a gene. Some transcription factors bind directly to specific sequences in the DNA (promoters, enhancers, and silencers), others bind to each

other. Most of them bind both to the DNA as well as to other transcription factors. The transcription rate can be positively or negatively affected by the action of transcription factors. When the transcription factor significantly decreases the transcription of a gene, it is called a repressor. If, on the other hand, the expression of a gene is upregulated, biologists speak of an activator [8].

4. Main components of problem solution

The proposed integration of bioinformatics and control is done within the so-called systems approach as it originated in the early 1920's. In addition, the main components of the solution are based on computational aspects and on the human metabolism considered as a precise control system.

4.1 Systems Approach

4.1.1 System Theory

System theory is an interdisciplinary theory about the nature of complex systems as they appear in nature, society, and science. It offers a framework through which it is possible to study any group of objects that work together to produce some prescribed result or goal. Systems theory first originated in biology in the 1920's out of the need to explain the correlation between organisms and ecosystems. As a technical and general academic area of study system theory encompasses the science of systems that resulted from Bertalanffy's general system theory (GST), among others, in initiating what became a project of systems research and practice. As far as control is concerned, if we take the example of parameter estimation, needed for most control applications, especially adaptive control, we can easily discern the heavy heritage of systems control *vis-a-vis* system theory. Thus, the systems approach is particularly useful for our proposed framework since it helps in the integration of intelligent control methods and bioinformatics in a coherent manner.

4.1.2 Systems Biology

The passage from DNA to the cell to the organ to the organism to community of organisms to ecosystems, and beyond, represents different living levels, usually addressed by systems theory. All these levels express different behaviors and cannot be reduced to, nor understood only from, lower levels. Systems biology is based on this holistic view of biology. Going back to antiquity, holism is based on the idea that the whole is more than the sum of its constituent parts. For example, the different parts of a living organism taken separately do not tell us about what that organism might be. The functions of organisms are based not only on its constituent parts but also on the relation between them. Because one of the objectives of systems biology is the modeling of biological processes *via* mathematical models and computer simulation, it can

therefore be a good candidate for the basis of the proposed framework and can represent, in its turn, a field of predilection of intelligent control application [6]. For many years, system biology has been part of the interests of control systems community [9].

4.2 Computational Issues Biology *vs.* Biology

4.2.1 Computational Biology vs. Biology

An area called computational biology preceded what is now called bioinformatics. Computational biologists also gathered their inspiration from biology and developed some very important algorithms that are now used by biologists. Computational biologists take justified pride in the formal aspects of their work which often involves proofs of algorithmic correctness, complexity estimates, and other themes that are central to theoretical computer science. Nevertheless, the biologists' needs are so pressing and broad that many other aspects related to computer science have to be explored. For example, biologists need software that is reliable enough that can deal with huge amounts of data, as well as interfaces that facilitate the human-computer interactions (HCI) with high-resolution graphics systems and intelligent search and retrieval processes [1].

4.2.2 Gene Regulation

The genome of a given organism contains thousands of genes, but not all these genes need to be active at any given moment. A gene is expressed when it is being transcribed into mRNA (and translated into protein), and there exist many cellular methods of controlling the expression of genes such that proteins are produced only when needed by the cell. Gene regulation gives the cell control over structure and function, and is the basis for cellular differentiation and morphogenesis. It is also responsible for the versatility and adaptability of any organism. Gene regulation may also serve as a substrate for change, since control of the timing, location, and amount of gene expression can have a profound effect on the functions (actions) of the gene in a cell or in a multicellular organism.

4.2.3 Biological Modeling and Control

Beside *in vivo* experimentation that characterizes biology, and as far as bioinformatics is concerned we have to inevitably use computational models for the understanding of the relevant biological phenomena [2]. Modeling is usually unavoidable because the production of data from techniques of genomic analysis is not always amenable to interpretation mainly due to the complexity of the data and to the large amount of data points. Modeling can handle the data and allow testing a given hypothesis; for instance, whether gene A is regulated by protein B that can be verified experimentally. Hence, modeling and simulation of genetic regulatory systems [10].

4.3 Human Metabolism as a Control System

4.3.1 Metabolic Chemical Reactions

Most of the structures that make up animals, plants and microbes are made from three basic classes of molecule: amino acids, carbohydrates and lipids (often called fats). As these molecules are vital for life, metabolic reactions focus on making these molecules during the construction of cells and tissues, or breaking them down and using them as a source of energy, in the digestion and use of food. Many important biochemicals can be joined together to make polymers such as DNA and proteins. Many proteins are the enzymes that catalyze the chemical reactions in metabolism *i.e.* the set of chemical reactions that happen in living organisms to maintain life. Other proteins have structural or mechanical functions, such as the proteins that form the cytoskeleton, a system of scaffolding that maintains the cell shape. Proteins are also important in cell signaling, immune responses, cell adhesion, active transport across membranes, and the cell cycle [11].

4.3.2 Metabolic Control Analysis

Metabolic control analysis (MCA) is a useful mathematical framework for describing metabolic, signaling and genetic pathways [3]. MCA quantifies how variables, such as fluxes and species concentrations, depend on network parameters. In particular it is able to describe how network dependent properties, called control coefficients, depend on local properties called elasticities. MCA was originally developed to describe the control in metabolic pathways but was subsequently extended to describe signaling and genetic networks. More recent work has shown that MCA can be mapped directly on to classical control theory and are as such equivalent [http://dbkgroup.org/mca_home.htm]. Concerning MCA useful set of FAQs is available at the site [http://bip.cnrs-mrs.fr/bip10/mcafaq.htm]. Biochemical systems theory is a similar formalism, though with a rather different objectives. Both are natural off-shoots of an earlier theoretical analysis of sequential reactions dating back to the early sixties.

5. Type-2 Fuzzy Control

Type-2 fuzzy control is one aspect of intelligent control. Roughly speaking, intelligent control is at the intersection of artificial intelligence (AI) and control. It uses various AI computing approaches like neural networks, Bayesian probability, fuzzy logic, machine learning, evolutionary computation, genetic algorithms, expert systems and consciousness / cognition to control a given dynamic system [12]. Type-2 fuzzy systems are part of the soft computing family of tools.

5.1 Soft computing

Soft computing is not a closed and clear-cut discipline. It incorporates an emerging family of problem-stating and problem-solving methods that attempt to mimic natural intelligence; this latter reduced, in our discourse, to approximate reasoning, heuristics and the power of generalization. Basically, there are two important components, *i.e.,* fuzzy logic-based models (FLMs) and experimental data learning methods such as neural networks (NNs) and support vector machines (SVMs). In addition, there are methods based on genetic algorithms (GAs), evolutionary algorithms (EAs), probabilistic reasoning, belief networks, rough sets, wavelets, fractal and chaos theories. Soft computing methods are used whenever it is not possible to devise a mathematical model from first principles. The aim of soft computing is to:
- Learn from experimental data (examples, samples, measurements, records, patterns, observations…) by NNs or SVMs.
- Embed existing structural human knowledge such as experience, expertise, and heuristics, rules of thumb into efficient mathematical framework such as IF-THEN rules.

5.2 Fuzzy Logic Paradigm

Classical or crisp logic is a mathematical system that operates on discrete values of either true or false, usually represented by 0 or 1. Fuzzy logic considers analog input values in terms of logical variables that take on continuous values between 0 and 1, called membership value or grade, in contrast to crisp logic.

5.2.1 Advantages of Fuzzy Logic Models (FLMs)

- *Human knowledge embedding.* Fuzzy logic models (FLMs) are efficient tools for embedding human knowledge into useful algorithms.
- *Approximators.* FLMs are good approximators of any multivariate nonlinear function.
- *No need for explicit modeling.* FLMs are useful when no mathematical model is available or when it is impossible to obtain it.
- *Robustness.* FLMs operate successfully under a lack of precise sensor information.
- *Genericity.* FLMs are appropriate tool in generic decision-making.

5.2.2 Disadvantages of Fuzzy Logic Models (FLMs)

- *Structuring knowledge*. Human experts may have problems in structuring their knowledge.
- *Inconsistencies and human subjectivity.* Human expert mat sway between extreme decisions or tend to hide their knowledge.
- *Exponential explosion.* The number of rules increases exponentially with increase in the number of fuzzy subsets per input variable.

- *High constraints.* Learning, *i.e.*, changing membership functions shapes is highly constrained, typically more complex than Neural Networks.

5.3 Type-2 Fuzzy Logic

5.3.1 From Type-1 to Type-2 Fuzzy Membership

As stressed above, in classical logic, the membership grade is either 0 or 1. In type-1 fuzzy logic, the membership grade is a number in the range [0,1]. Type-2 fuzzy logic is an answer to the question of what to do when there is uncertainty about the value of the membership function itself. In type-2 fuzzy logic, the membership grade is itself a fuzzy set in [0,1]. As a result, a type-2 fuzzy system is governed by fuzzy membership functions that are three dimensional and include a mark of uncertainty. It is the new third dimension of type-2 fuzzy sets and the mark of uncertainty that provide additional degrees of freedom that make it possible to directly model and handle uncertainties. A type-2 fuzzy set allows designers to incorporate uncertainty about the membership function into fuzzy set theory. It is a way to address the criticism of type-1 fuzzy sets that paradoxically relied on crisp membership functions. Obviously, type-2 systems reduce to type-1 systems if there is no uncertainty; this being analogous to probability reducing to determinism when unpredictability disappears.

The type-2 fuzzy sets are useful wherever it is difficult to determine the exact and precise membership functions. Not only have type-1 fuzzy systems been around since 1965, they have also been successfully used in many applications including systems control. However, such fuzzy systems have limited capabilities to directly model and minimize the effect of data uncertainties. Although type-2 fuzzy sets were introduced in 1975, very little was published about them until the mid-to late nineties. In the 1970's, applied researches were undertaken using type-1 fuzzy sets, *e.g.*, fuzzy control. Once it was clear what could be done with type-1 fuzzy sets, it was only natural for researchers to then undertake more challenging problems such as those tackled by type-2 fuzzy systems. Type-2 fuzzy logic systems have been used to date with great success [13].

5.3.2 Type-2 FSs, Probability and Min Variance Design

There are two important kinds of uncertainties, namely linguistic and random. Linguistic uncertainty is related to the fact that words can mean different things to different people. Random uncertainty is associated with unpredictability, tackled by probability theory. Fuzzy systems are used to handle linguistic uncertainty, and sometimes both kinds of uncertainty, because a fuzzy system may use noisy measurements or operate under random disturbances. Within probability theory, the designer begins with a probability density function (pdf) that embodies total information about random uncertainties characterized by the pdf's moments. However, in most practical applications, it is impossible to know or determine the pdf. For most pdf's, an infinite number of moments are required which represents an impossible task in practice. At the very least, two moments are used, namely the mean and variance. To just use first order moments would not be very useful because random uncertainty requires an understanding of dispersion about the mean. This information is provided by the variance. So, the accepted probabilistic modeling of random uncertainty focuses, to a large extent, on methods that use at least the first two moments of a pdf. This explains mean-squared errors designs. Just as variance provides a measure of dispersion about the mean, a fuzzy system also needs some measure of dispersion to capture more about linguistic uncertainties than just a single membership function, which is all that is obtained when a type-1 fuzzy system is used. A type-2 fuzzy system provides the additional measure of dispersion [14].

5.3.3 Fuzzy Control Systems (FCS) Design

A fuzzy control system incorporates fuzzy logic an inference process. From a control theoretical point of view, fuzzy logic has been intermixed with all the important aspects of systems theory: modeling, identification, analysis, stability, synthesis, filtering, and estimation. A number of assumptions are implicit in a fuzzy control system (FCS) design. Six basic assumptions are commonly made whenever a fuzzy rule-based control policy is selected, namely:

- A solution exists.
- The plant is observable and controllable: state, input, and output variables are usually available for observation and measurement or computation.
- There exists a body of knowledge comprised of a set of linguistic rules, engineering common sense, intuition, or a set of input–output measurements data from which rules can be extracted.
- The control engineer is looking for a ''good enough'' solution, not necessarily the optimum one.
- The controller is to be designed within an acceptable range of precision.

The problems of stability and optimality are not addressed explicitly; such issues are, to a great extent, still open problems in fuzzy controller design. However, to account for this limitation, interest in stability criteria for fuzzy control systems has grown in recent years.

5.3.4 General FCS Methodology

The general fuzzy control system (FCS) methodology is based on the procedure for obtaining a control surface from approximations based on a collection of fuzzy IF–THEN rules that describe the dynamics of the controller. One of the most important difficulties with the creation of new stability criteria for any fuzzy control system has been the analytical interpretation of the linguistic part of fuzzy controller IF-THEN rules. Often fuzzy control systems are

designed with very modest or no prior knowledge of a solid mathematical model, which, in turn, makes it relatively difficult to tap into many tools for the stability of conventional control systems. With the help of Takagi-Sugeno fuzzy IF-THEN rules in which the consequences are analytically derived, sufficient conditions to check the stability of fuzzy control systems are now available. These schemes are based on the stability theory of interval matrices and those of the Lyapunov approach. Frequency-domain methods such as describing functions are also being employed for this purpose [15].

5.4 ANFIS Control

5.4.1 Example of ANFIS Application

An adaptive neuro-fuzzy inference system (ANFIS) [15] is a method incorporating a neural network and a fuzzy inference system (FIS). An adaptive network is a multi-layer feed-forward network in which each node (neuron) performs a particular function on incoming signals. The form of the node functions may vary from node to node. In an adaptive network, there are two types of nodes: adaptive and fixed. The function and the grouping of the neurons are dependent on the overall function of the network. Based on the ability of an ANFIS to learn from training data, it is possible to create an ANFIS structure from an extremely limited mathematical representation of the system. The ANFIS architecture can identify the near-optimal membership functions of fuzzy logic controller for achieving desired input-output mappings. The network applies a combination of the least squares method and the back propagation gradient descent method for training FIS membership function parameters to emulate a given training data set. The system converges when the training and checking errors are within an acceptable bound [16]. The ANFIS system generated by the fuzzy toolbox available in MATLAB™ allows for the generation of a standard Sugeno style fuzzy inference system or a fuzzy inference system based on sub-clustering of the data.

5.4.2 Example: ANFIS Control Application to Cell Culture

The development of a neuro-fuzzy control system for recombinant cell culture has been developed [17]. The introduced system has learnt the dynamics of the bioprocess in the form of a fuzzy inference system and also estimated major parameters of the controlled process. To produce a recombinant protein, it is critically important to optimize and control bioprocesses based on knowledge of a cell's genetic, metabolic, and kinetic behavior. It is, however, not straightforward due to the fact that the biosystem is highly nonlinear, time variant, and complex. Some intelligent control systems have been implemented for control of fed-batch cultivation of recombinant *E. coli* and yeast, namely, fuzzy pH-stat, fuzzy neural network,

and fuzzy control coupled with a neural network estimator. In a fuzzy pH-stat control system, the relationship between pH change in the medium and glucose consumption rate is modeled by a fuzzy set and thereafter used to control the feed rate of glucose to obtain cell density as high as 72 g/L. In a fuzzy neural network (FNN) control system, an FNN was constructed to learn fuzzy control inference and then was applied to fed-batch cultivation of recombinant *E. coli* to attain a high expression of recombinant protein. In addition, a fuzzy control system was developed and coupled with neural network estimators that can on-line estimate residual glucose and galactose concentrations, which were utilized to control the feed rate of glucose (during the cell growth phase) and the feed rate of galactose (during the expression phase). Results of these control strategies are presented and their usefulness in the fed-batch cultivation of recombinant strains has been demonstrated. The idea behind these studies is to utilize predetermined experimental data to develop repetitive learning control using intelligent techniques**.**

6. Conclusion

We contributed to the study and integration of type-2 fuzzy control within bioinformatics. This framework constitutes a contribution to our understanding of biological processes based on the most powerful theoretical and technological tools available to computer and control scientists, entailing a better understanding of molecular biology. The impacts on many fields of research are expected to be important, not only on computer science and control theory as such but also on technology, medicine and pharmacy at large. Implementation of the present framework will represent an important asset for future bioinformatics platforms.

References
[1] J. Cohen "Bioinformatics—An introduction for computer scientists", *ACM Computing Surveys*, vol. 36, no. 2, pp.122-158, June 2004.
[2] E. Keedwell, A. Narayanan *"Intelligent Bioinformatics - The Application of Artificial Intelligence Techniques to Bioinformatics Problems"*, John Wiley & Sons Ltd., 2005.
[3] D. Fell *"Understanding the Control of Metabolism"*, Portland Press, 1997
[4] A. Hamdi-Cherif "Integrating Machine Learning in Intelligent Bioinformatics", *WSEAS Trans. on Computers,* vol. 9, no. 4, pp. 406-417, April 2010.
[5] A. Hamdi-Cherif "Machine Learning for Intelligent Bioinformatics – Part 2 Intelligent Control Integration", Invited Book Chapter In: *Recent Advances in Artificial Intelligence, Knowledge Engineering and Database*

(AIKED'10), Cambridge, UK pp. 321-326, February 22-25, 2010.

[6] M. Jardon "Systems biology: an overview", *The Science Creative Quaterly*, Issue 4, July 2009,
http://www.scq.ubc.ca/systems-biology-an-overview/

[7] A. Hamdi-Cherif "The CASCIDA Project - A computer-aided system control for interactive design and analysis". *Proc. of IEEE/IFAC Joint Symp. on CACSD (CASCD'94)*, Tucson, AZ, USA, pp. 247-251, 1994.

[8] Y. Moreau, F. De Smet, G. Thijs, K. Marchal, B. De Moor. "Functional bioinformatics of microarray data: from expression to regulation", *Proc. Of the IEEE,* vol. 90, no. 11, pp. 1722-1743, Nov. 2002.

[9] P. Wellstead, "Systems Biology and the Spirit of Tustin", *IEEE Control Systems Magazine*, pp. 57-71, Feb. 2010.

[10] H. DeJong, "Modeling and simulation of genetic regulatory systems: A literature review, J. Comput. Biol. vol. 9, no. 1, pp. 67–103, 2002.

[11] M. Salter, R. Knowles, C. Pogson "Metabolic control". *Essays Biochem* vol. 28, pp. 1–12, 1994.

[12] V. Kecman *"Learning and Soft Computing : Support Vector Machines, Neural Networks and Fuzzy Logic Models",* MIT Press, 2001.

[13] R. John, S. Coupland "Type-2 Fuzzy Logic : A historical view", *IEEE Comput. Intel.* vol. 2, no. 1, pp. 57-62, Feb. 2007.

[14] J.M. Mendel "Type-2 fuzzy systems – an overview", *IEEE Comput. Intel.* vol. 2, no. 1, pp.20-29, Feb. 2007.

[15] J.A. Farrell., M.M. Polycarpou. *"Adaptive Approximation Based Control: Unifying Neural, Fuzzy and Traditional Adaptive Approximation Approaches",* John Wiley & Sons Ltd., 2006.

[16] J-S. R. Jang "ANFIS : Adap tive-Ne twork-Based Fuzzy Inference System". *IEEE Trans. On Syst. Man and Cyber.* vol. 23 no. 3, May-Iune 1993.

[17] K. Ye, S. Jin, K. Shimizu "On the development of an intelligent control system for recombinant cell culture", *Int. J. of Intel. Syst.*, vol. 13, no. 6, pp. 539 – 560, 1998.

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