Adaptive Control for MAPK Cascade Models Using RBF Neural Networks

by

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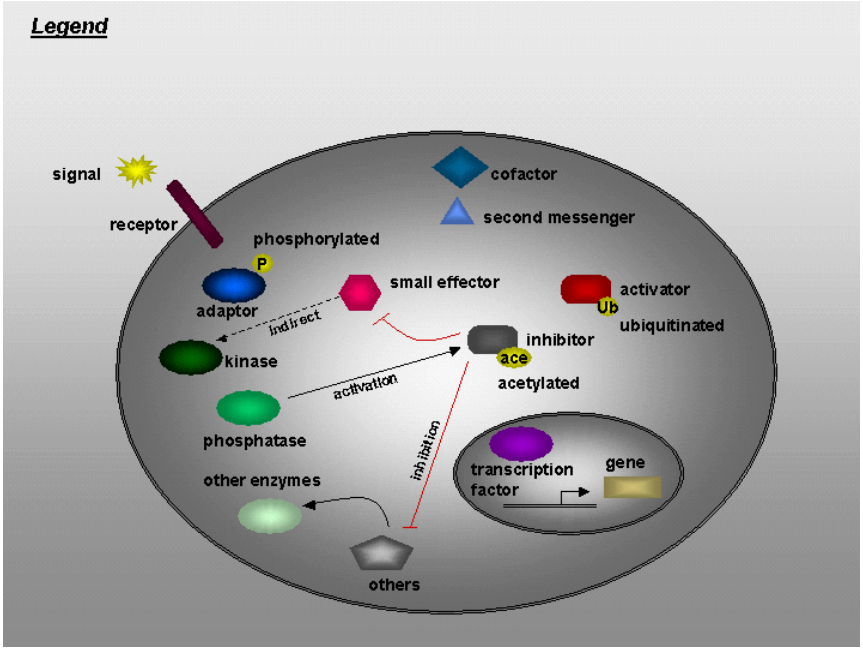

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To my family George, Evgenia

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ABSTRACT

Recent technological developments have forced control engineers to deal with extremely complex systems that include uncertain and possibly unknown nonlinearities, operating in highly uncertain environments. Man has two principal objectives in the scientific study of his environment: he wants to understand and to control. The two goals reinforce each other, since deeper understanding permits firmer control, and, on the other hand, systematic application of scientific theories inevitably generates new problems which require further investigation, and so on.

In this project, an Adaptive Backstepping Neural Network control approach is used for a class of affine nonlinear systems which describe the Mitogen Activated Protein Kinase (MAPK) cascade models in the strict feedback form, in interlaced and mixed interlaced forms. We consider the forms of the MAPK cascade [4]. The close loop signals are semiglobally uniformly ultimately bounded and the output of the system is proven to follow a desired trajectory. Simulation results are presented to show the effectiveness of the approach proposed in order to control the MAPK output.

Nowadays MAPK cascade models are being used to control the cell division processes and are based on the kinetic properties of three kinases and phosphatases in specific signalling pathways that transmit the information delivered to the cell by stimuli and acts like feedback controller able to adapt to it. Furthermore one possible function of the MAPK is to amplify the signal and to integrate many inputs. When the final kinase of the pathway is activated, MAPK is delivered to the nucleus to affect gene expression. Biologists work is supported by various remarks from recent Nobel Prize winners. Because of that, recently interest in modelling of biological systems has been increased. In the present work we focus on the control of signals, the kinases produce as partial outputs (virtual control inputs) via a well known adaptive backstepping technique [1] through an appropriate selection of the controller. The system exhibits unknown nonlinearities. We use adaptive control [13] in order to

track the desired output. Adaptive control approaches enjoy the property of on line control. We use specific adaptation laws in order to reduce uncertainty. This method can be used in drug discovery and sickness therapy, especially in personalized medicine (i.e., for a specific disease, for a specific person, the appropriate medicine). It is obvious that we do not need to know the interconnections between the signalling pathways. We do need to know the states of the system which are the protein concentrations. We also need an appropriate input (state feedback control input) to make the output to follow the desired behaviour.

The kinases and phosphatases of our model have the following properties:

Each kinase can be found in an active and an inactive form.

Activation of kinases takes place by phosphorylation.

When the kinases are in their active forms they may phosphorylate other kinases and inactivation of the kinases takes place by dephosphorylation catalyzed by phosphatases which are sequentially active. Effects of multiple phosphorylations are neglected and we do not consider the action of scaffolds and adaptors.

Assumption: Initial activation of kinases occurs by their interaction with an external receptor $u(t)$.

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INTRODUCTION

Recent technological developments have forced control engineers to deal with extremely complex systems that include uncertain and possibly unknown nonlinearities, operating in highly uncertain environments. Man has two principal objectives in the scientific study of his environment: he wants to understand and to control. The two goals reinforce each other, since deeper understanding permits firmer control, and, on the other hand, systematic application of scientific theories inevitably generates new problems which require further investigation, and so on.

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Chapter 2

A GENERAL OVERVIEW IN SYSTEMS BIOLOGY AND ADAPTIVE CONTROL

Since this work deals with systems biology and adaptive control it is necessary to tell something about them.

2.1 Systems Biology

The discovery of DNA and its important attendance to all the cell functions has increased the interesting of the scientists to deal with new emerging parts of Biology. Systems biology is a new established research area that combines systems theory and cell biology and has led to important Biology developments that improve human health. A lot of universities make research on this field and create important ascertainments. Examples of Biological Systems are as old as classical biology. Systems biology focuses to the dynamic behaviour of biochemical networks that are called signalling pathways and characterize many of the components that make up a living cell and maintain its function. Signalling pathways are like the block diagrams control engineers use in order to analyze systems and represent interconnections between the blocks with mathematical models and modern simulation. Such pathways are collected in large biological databases and their purpose of existence is to simulate the biochemical reactions of cells. These biochemical reactions include cell growth, cell death and cell division.

Systems biology makes control engineers and biologists to share the same language in order to represent most of the cell functions. This cooperation is made in order to find the proper treatment of many diseases.

Cell division is the basic function of the cell. It is a process in which cell duplicates and divides itself with cyclic changes in concentrations and periodic activation. Changes in concentrations can be measured with protein microarrays. Furthermore one also basic function is cell signalling (see figure 1). Cells transmit signals each other, to communicate, combine into networks and realize higher levels of organization, such as organs and tissue. The communication between the inside and outside of the cell happens with the receptors that transmit the information delivered to the cell by stimuli. Feedback loops play a very important role in signalling pathways and are related to the basic cell functions. If basic functions of the cell do not operate properly then disease, such as cancer may occurs. Pharmaceutical companies have included to their program, special issues and projects for drug discovery that are based on understanding and modelling the operation of signalling pathways.

For the simulation and the depiction of the signalling pathways, it is widely used by the scientific community a lot of software tools with prevailing tool SBML (Systems Biology Markup Language). SBML can be applied extensively in many areas of systems biology such as cell signalling.

With the technology progress, we will soon be able to provide new methods for data collecting, simulations and validations. The results from the previous will be the driver for a joint research effort and link the experimental results that are taken from the laboratories, with the system and module level results. Control engineers must be the leaders to every research effort and must give their pledges to study important signalling networks properties such as robustness and stability.

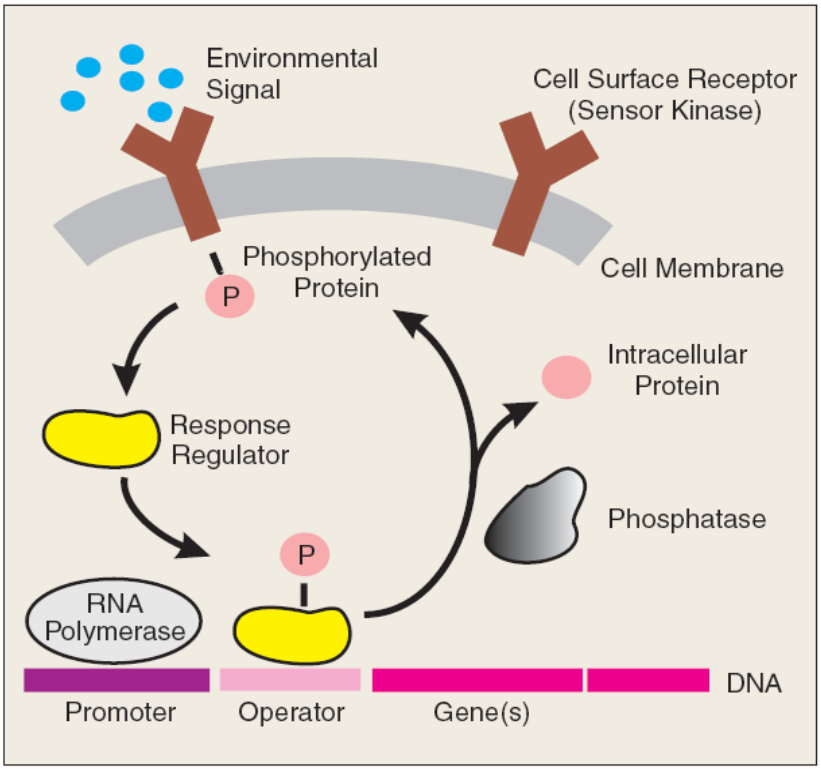


Figure 2.1: *Schematic representation of cell signaling.*

The dynamic point of the biochemical reactions has drawn engineers to engage with Systems Biology and has more to do with the application of control theory rather than with the application of physics theory to molecular biology in order to lead to a more complete understanding of cells function. Mathematical models in Systems Biology provide us an abstract representation of the principles we observe. The most interesting fact, this area works on, is the modelling of the operations of a signalling pathway with nonlinear ordinary differential equations and cellular automata. The data, scientists need in order to represent biochemical reactions in signalling pathways, is found into biological experiments in well organized laboratories with advanced equipment. This has to do with quantitative stimulus response time series.

2.2 Signal Transduction Networks

Cells are the basic type of life and they act autonomously. Cells should be capable to react in each change of their environment, for this reason they are provided with systems of sensors which depending on the various activities of the cell, promote the suitable signals via suitable structures for the most optimal solution of such situations.

In order to become more comprehensibly those who will be reported, it will be supposed to give a description of a cell. The cells are surrounded by a membrane that helps them to be autonomous and protects them from external and most times harmful situations. The cellular membrane is very important for the communication between cells for all the functions of an organism. Each time where a stimulus becomes perceptible in the cellular membrane then we have the transport of signal in the point of action which may be either the DNA or enzymes inside the cytoplasm. This process is named signal transduction and includes processing of signals.

Enzymes are modified suitably, in order that their catalytic activities are changed proportionally with the extracellular signal and for DNA the above process detects proteins that are responsible for gene functioning and according to that, new proteins become with base elements from the chain of DNA. In prokaryotic cells, such as bacteria, DNA is found freely in cytoplasm. On the contrary in more complex cells that we call eukaryotic cells DNA is found into nucleus.

The process of cell signalling modifies concentrations of proteins. The most useful process that changes the concentrations of proteins is phosphorylation. Proteins are constituted by amino-acids and for this reason phosphorylation occurs in concrete parts of them and catalyzed by the kinases which are specific enzymes. The reverse process is catalyzed by other enzymes that we call phosphatases and is the result of signal transduction processes. The previous acts like a control system that increases the reliability of signal transduction.

In this project we deal only with eukaryotic cells that are more complex than prokaryotic because we have many interconnections between signalling pathways. Every signalling pathway is activated by another one. The previous process is well known as crosstalk. In eukaryotic cells there are some membrane proteins that have very important role in recognizing specific signals. These proteins are known as

receptors. There are many types of receptors that are known in biology. A very important category of receptors are the RTKs (receptor tyrosine kinases) that are shared a lot of recourses.

Very important for cell signalling are the adaptor proteins that can be committed by other proteins and have enzymatic activities. These proteins have concrete structure that helps them to come together with different type of proteins and initializing signalling pathways in which signal can be amplified.

There are two possibilities for how the signal can be transmitted into the cell. The first possibility is the activation of a cascade of successive kinases, and the second possibility is the creation of second messengers. The second messengers can transfer the signal to different areas of the cell and can interact with different proteins. One of the most important examples of cascade kinases is the MAPK (Mitogen Activated Protein Kinase) which consists of three kinases that are activated sequentially (see figure 2). MAPK can be found in all eukaryotic cells and it participates in many functions of signal transductions, such as cell-cycle control, cell-wall-construction, growth, differentiation and stress response. Moreover MAPK cascades implement feedback and feedforward loops that strengthen their variability and decrease the response time. With the feedback loops MAPK cascades become bistable and this gives the spark for an immutable binary response to stimulus. On the other hand feedforward loops can return the systems to track a desired output via appropriate adaptation.

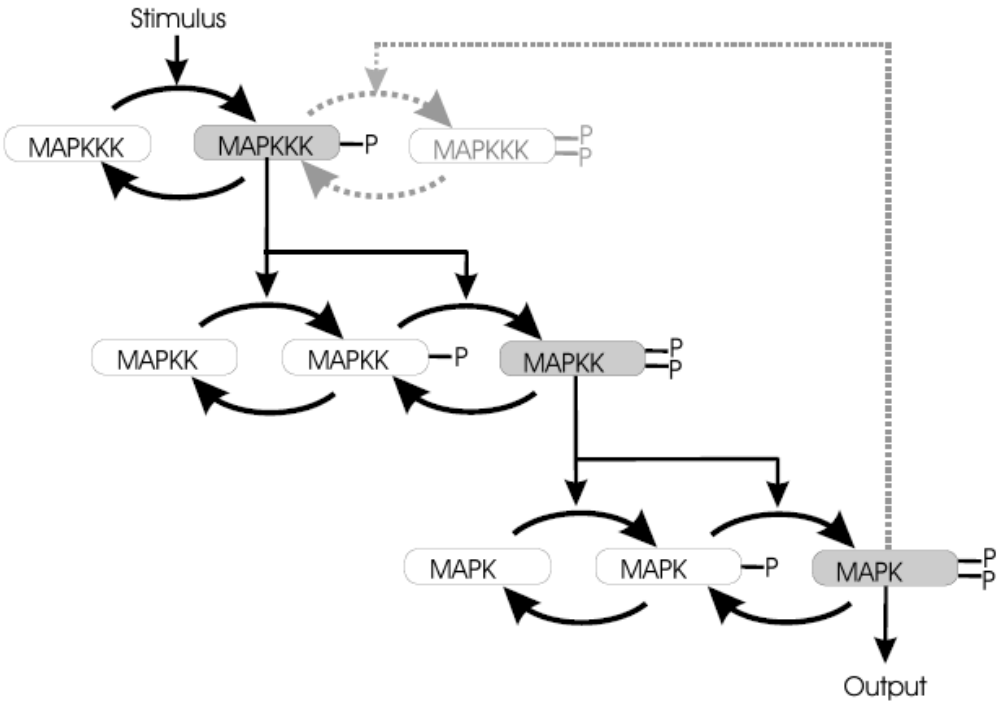


Figure 2.2: *Representation of MAPK cascade model.*

Signal transduction networks are depicted with ordinary differential equations. In order to study them, it is useful to decompose into smaller elements in order to handle the complexity of cell processes. These smaller elements can be studied and analyzed more easily. Finally we regroup the smaller elements and study the system as a whole. Moreover with systems theory we analyze systems without retrospection. In such biological systems we use network theory in order to approach them.

The most important factor in analyzing signal transduction networks is their dynamic behaviour that is determined by the properties of the signal. Such properties are signal duration, signal amplitude, signalling time etc. In order to be calculated numerically Heinrich et al. [21] proposed three equations that are:

$$\tau = \frac{\int_0^\infty ty(t)dt}{\int_0^\infty y(t)dt},$$

$$\theta = \sqrt{\frac{\int_0^\infty t^2 y(t)dt}{\int_0^\infty y(t)dt} - \tau^2},$$

$$S = \frac{\int_0^\infty y(t)dt}{2\theta}$$

Which are τ for signalling time, θ for signal duration and S for signal amplitude. These values are useful and logical until the output returns to zero after a specific time. But in case this is not feasible τ, θ tend to infinity.

Bacteria use a two-component signal transduction network in order to react to environmental changes. The above systems use, not only a sensor kinase but also and a response regulator. When a stimulus becomes perceptible by the cell then happens the so called autophosphorylation with the support of ATP (Adenosine Triphosphate).

2.3 MAPK signaling cascades

MAPK signalling cascades [23] are the main routes with which the plasma membrane communicates with concrete parts in the interior of cell. A lot of operations of cell emanate from sequentially activation of protein kinase cascades. A lot of these cascades are clarified during the last years and are known as Mitogen Activated Protein Kinase (MAPK) signalling cascades. Every of the previous sequences is constituted by 5 levels from protein kinases that are activated sequentially by phosphorylation. Most known sequences of MAPK cascades are four and are named according to the subgroup of their MAPK elements (ERK, JNK, SPK, MBK). They initiate cell processes such as proliferation, differentiation, apoptosis.

The previous signaling cascades have a receptor tyrosine kinase at their plasma membrane where the signal is passed first to adaptor proteins. These proteins are called G-proteins and they interact with the MAPKKK which is the first level in MAPK signaling cascades.

ERK and MEK play important role in the transportation of many signals and the definition of uniqueness of each signal. A research area that many research groups are concentrated is the development of anti-phospho-MAPK antibodies. This become more serious when it is realized that ERK plays important role in differentiation and development. Experiments are made to create antibodies in vivo and in vitro.

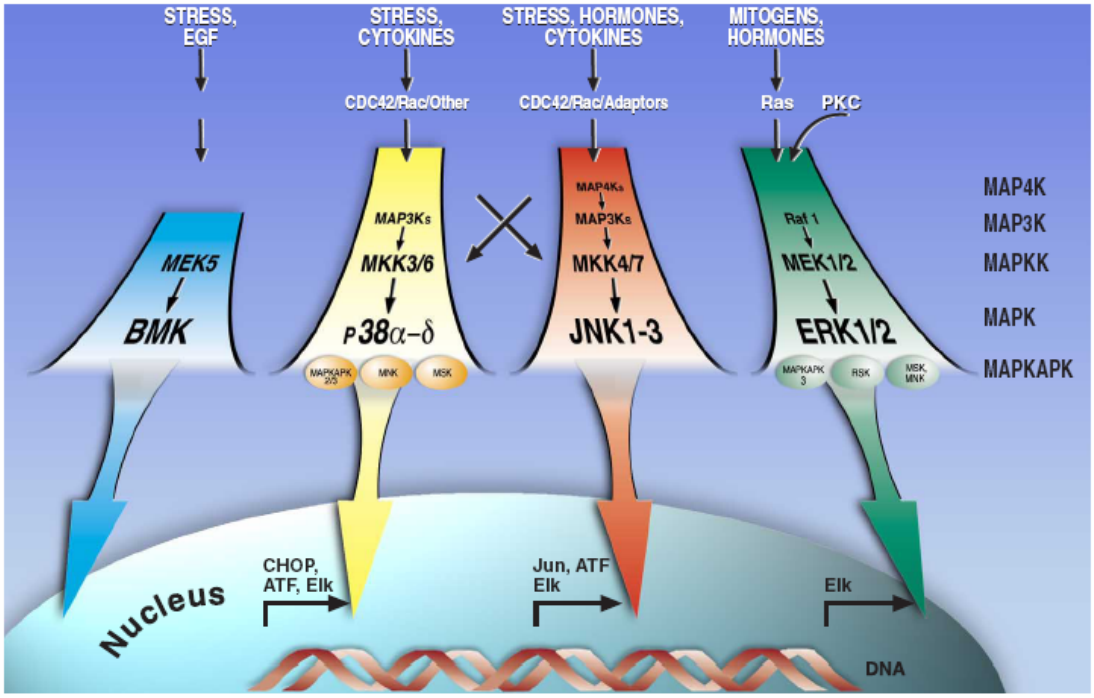


Figure 2.3: *MAPK signalling cascades*.

2.4 Epidermal Growth Factor Receptor (EGFR)

EGFR belongs to RTK family and has important role in the cell. EGF is a polypeptide consisting of 53 amino acids. When EGFR is activated, then cell functions such as cell migration and cell division may happen. EGFR is unbreakably connected to the creation of cancer tumours, that's why many cancer medicines are straight directed to EGF signalling pathway. Furthermore, excessive activation of EGFR on the cancer cell surface is now known to be associated with advanced disease, the development of a metastatic phenotype and a poor prognosis in cancer patients.

EGFR activates the MAPK cascade pathway after it committed various proteins. This activation needs the commitment of the adapter molecules Grb2, Shc, Sos, Gap to the EGF receptor and especially by means of Shc-independent pathway and Shc-dependent pathway. MAPK takes the signal through the cytoplasm to the nucleus where it triggers specific functions, which drive cells into duplication.

Moreover there are and some other kind of receptors that are called internalized receptors and their operation is not clear. When the receptor internalized, then EGFR can commit the same compounds as the surface receptors do.

2.5 Adaptive Control

The history of adaptive control began from the early 1950's. With the passing of the years a lot of papers and books have been published. These research activities have proposed solutions for basic problems and for broader classes of systems. Especially the interest for nonlinear adaptive control began from the mid-1980's. A lot of great scientists, such as Kokotovic, Kanellakopoulos and Krstic [1] and Lewis, et al [2] have studied adaptive control and its applications extensively.

Adaptive control [1], [2] is a powerful tool that deals with modelling uncertainties in nonlinear (and linear) systems by on line tuning of parameters. Very important research activities include on-line identification and pattern recognition inside the feedback control loop.

Through time, adaptive control has existed big development in order to control plants with unknown dynamics that appear linearly. Adaptive control is based on Lyapunov design.

It is well known that global stability properties of model reference adaptive systems are guaranteed under the "matching assumption" that the model order in not lower than that of the unknown plant. This restrictive assumption is likely to be violated in applications. Hence, it is important to determine stability and robustness properties of adaptive schemes with respect to modeling errors.

In order to make it clear, a short example will be reported. Let us consider the nonlinear plant:

$$\dot{x} = u + \theta x^2$$

and we select the control law as:

$$u = -qx - \hat{\theta} x^2$$

which, if the estimated θ ($\hat{\theta}$) is equal to real θ such that $\hat{\theta} \equiv \theta$, then the result is a close loop system of the form:

$$\dot{x} = -qx$$

The filtered version of the signals x is:

$$x_f = \frac{1}{s+1}x^2$$

The prediction error e is:

$$e = x - \hat{x} = (\theta - \hat{\theta})x_f = \tilde{\theta}x_f$$

We use the commonly normalized update law:

$$\dot{\hat{\theta}} = -\frac{\gamma}{1+{x_f}^2}{x_f}^2\tilde{\theta}$$

The previous update law is linear. It can be proved that $\tilde{\theta}$ does not converge to zero faster than exponentially and the easiest case is:

$$\tilde{\theta} = e^{-\gamma t}\tilde{\theta}(0)$$

Finally the close loop system has the following form:

$$\dot{x} = -x + \tilde{\theta}x^2$$

where for simplicity q substituted with 1 and by substituting $\tilde{\theta}$ from the previous equation is obtained:

$$\dot{x} = -x + e^{-t}\tilde{\theta}(0)x^2$$

where for simplicity γ substituted with 1.

It is easy to see that the explicit solution of the previous is determined by the following equation:

$$x = \frac{2x(0)}{x(0)\tilde{\theta}(0)e^{-t} + [2 - x(0)\tilde{\theta}(0)]e^{-t}}$$

From the previous it is clear that if $x(0)\tilde{\theta}(0) < 2$ then it is obvious that x converge to zero as $t \to \infty$. At the case that $x(0)\tilde{\theta}(0) > 2$, at the time:

$$t_{esc} = \frac{1}{2}\ln\frac{x(0)\tilde{\theta}(0)}{x(0)\tilde{\theta}(0) - 2}$$

the difference of the two terms of the exponential in the denominator becomes zero, that is:

$$|x(t)| \to \infty \text{ as } t \to t_{esc}$$

The previous model is unstable (x goes to infinity at t_{esc}) and Lyapunov design models must be specified in order to achieve stabilization.

Let choose the following Lyapunov function:

$$V = \frac{1}{2}x^2 + \frac{1}{2}(\hat{\theta} - \theta)^2$$

The derivative of the Lyapunov function for our nonlinear plant is:

$$\dot{V} = x(u + \theta x^2) + (\hat{\theta} - \theta)^2\dot{\hat{\theta}}$$

In order to find a control and an update law we must specify:

$$\dot{V} \le -x^2 \Rightarrow x(u + \theta x^2) + (\hat{\theta} - \theta)^2 \dot{\hat{\theta}} \le -x^2$$

From the previous equation in order to remove the unknown θ we use the update law:

$$\dot{\hat{\theta}} = x^3$$

And the control law is:

$$u = -x - \hat{\theta} x^2$$

Both control law and update law yield $\dot{V} \le -x^2$ such that stability maintains in opposition to the previous approach without Lyapunov.

Adaptive control in most cases has tracking error that converges to zero.

2.6 Adaptive Backstepping design

Backstepping [1] is a recursive design for systems of the form:

$$\dot{x}_1 = x_2 + \phi_1^{\mathrm{T}}(x_1, x_2)\theta$$
$$\dot{x}_2 = x_3 + \phi_2^{\mathrm{T}}(x_1, x_2, x_3)\theta$$
$$\dot{x}_3 = u + \phi_3^{\mathrm{T}}(x_1, x_2, x_3)\theta$$

with state $x=[x_1^T, x_2^T, x_3^T]$ and control input u. The value θ is a $p \times 1$ vector which is constant and unknown. The function φ_1 depends only to x_1, x_2 function φ_2, φ_3 depends only to x_1, x_2, x_3.

The purpose of backstepping is the recursive design of a controller for the previous system by selecting appropriate virtual controllers. The virtual controller for the first equation of the system is x_2 and is used to stabilize the first equations, the virtual controller for the middle equation is x_3 and is used to stabilize the first two equations, and finally the controller for the last is u. We use separate virtual controllers in order to stabilize every equation of the system. In every step we select appropriate update laws.

In classical backstepping, the output is selected as the state x_1 and the purpose of adaptive control is to make this state to follow a desired trajectory x_{1d}.

Adaptive backstepping design is a Lyapunov based design. The previous procedure can be applied only to systems that have (or transformed to) the previous form (strict feedback).

2.7 Adaptive Forwarding design

Forwarding is something like backstepping but for strict feedforward systems. Let us introduce forwarding technique with an example such as:

$$\dot{x}_1 = x_2 + x_3^{\,2} + x_2 u$$
$$\dot{x}_2 = x_3 - x_3^{\,2} u$$
$$\dot{x}_3 = u$$

In the previous example we do not have feedback paths.

Firstly we stabilize the last equation ($\dot{x}_3 = u$). We take the following Lyapunov function: $V_3 = \frac{1}{2} x_3^{\,2}$ and a feedback to stabilize the system is $u = -x_3$. With the previous we augment $\dot{x}_3 = -x_3$ by the middle equation, and write our system in the cascade form:

$$\dot{x}_2 = \phi_2(x_3)$$
$$\dot{x}_3 = -x_3$$

where $\phi_2(x_3) = x_3 - x_3^{\,3}$ is the interconnection term. $\dot{x}_2 = 0$ is stable and $\dot{x}_3 = -x_3$ is GAS and LES. The next step is to construct Lyapunov function V_2 for the augmented system when V_3 is given.

After some specific steps we reach the following control law:

$$u = -x_3 - (x_2 + x_3 + \frac{x_3^{\,3}}{3})(1 + x_3^{\,2})$$

Chapter 3

PROBLEM ANALYSIS

3.1. System Description

The MAPK cascade model is described by the following set of differential equations [4]-[6]:

$$\frac{dX_i}{dt} = u(t)\delta_i \widetilde{X}_i + \sum_{j \neq i}^{n} a_{ij} \widetilde{X}_i X_j - \beta_i X_i \qquad (1)$$

where $\widetilde{X}_i$ and X_i are the concentrations of the inactive and active forms respectively, of the ith kinase. They can be related with each other with the following equation $\widetilde{X}_i + X_i = C = const.$, where a_{ij} and β_i are the rate constants of kinases and phosphatases, and $u(t)$ is the time dependent concentration of the receptor. The receptor converts the inactive input kinases into active. The rate constant δ_i is chosen such that: $\delta_i = 1$ for input kinases and $\delta_i = 0$ otherwise. The above hypothesis is made because the receptor affects only the input kinases.

Feedback Forms

- Special cases of (1) can be expressed in (or transformed to) the following nonlinear state space form:

$$
\begin{aligned}
&x_i = f_i(\bar{x}_i) + g_i(\bar{x}_i)x_{i+1}, 1 \le i \le n-1 \\
&x_i = f_i(\bar{x}_i) + g_n(\bar{x}_n)u \ , n \ge 2 \\
&y = x_1
\end{aligned} \tag{2}
$$

where $\bar{x}_i = [x_1, x_2, ...x_i]^T \in R^i, i = 1,...n, u \in R, y \in R$ are state variables, input and output respectively. Our purpose is to construct a specific adaptive Neural Network controller such that:

i) all the signals in the close loop remain semiglobally ultimately bounded

ii) the output signal y follows a desired trajectory signal y_d, with bounded derivatives up to $(m+1)th$ order.

In order to approximate some unknown nonlinearities we use Neural Networks [12], [14]. This approximation is guaranteed within some compact sets Ω.

Since $g_i(.)$, $i = 1,...n$ are smooth functions, they are therefore bounded within some compact set. According to the previous we can make two assumptions.

Assumption 1: The signs of $g_i(.)$ are bounded for example there exist constants $g_{i1}(.) \ge g_{i0}(.) > 0$ such that, $g_{i1}(.) \ge |g_{i1}(.)| \ge |g_{i0}(.)|, \forall \bar{x}_n \in \Omega \in R^n$. The $g_i(.)$ functions in the MAPK cascade are strictly positive because concentrations of kinases and phosphatases are positive numbers.

Assumption 2: There exist constants $g_{id}(.) > 0$ such that $g_i(.) \le g_{id}(.)$ $\forall \bar{x}_n \in \Omega \in R^n$.

Interlaced Forms

- Other cases of equation (1) are part of a larger class of systems that are called interlaced systems as described by Kokotovic et al [19], and Kristic [20]. In these systems we combine backstepping and forwarding techniques together in order to recursively design feedback control laws. Interlaced systems are not in feedback form, nor in feedforward form. These systems have a specific methodology that differs from backstepping and forwarding. We don't start from the top equation, neither from the bottom. We start from the middle equation and treat x_3 as virtual control.

Mixed Interlaced Forms

- Other special cases of equation (1) are part of other forms that we call mixed interlaced. The methodology is based on classical interlaced systems and is developed by the authors. We want to make the systems solvable by one of the well known backstepping and forwarding methods. This can be reached after some specific steps that convert the system into a known form. We start from the middle equation and we continue with the top.

3.2. RBF Neural Networks

Artificial Neural Networks have been studied for many years with the hope of achieving human-like performance in solving certain problems in speech and image processing. There has been a recent resurgence in the filed of neural networks owing to the introduction of new network topologies, training algorithms and VLSI implementation techniques. The potential benefits of neural networks such as parallel distributed processing, high computation rates, fault tolerance and adaptive capability, have lured researchers from other fields such as controls, robotics etc. to seek solution to their complicated problems.

Dynamical Neural Networks are well established tools used in the control of nonlinear and complex systems. We use RBF Neural Networks [9] in order to approximate the nonlinear functions of our systems [15]. The idea behind this is described fully at [2], [3], [8], [10], [11]. The RBF NN we use are of the general form $F(.) = \theta^{\mathrm{T}}\xi(.)$, where $\theta \in R^p$ is a vector of regulated weights and $\xi(.)$ a vector of RBF's. It has been shown that given a smooth function $\mathrm{F}:\Omega \to R$, where Ω is a compact subset of R^m (m is an appropriate integer) and $\varepsilon > 0$, there exists an RBF vector $\xi:\mathrm{R}^{\mathrm{m}} \to R^p$ and a weight vector $\theta^* \in R^p$ such that $\left|\mathrm{F}(\mathrm{x}) - \theta^{*\mathrm{T}}\xi(\mathrm{x})\right| \le \varepsilon \ \forall x \in \Omega$. Here ε is called the network reconstruction error. The optimal weight vector is chosen as an appropriate value that minimizes the reconstruction error over Ω.

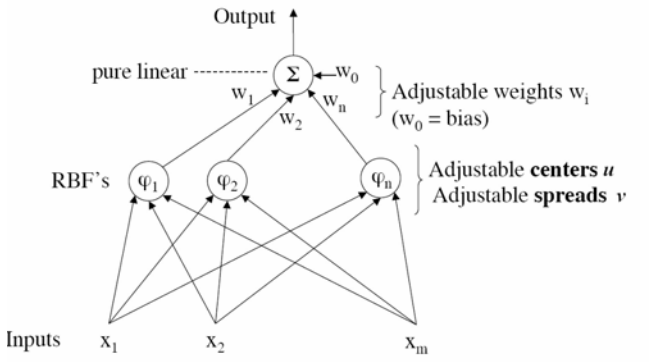


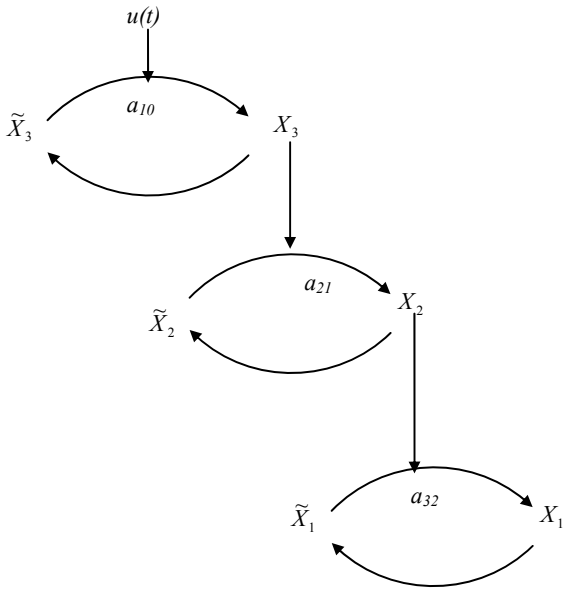
Figure 3.1: *Schematic representation of RBF Neural Networks.*

3.3. MAPK cascade models

In this project we apply the backstepping technique to the following pathways consisting of three kinases and three phosphatases:

Feedback Forms

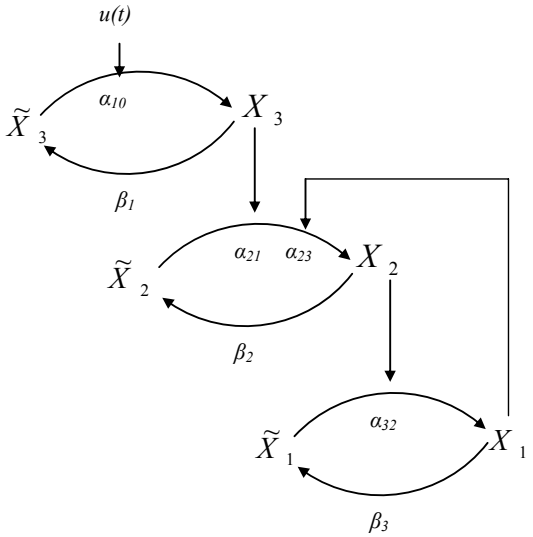
i)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

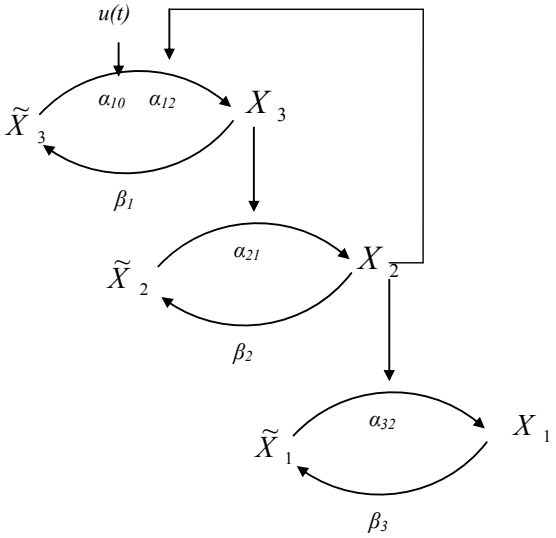
ii)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

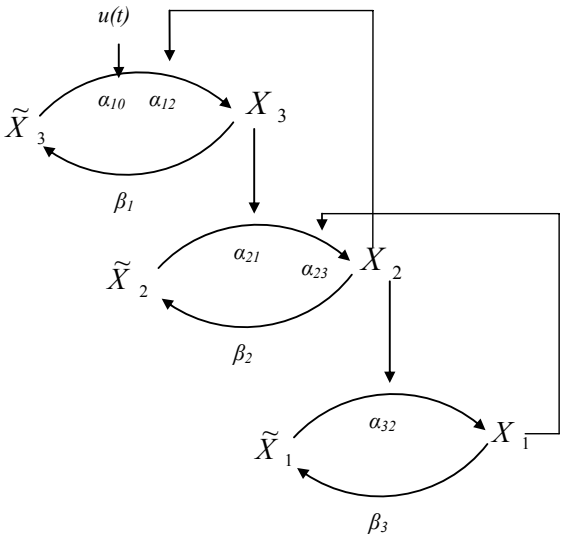
iii)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + (c_1 - x_3)u(t)$$
$$y = x_1$$

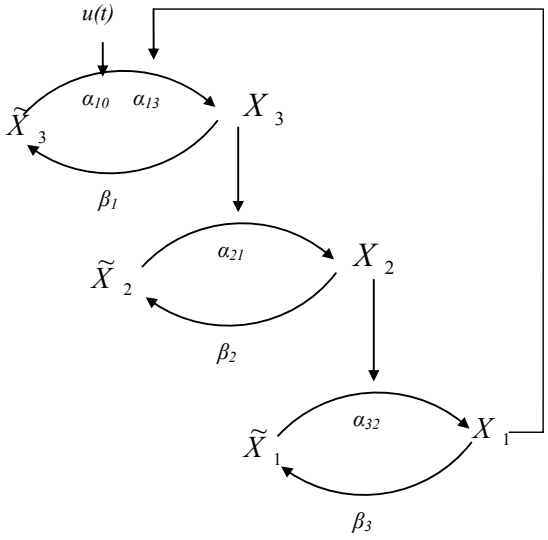
iv)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + (c_1 - x_3)u(t)$$
$$y = x_1$$

v)

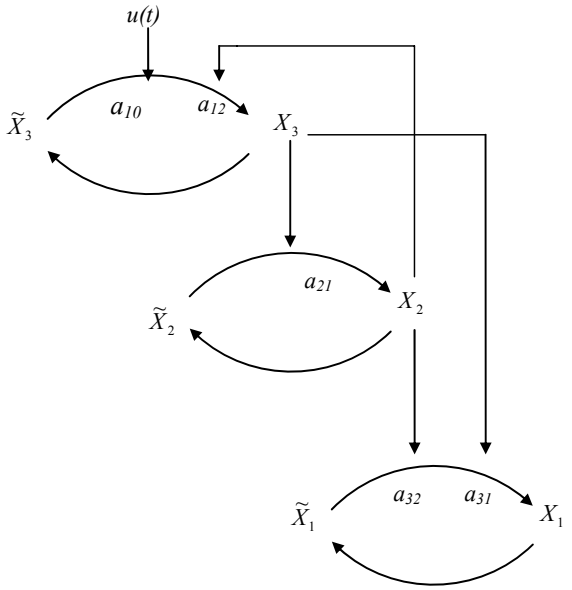


The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{13}(c_1 - x_3)x_1 + (c_1 - x_3)u(t)$$
$$y = x_1$$

Interlaced Forms

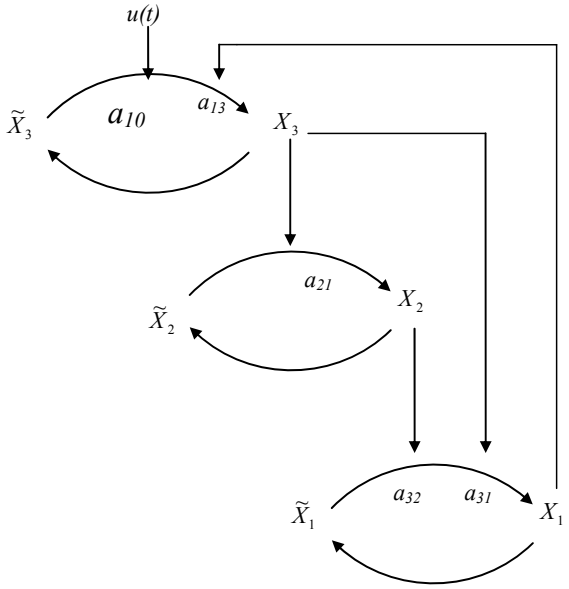
vi)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + (c_1 - x_3)u(t)$$
$$y = x_1$$

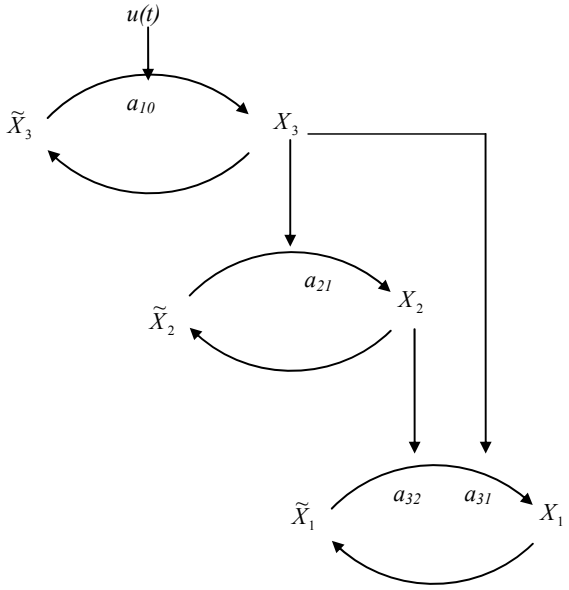
vii)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{13}(c_1 - x_3)x_1 + (c_1 - x_3)u(t)$$
$$y = x_1$$

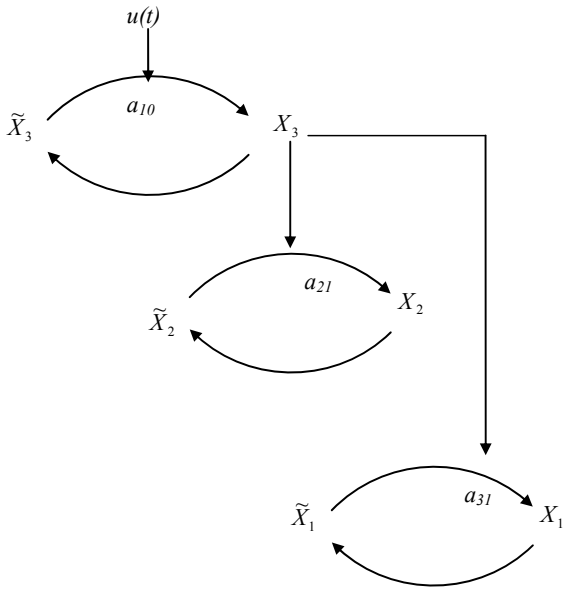
viii)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

ix)

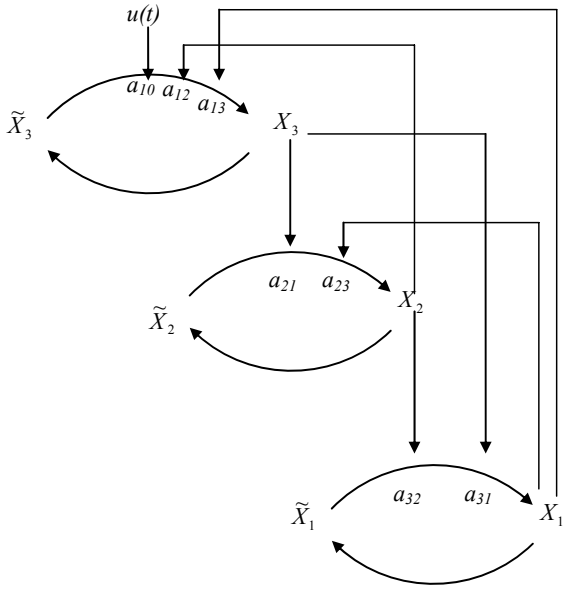


The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

Mixed Interlaced Forms

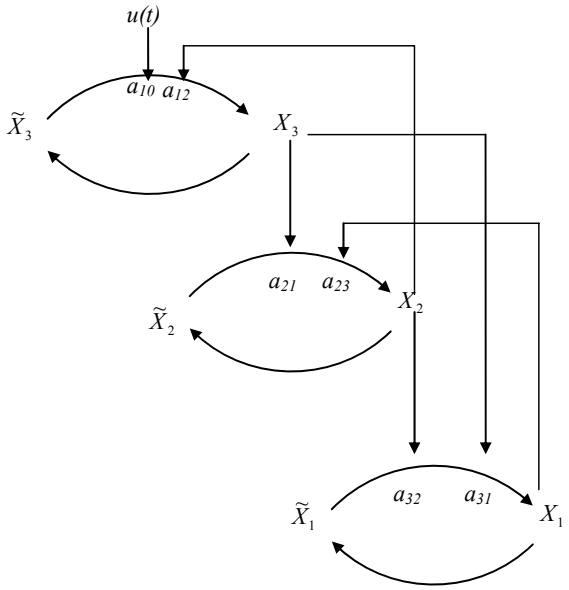
x)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + a_{13}(c_1 - x_3)x_1 + (c_1 - x_3)u(t)$$
$$y = x_1$$

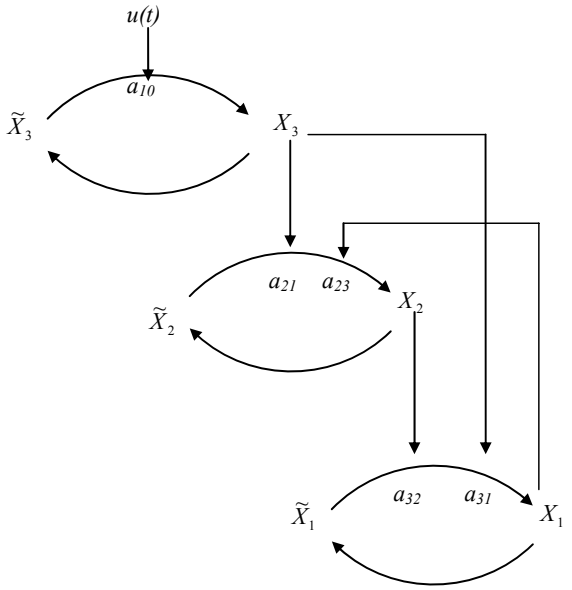
xi)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + (c_1 - x_3)u(t)$$
$$y = x_1$$

xii)

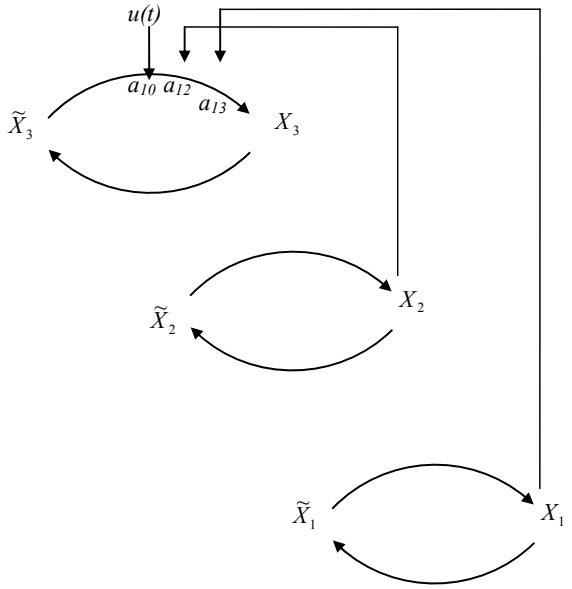


The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

Uncontrollable Form

xiii)



The previous pathway is described by the following equations:

$$\dot{x}_1 = -\beta_3 x_1$$
$$\dot{x}_2 = -\beta_2 x_2$$
$$\dot{x}_3 = -\beta_1 x_3 + a_{12}(c_1 - x_3)x_2 + a_{13}(c_1 - x_3)x_1 + (c_1 - x_3)u(t)$$
$$y = x_1$$

3.4. Controller Design

The procedure presented is described by the following figure:

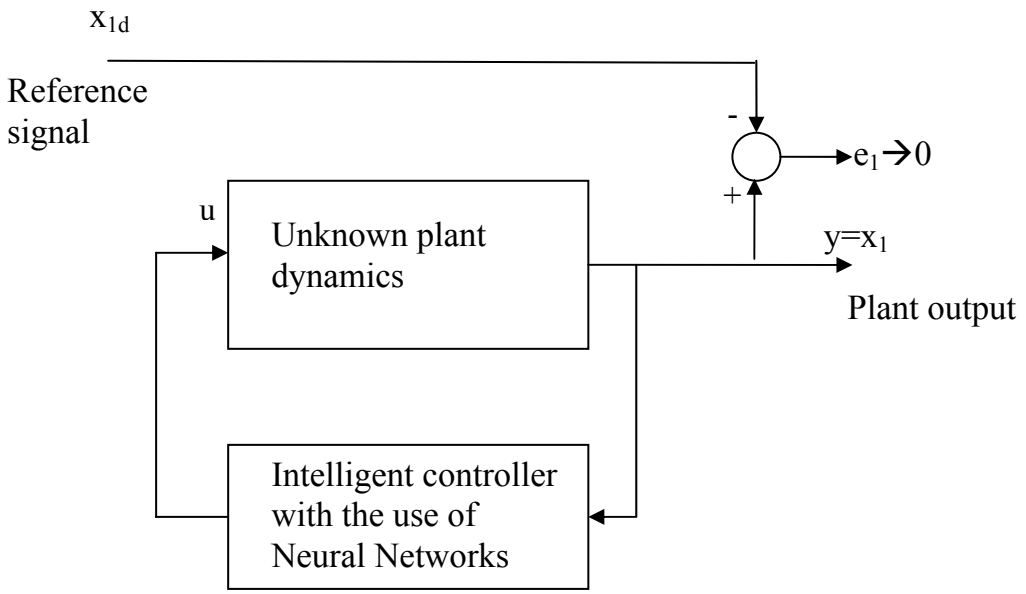


Figure 3.2: *Adaptive Controller*.

➢ In order to apply the backstepping technique to interlaced forms (MAPK cascade with graphs (vi)-(ix)) we must start from the middle equation and treat x_3 as virtual control and we want $\dot{x}_2 = -x_2$ for stability. There exists a Lyapunov function of the form $V_1 = \frac{1}{2}x_2^2$ and a stabilizing feedback is $x_3 = \frac{(\beta_2 - 1)x_2}{a_{21}(c_2 - x_2)}$ which is $x_3=a(x_2)$. With this technique we eliminate x_3 from the top equation and we apply the backstepping technique that is documented fully in the next paragraphs, to control the MAPK cascade models that are in interlaced forms.

➢ Also in order to apply the backstepping technique to mixed interlaced forms (MAPK cascade with graphs (x)-(xii)) we must start from the middle equation and treat x_3 as virtual control and we want $\dot{x}_2 = -x_2$ for stability. There exists a Lyapunov function of the form $V_1 = \frac{1}{2}x_2^2$ and a stabilizing feedback is

$x_3 = \frac{-\beta_2 x_2 + a_{23} c_2 x_1 - a_{23} x_2 x_1 + x_2}{a_{21} x_2 - a_{21} c_2}$ which is $x_3=a(x_1,x_2)$. With this technique we eliminate x_3 from the top equation and we apply the backstepping technique that is documented fully in the next paragraphs, to control the MAPK cascade models that are in mixed interlaced forms.

- The models with graphs (i)-(v) are in feedback forms so the following backstepping adaptive control is applied directly without any other actions.

- The last (MAPK cascade with graph (xiii)) model representation cannot be controlled. Because the top and the middle state equations are input uncontrollable.

At this point, we should mention that for the construction of the neural model of the controller there exist further possibilities beside the mean squared error between the real output and the reference input , $x_1 - y_d$, as well as the input u to the plant. The inclusion of u in the cost function is desirable, in order to preserve control energy. In the same way, the rate of u can also be included, so that the transition from one extreme value u to another can be avoided. On the other, each one of the terms that participate in the cost function can be assigned a weight.

In [16], a desired feedback control law was initially proposed for system (2) and Neural Networks are used to parameterize the desired feedback control law. Finally adaptation laws are used to tune the weights of neural networks for closed loop stability. In our project we use the controller designed by Kaynak et al. [7]. The design procedure is described in 3 steps because in the MAPK cascade models above we have 3 states. Each backstepping stage results in a new virtual control design obtained from the preceding design stages. When the procedure ends, the feedback design for the control input is obtained, which achieves the original design objective.

Step1: In this step we want to make the error between x_1 and x_{1d} $(=y_d)$ as small as possible.

The previous is described by the following equation:

$$e_1 = x_1 - x_{1d} \tag{3}$$

We take the derivative of e_1. After that we have:

$$\dot{e}_1 = \dot{x}_1 - \dot{x}_{1d} \Rightarrow \dot{e}_1 = f_1(x_1) + g_1(x_1)x_2 - \dot{x}_{1d} \tag{4}$$

by using x_2 as the virtual control input. The previous equation can be changed by multiplication and division with $g_1(x_1)$ to the following form:

$$\dot{e}_1 = g_1(x_1)[g_1^{-1}(x_1)f_1(x_1) + x_2 - g_1^{-1}(x_1)\dot{x}_{1d}] \tag{5}$$

We choose the virtual controller as:

$$x_{2d} = x_2 = -g_1^{-1}(x_1)f_1(x_1) + g_1^{-1}(x_1)\dot{x}_{1d} - k_1 e_1 \tag{6}$$

where k_1 is a positive constant. In order to approximate the unknown nonlinearities (functions $f_1(x_1)$ and $g_1(x_1)$) we use RBF Neural Networks. A Neural Network based virtual controller is used as follows:

$$x_{2d} = -\theta_1^{\mathrm{T}}\xi_1(x_1) + \delta_1^{\mathrm{T}}n_1(x_1)\dot{x}_{1d} - k_1 e_1 \tag{7}$$

where we have substituted the unknown nonlinearities $g_1(x_1)^{-1}f_1(x_1)$ and $g_1(x_1)^{-1}$ with the RBF Neural Networks $\theta_1^{\mathrm{T}}\xi_1(x_1)$ and $\delta_1^{\mathrm{T}}n_1(x_1)$ respectively based on Lyapunov stability [16], [17].

We take the following adaptation laws (σ-modification) in order to avoid large values of the weights:

$$\dot{\theta}_1 = \Gamma_{11}[e_1\xi_1(x_1) - \sigma_1\theta_1]$$

$$\dot{\delta}_1 = \Gamma_{12}[-e_1 n_1(x_1)\dot{x}_{1d} - \gamma_1 \delta_1] \tag{8}$$

with σ_1, γ_1 small and positive constants and $\Gamma_{11}=\Gamma_{11}^T>0$, $\Gamma_{12}=\Gamma_{12}^T>0$ are the adaptive gain matrices.

Step 2: In this step we make the error between x_2 and x_{2d} as small as possible. The previous is described by the following equation:

$$e_2 = x_2 - x_{2d} \tag{9}$$

We take the derivative of e_2. After that we have:

$$\begin{aligned} \dot{e}_2 &= \dot{x}_2 - \dot{x}_{2d} = f_2(\bar{x}_2) + g_2(\bar{x}_2)x_3 - \dot{x}_{2d} \\ &= g_2(\bar{x}_2)[g_2(\bar{x}_2)^{-1} f_2(\bar{x}_2) + x_3 - g_2(\bar{x}_2)^{-1}\dot{x}_{2d}] \end{aligned} \tag{10}$$

By taking the x_{3d} as a virtual control input and by substituting the unknown nonlinearities $g_2(\bar{x}_2)^{-1} f_2(\bar{x}_2)$ and $g_2(\bar{x}_2)^{-1}$ with the RBF Neural Networks $\theta_2^{\mathrm{T}}\xi_2(\bar{x}_2)$ and $\delta_2^{\mathrm{T}} n_2(\bar{x}_2)$ respectively based on Lyapunov stability [16], [17], we have:

$$x_{3d} = -e_1 - \theta_2^{\mathrm{T}}\xi_2(\bar{x}_2) + \delta_2^{\mathrm{T}} n_2(\bar{x}_2)\dot{x}_{2d} - k_2 e_2 \tag{11}$$

We take the following adaptation laws (σ-modification) in order to avoid large values of the weights:

$$\begin{aligned} \dot{\theta}_2 &= \Gamma_{21}[e_2\xi_2(\bar{x}_2) - \sigma_2\theta_2] \\ \dot{\delta}_2 &= \Gamma_{22}[-e_2 n_2(\bar{x}_2)\dot{x}_{2d} - \gamma_2\delta_2] \end{aligned} \tag{12}$$

with σ_2, γ_2 small and positive constants and $\Gamma_{21}=\Gamma_{21}^T>0$, $\Gamma_{22}=\Gamma_{22}^T>0$ are the adaptive gain matrices.

Step 3(Final): In this step we make the error between x_3 and x_{3d} as small as possible. The previous is described by the following equation:

$$e_3 = x_3 - x_{3d} \tag{13}$$

We take the derivative of e_3. After that we have:

$$\begin{aligned} \dot{e}_3 &= \dot{x}_3 - \dot{x}_{3d} = f_3(\bar{x}_3) + g_3(\bar{x}_3)u \; - \dot{x}_{3d} \\ &= g_3(\bar{x}_3)[g_3(\bar{x}_3)^{-1} f_3(\bar{x}_3) + u - g_3(\bar{x}_3)^{-1}\dot{x}_{3d}] \end{aligned} \tag{14}$$

Where u is the control input and by substituting the unknown nonlinearities $g_3(\bar{x}_3)^{-1} f_3(\bar{x}_3)$ and $g_3(\bar{x}_3)^{-1}$ with the RBF Neural Networks $\theta_3^{\mathrm{T}}\xi_3(\bar{x}_3)$ and $\delta_3^{\mathrm{T}} n_3(\bar{x}_3)$ respectively, we have:

$$u = -e_2 - \theta_3^{\mathrm{T}}\xi_3(\bar{x}_3) + \delta_3^{\mathrm{T}} n_3(\bar{x}_3)\dot{x}_{3d} - k_3 e_3 \tag{15}$$

We take the following adaptation laws (σ-modification) in order to avoid large values of the weights:

$$\begin{aligned} \dot{\theta}_3 &= \Gamma_{31}[e_3\xi_3(\bar{x}_3) - \sigma_3\theta_3] \\ \dot{\delta}_3 &= \Gamma_{32}[-e_3 n_3(\bar{x}_3)\dot{x}_{3d} - \gamma_3\delta_3] \end{aligned} \tag{16}$$

with σ_3, γ_3 small and positive constants and $\Gamma_{31}=\Gamma_{31}^{T}>0$, $\Gamma_{32}=\Gamma_{32}^{T}>0$ are the adaptive gain matrices.

3.5. Simulation

In order to show the effectiveness and apply the above approach a simulation is presented for the (i) form of the MAPK cascade model (as described before):

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$
$$y = x_1$$

where x_1, x_2, x_3 and y are states (concentrations) and output of the system respectively. The initial conditions (concentrations) are $x_0=[x_{10}, x_{20}, x_{30}]^T=[0.7, 0.8, 1.0]^T$ and the desired output signal of the system is $y_d=sin(t)$.

We make the assumption that $c_1>>x_1$, $c_2>>x_2$, $c_3>>x_3$ in order $g(.)$ functions to be strictly positive and $a_{21}=a_{32}=\beta_1=\beta_2=\beta_3=1$, $c_1=9.99$, $c_2=6.66$, $c_3=3.33$.

All the basis function of the NNs have the form $G(\bar{x}_i) = \exp[-\frac{(\bar{x}_i - u_i)^T(\bar{x}_i - u_i)}{v_i^2}]$ (as described in [8]) where $u_i=[u_{i1}, u_{i2}, ..., u_{ij}]^T$ are the centers of the receptive field and v_i are the widths of the Gaussian function.

The Neural Networks $\theta_1^T\xi_1(x_1)$ and $\delta_1^T\eta_1(x_1)$ have 5 nodes with centres u_j evenly spaced in [-6, 6] and widths $v_j=1$, $\theta_2^T\xi_2(\bar{x}_2)$ and $\delta_2^T\eta_2(\bar{x}_2)$ have 25 nodes with centres u_j evenly spaced in [-6, 6] x [-6, 6] and widths $v_j=1$ and $\theta_3^T\xi_3(\bar{x}_3)$, $\delta_3^T\eta_3(\bar{x}3)$ have 125 nodes with centers u_j evenly spaced in [-6, 6] x [-6, 6] x [-6, 6] and widths v_j=1. We select the design parameters of the above controller as $k_1=k_2=3.5$, $\Gamma_1=\Gamma_2=diag\{2\}$, $\sigma_1=\sigma_2=\gamma_1=\gamma_2=0.2$. The initial weights θ_1, θ_2, θ_3 are arbitrarily taken in [-1.2, 1.2] and δ_1, δ_2, δ_3 in [0, 1.2].

Figs. 3.3-3.8 show the simulation results of applying the controller for tracking the desired signal y_d. From figure 3.3 we can see that good tracking performance is obtained. Figure 3.4 shows the trajectory of the controller. Figure 3.5 shows the phase plane of the system. Figure 3.6 shows the error e_1, Figure 3.7 shows the error e_2 and finally Figure 3.8 shows the error e_3.

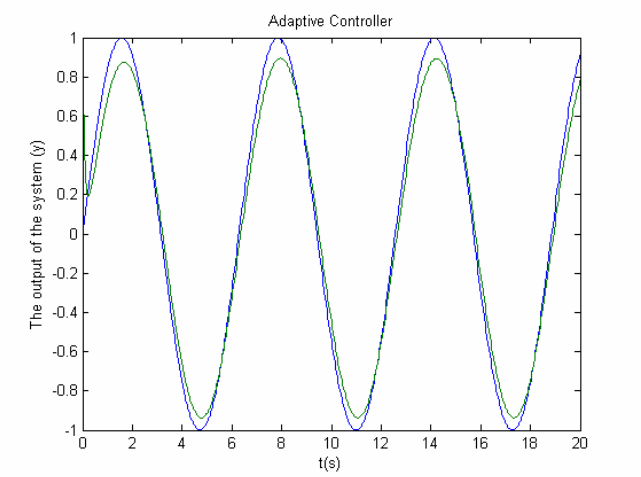


Figure 3.3: *The output of the system under adaptive controller.*

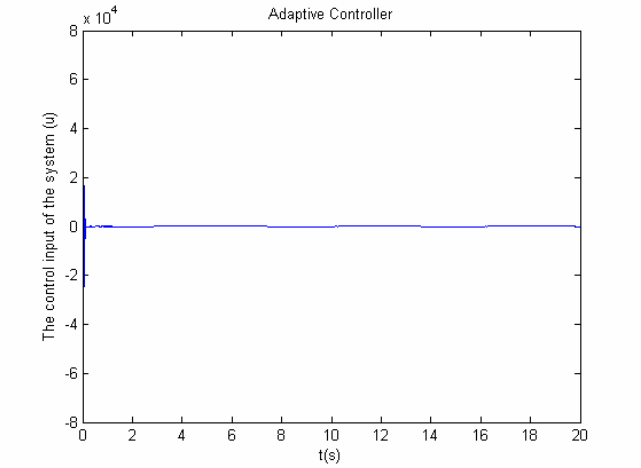


Figure 3.4: *The trajectory of the adaptive controller.*

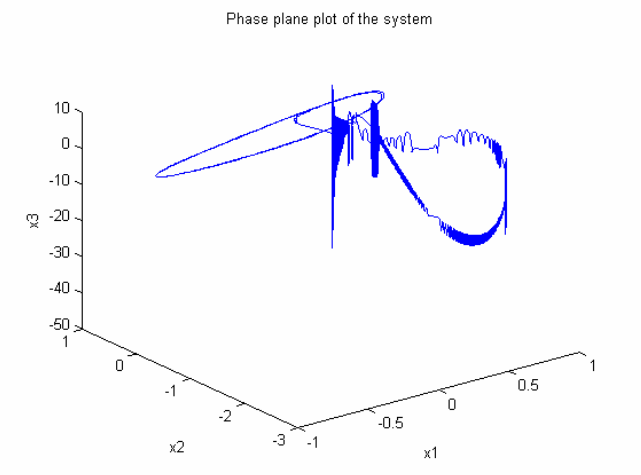


Figure 3.5: *The phase plane plot of the system.*

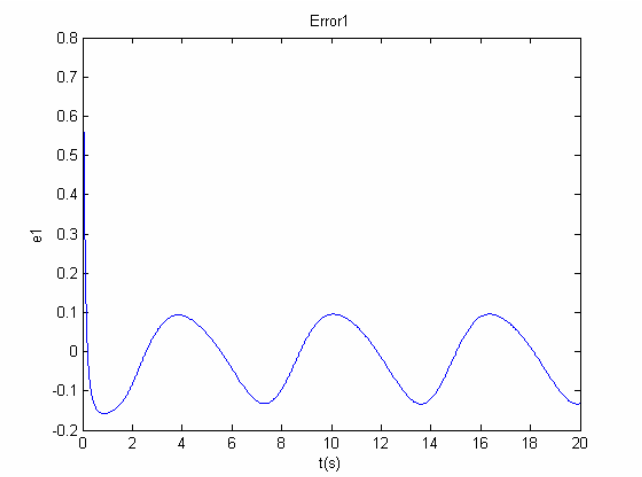


Figure 3.6: *Error e_1.*

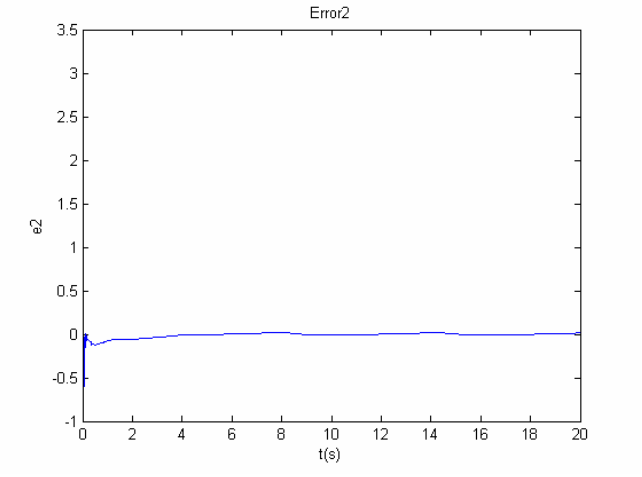


Figure 3.7: *Error e_2.*

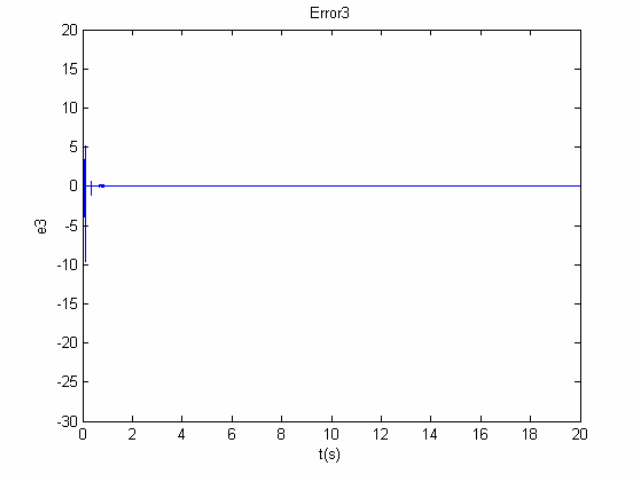


Figure 3.8: *Error e_3.*

In order to test the above controller in more abrupt changes that are more usual in Systems Biology, we changed the desired output to $y_d=(atan(10*(t-10))/\pi)+0.5$ and holding the other constant values unchanged, we have the following figures: from figure 3.9 we can see that good tracking performance is obtained. Figure 3.10 shows the trajectory of the controller. Figure 3.11 shows the phase plane of the system. Figure 3.12 shows the error e_1, Figure 3.13 shows the error e_2 and finally Figure 3.14 shows the error e_3:

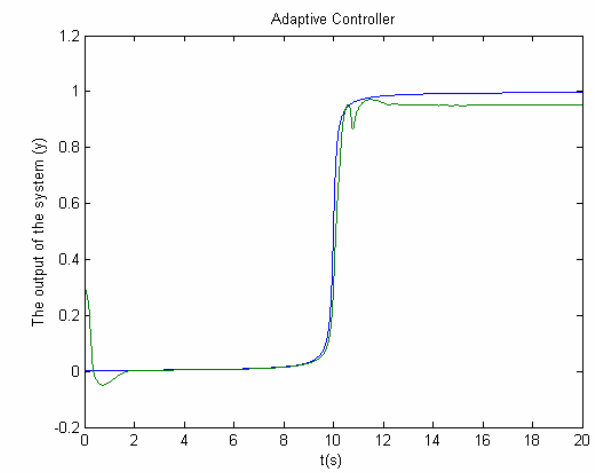


Figure 3.9: *The output of the system under adaptive controller.*

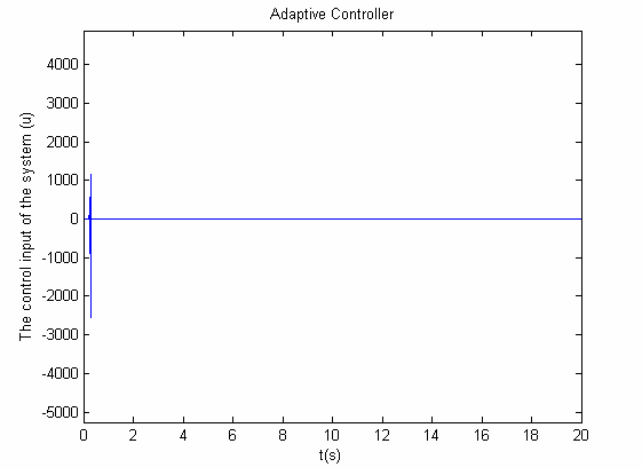


Figure 3.10: *The trajectory of the adaptive controller.*

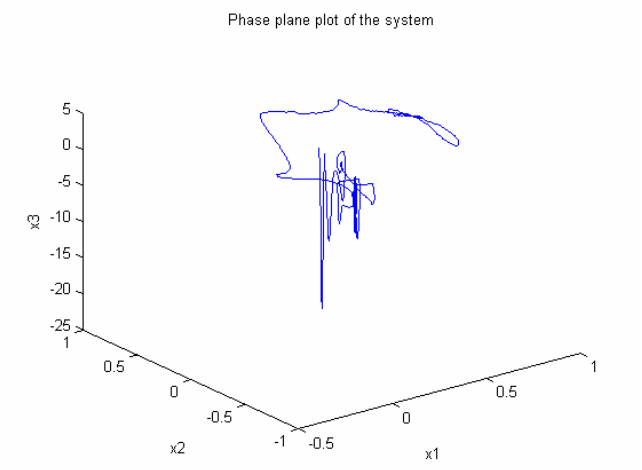


Figure 3.11: *The phase plane plot of the system.*

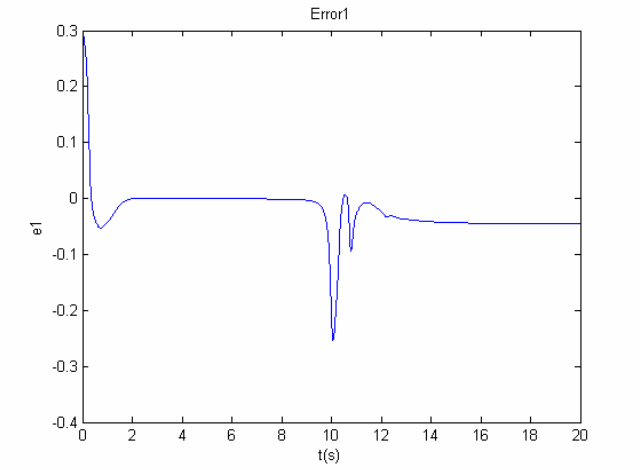


Figure 3.12: *Error* e_1.

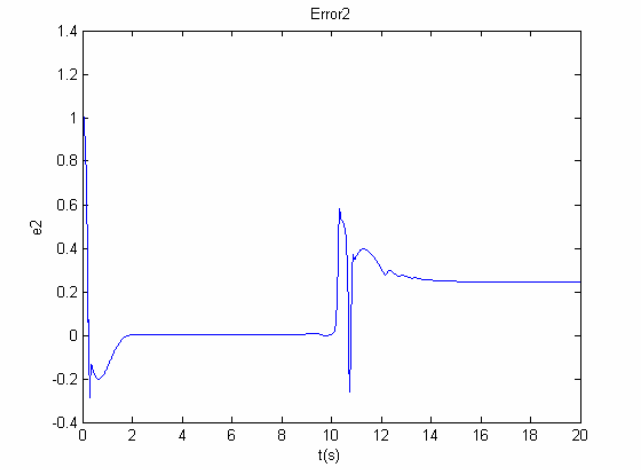


Figure 3.13: *Error* e_2.

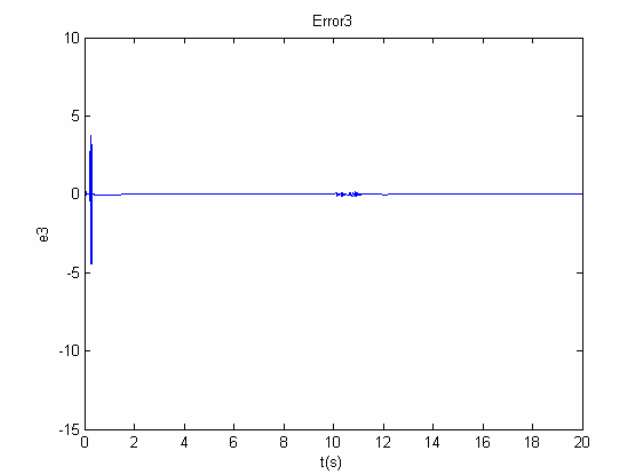


Figure 3.14: *Error e_3.*

Finally we test the above controller with desired output y_d=*(atan(10*(t-10))/π)+0.5* and holding the other constant values unchanged, we have the following figures: from figure 3.15 we can see that good tracking performance is obtained. Figure 3.16 shows the trajectory of the controller. Figure 3.17 shows the phase plane of the system. Figure 3.18 shows the error e_1, Figure 3.19 shows the error e_2 and finally Figure 3.20 shows the error e_3:

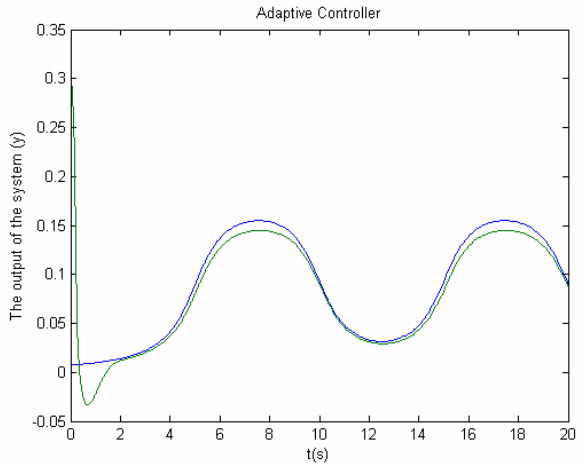


Figure 3.15: *The output of the system under adaptive controller.*

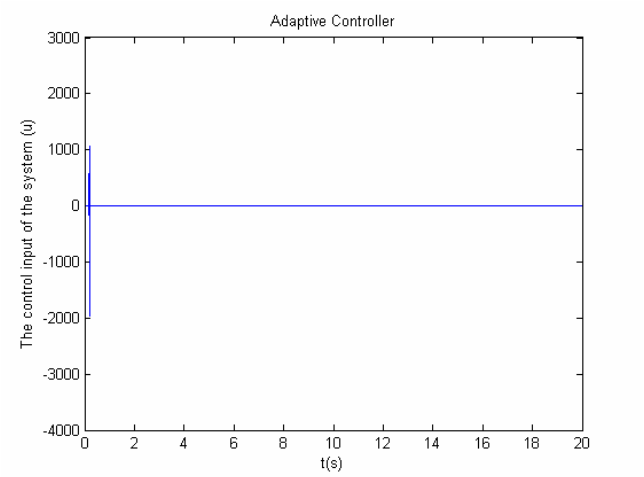


Figure 3.16: *The trajectory of the adaptive controller.*

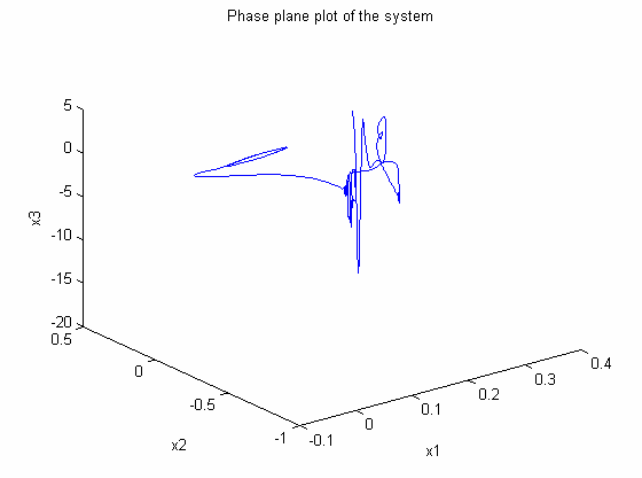


Figure 3.17: *The phase plane plot of the system.*

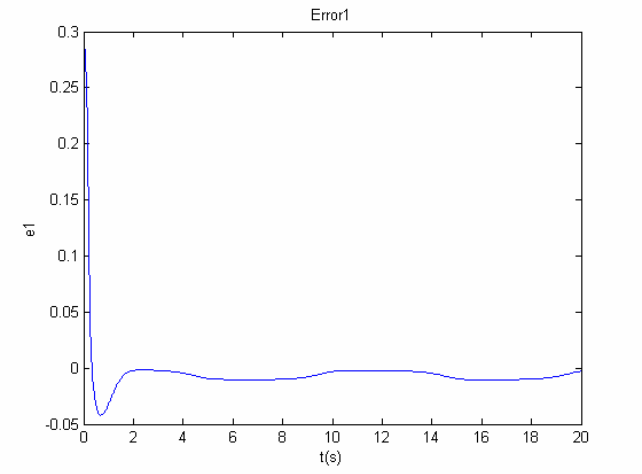


Figure 3.18: *Error e_1.*

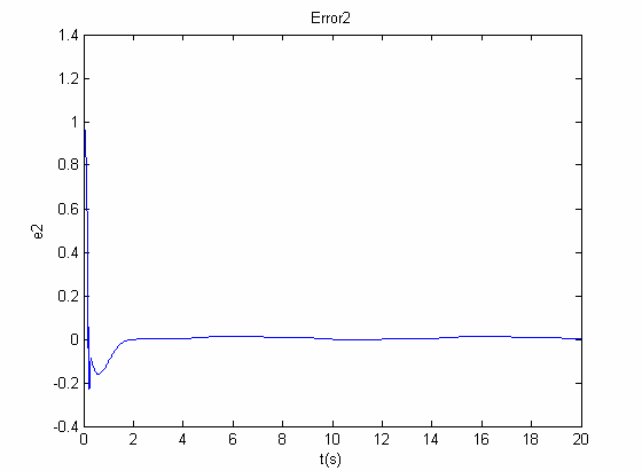


Figure 3.19: *Error e_2.*

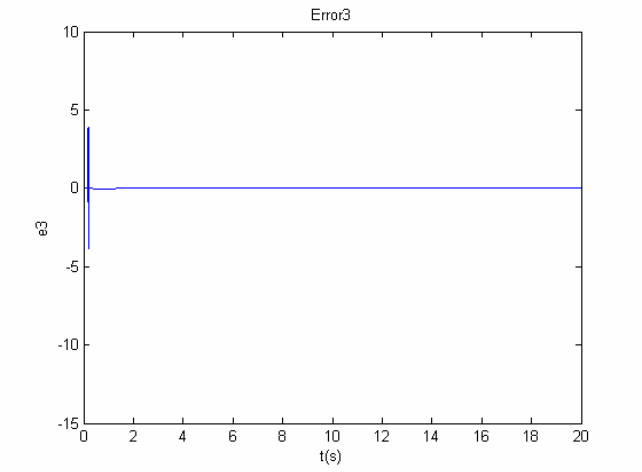


Figure 3.20: *Error e_3.*

Chapter 4

CONCLUSION AND FUTURE DEVELOPMENTS

In this project, we apply the controller scheme [7] to control the output of the MAPK cascade models that are in either feedback, interlaced forms, or mixed interlaced forms to reach a specific behaviour without knowing the interconnections of them. The tracking error is bounded and is established on the basis of the Lyapunov approach. It is an adaptive control application that can be applied extensively into medicine, drug discovery and can find costumers to university research teams, hospital clinicians, patients, agrobiotechnology etc. Also one of our goals has been to show how engineering tools can be applied to the control of metabolic systems.

A simulation of this work is provided and is very useful for the biologists in order to understand the function of cells if we provide a suitable input. The experiments in cell are very difficult. Control theory provides us powerful mathematical tools to control and identify a lot of cell functions. Finally, only the states of the unknown plant which are related to the reduced order model, are assumed to be available for measurement.

All the signals of the close loop system are guaranteed to be semiglobally uniformly bounded, and the output of the system is proven to converge to a small neighbourhood of the desired trajectory.

As long as future developments, the most significant is to control more complicated cascade models that are not only MAPK cascade. More complicated models are models with more than 3 states and more than 2 feedback or feedforward loops.

In order to study more complicated pathways [22] it is necessary to develop new high throughput experimental tools such as software tools that gather and configure experimental data. Such software is Bio Spice and SBML that have professional standards. Furthermore it is required improved and facile plant cell imaging to track interacting proteins and count their concentrations.

Also new mathematical concepts and tools have been provided from new publications of control theory that are necessary for modelling and simulating the functioning of cells.

"Not every end is a goal. The end of a melody is not its goal;
but nonetheless, if the melody had not reached its end it
would not have reached its goal either. A parable."
Nietzsche, *The Wanderer and His Shadow*, 1880

Appendix

Mixed Interlaced Forms

A. Introduction

Recent technological developments have forced control engineers to deal with extremely complex systems that include uncertain and possibly unknown nonlinearities, operating in highly uncertain environments. Man has two principal objectives in the scientific study of his environment: he wants to understand and to control. The two goals reinforce each other, since deeper understanding permits firmer control, and, on the other hand, systematic application of scientific theories inevitably generates new problems which require further investigation, and so on. Nonlinear control includes two basic forms of systems, the feedforward systems and the feedback systems.

The strict feedback systems can be controlled using the well known backstepping technique. The purpose of backstepping is the recursive design of a controller for the system by selecting appropriate virtual controllers. We use separate virtual controllers in order to stabilize every equation of the system. In every step we select appropriate update laws. The strict feedforward systems can be controlled using the forwarding technique that is something like backstepping but in reverse order.

Other cases of systems that can be converted to the previous forms are part of a larger class of systems that are called interlaced systems as described by Kokotovic et al, and Krstic. In these systems we combine backstepping and forwarding techniques together in order to recursively design feedback control laws. Interlaced systems are not in feedback form, nor in feedforward form. These systems have a specific

methodology that differs from backstepping and forwarding. We don't start from the top equation, neither from the bottom.

Other special cases of systems are part of other forms that we call mixed interlaced. The methodology is based on classical interlaced systems and is developed by the authors. We want to make the systems solvable by one of the well known backstepping and forwarding methods. This can be reached after some specific steps that convert the system into a known form. We start from the middle equation and we continue with the top.

A lot of researchers developed a series of results that generalized and explained the basic idea of nonlinear control. Teel in his dissertation introduced the idea of nested saturations with careful selection of their parameters to achieve robustness to nonlinear controllers. After Teel, Jankovic et al. proposed a new solution to the problem of forwarding that is based on a different Lyapunov solution.

B.Problem Analysis

To begin with we consider the following third order mixed interlaced system:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)x_3$$
$$\dot{x}_2 = -\beta_2 x_2 + a_{23}(c_2 - x_2)x_1 + a_{21}(c_2 - x_2)x_3$$
$$\dot{x}_3 = -\beta_1 x_3 + (c_1 - x_3)u(t)$$

The previous system is not in feedback nor is it in feedforward form because of specific terms such as x_1x_2, x_1x_3, x_2x_3. The Jacobi linearization of the previous system is a chain of integrators.

Instead from starting from the top, we start from the middle equation and treat x_3 as virtual control and we want $\dot{x}_2 = -x_2$ for stability. There exists a Lyapunov function of the form $V_1 = \frac{1}{2}x_2^{\,2}$ and a stabilizing feedback is $x_3 = \frac{-\beta_2 x_2 + a_{23}c_2x_1 - a_{23}x_2x_1 + x_2}{a_{21}x_2 - a_{21}c_2}$ which is $x_3=a(x_1,x_2)$. We employ one step of backstepping to stabilize the middle equation augmented by the top equation of our system:

$$\dot{x}_1 = -\beta_3 x_1 + a_{32}(c_3 - x_1)x_2 + a_{31}(c_3 - x_1)\left(\frac{-\beta_2 x_2 + a_{23}c_2x_1 - a_{23}x_2x_1 + x_2}{a_{21}x_2 - a_{21}c_2}\right) + a_{31}(c_3 - x_1)v$$
$$\dot{x}_2 = -x_2 + v$$

where the control x_3 has been augmented to $x_3=a(x_1,x_2)+v$. With v=0, the equilibrium $(x_1,x_2)=(0, 0)$ is globally stable and forwarding yields the following Lyapunov function:

$$V_2 = V_1 + \lim \tilde{x}_1(s)$$
$$= \frac{1}{2} x_2{}^2 + \frac{1}{2} \xi_1{}^2,$$
$$\xi_1 = x_1 + x_2 - \frac{1}{2} x_2{}^2 - \frac{1}{3} x_2{}^3$$

The feedback law: $v = -(1 - x_2{}^2)\xi_1$ maintains the system globally stable and the augmented control is

$$x_3 = a_1(x_1, x_2) \; + v = \frac{-\beta_2 x_2 + a_{23} c_2 x_1 - a_{23} x_2 x_1 + x_2}{a_{21} x_2 - a_{21} c_2} - (1 - x_2{}^2)\xi_1 \; = a_2(x_1, x_2, \xi_1)$$

In order to stabilize our system we apply the backstepping technique.

Mixed Interlaced Forms, Adaptive Control and Simulations

Adaptive Control of dynamical systems has been an active area of research since the 1960's.

In order to prove the stabilization of mixed interlaced systems we apply the kaynak et al. controller as mentioned before and we take the following simulations:

We make the assumption that $c_1 >> x_1$, $c_2 >> x_2$, $c_3 >> x_3$ and $a_{21}=a_{32}=\beta_1=\beta_2=\beta_3=1$, $c_1=9.99$, $c_2=6.66$, $c_3=3.33$. Also we want our desired output to be y_d=sint.

Figs. 1-6 show the simulation results of applying the controller for tracking the desired signal y_d. From figure 1 we can see that good tracking performance is obtained. Figure 2 shows the trajectory of the controller. Figure 3 shows the phase plane of the system. Figure 4 shows the error e_1, Figure 5 shows the error e_2 and finally Figure 6 shows the error e_3.

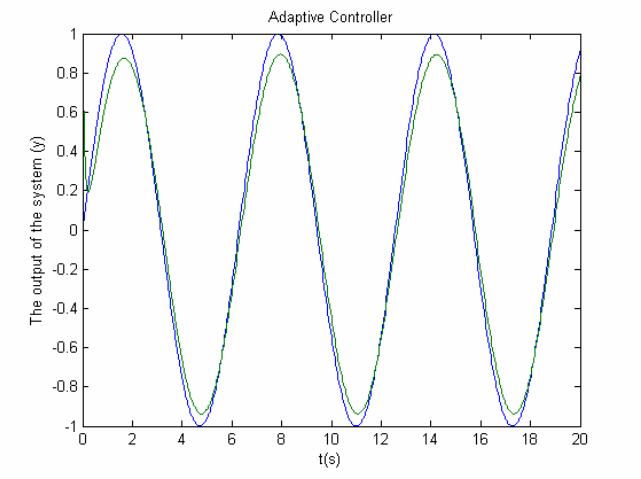


Fig. 1: *The output of the system under adaptive controller.*

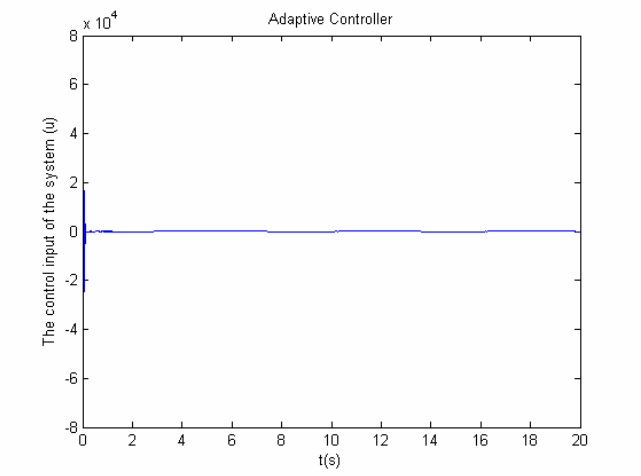


Fig. 2: *The trajectory of the adaptive controller.*

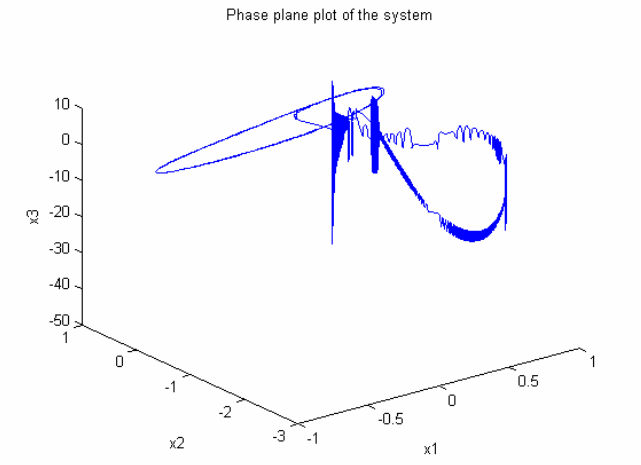


Fig. 3: *The phase plane plot of the system.*

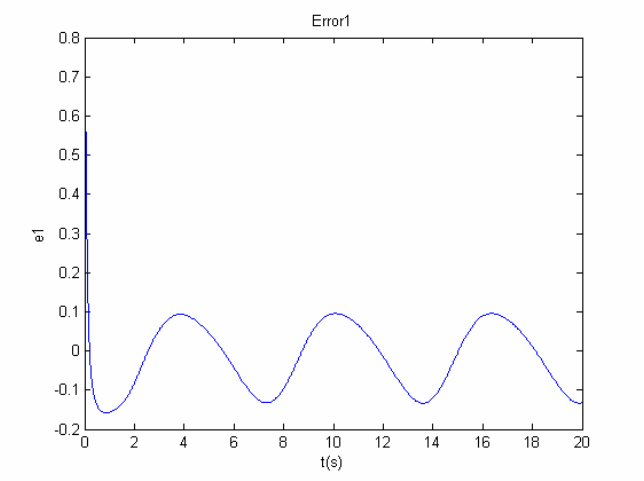


Fig. 4: *Error e_1.*

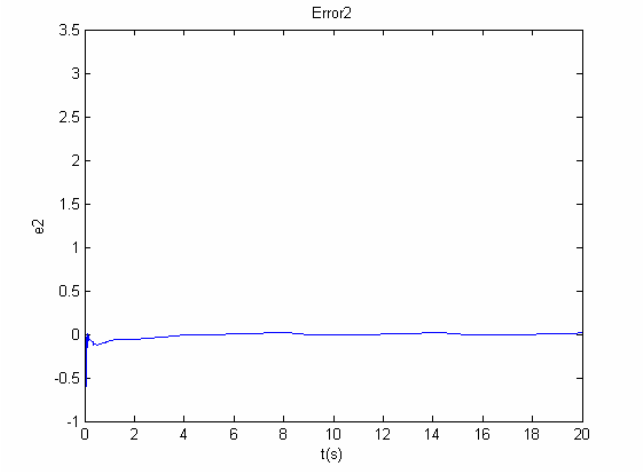


Fig. 5: *Error e_2.*

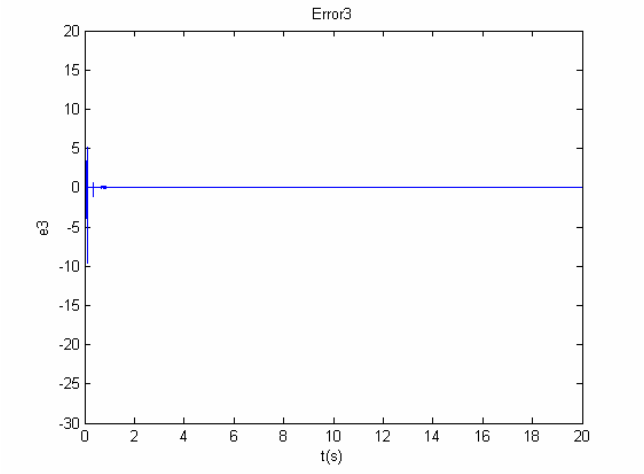


Fig. 6: *Error* e_3.

C. Conclusion

In the appendix, we recognize a new form of systems that we call mixed interlaced form. We apply the well known backstepping and forwarding techniques via specific steps. Also Lyapunov functions can be selected to approve convergence and stability. A lot of systems have the mixed interlaced form. For example we can think systems in biological models that have many terms from different states. After the appropriate selection of the controller we can apply adaptive control to make the systems follow a desired trajectory.

The tracking error is bounded and is established on the basis of the Lyapunov approach. Finally, only the states of the unknown plant which are related to the reduced order model are assumed to be available for measurement.

The authors hope that the proposed approach would serve as a promising tool to analyze more complex systems.

PUBLICATIONS FROM THIS WORK

Journals

[1] Kyriakos G. Vamvoudakis, Manolis A. Christodoulou, "Adaptive Nonlinear Control for MAPK Cascade Models in Biology Using RBF Neural Networks," *IEEE Trans. on Circuit and Systems*, submitted for publication.

[2] Kyriakos G. Vamvoudakis, Manolis A. Christodoulou, "Adaptive control of mixed interlaced forms," International Journal of Systems Science, submitted for publication.

Conferences

[3] Kyriakos G. Vamvoudakis, Manolis A. Christodoulou, "Adaptive Backstepping Control for MAPK Cascade Models Using RBF Neural Networks," Conference on Decision and Control 2006, submitted.

[4] Kyriakos G. Vamvoudakis, Manolis A. Christodoulou, "Backstepping, Interlaced and Mixed Interlaced Adaptive Nonlinear Control for Biological Models," ISYC 2006, accepted and presented.

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