GENETIC SEQUENTIAL DYNAMICAL SYSTEMS

M. A. AVÍÑO, H. ORTIZ, AND O. MORENO

ABSTRACT. The whole complex process to obtain a protein encoded by a gene is difficult to include in a mathematical model. There are many models for describing different aspects of a genetic network. Finding a better model is one of the most important and interesting questions in computational biology. Sequential dynamical systems have been developed for a theory of computer simulation, and in this paper, a genetic sequential dynamical system is introduced. A gene is considered to be a function which can take a finite number of values. We prove that a genetic sequential dynamical system is a mathematical good description for a finite state linear model introduced by Brazma [3, 4].

1. Introduction

One important and interesting question in biology is how genes are regulated. The most important models for gene regulation networks are boolean models and differential equation based models. Boolean models [13, 14, 1] describe the activity of genes using an element of $\mathbb{Z}_2 = \{0, 1\}^n$, that is an $n$ dimensional vector with entries in $\{0, 1\}$. Each entry $x_i$ means the activation of the gene $i$. In the Boolean model we have the vector space $\mathbb{Z}_2^n$ with an attached function $f : \mathbb{Z}_2^n \rightarrow \mathbb{Z}_2^n$. The iteration of $f$ means the time passed. The properties of the digraph associated with these iterations are the characteristics of the network. There are different ways to generalize this model: using more than two possibilities for each gene, and second using several functions for each gene, (PBN). Recently, a new mathematical model Probabilistic Boolean Networks (PBN) was introduced by Ilya Shmulevich, [27]. This model introduced the probabilistic behavior in Boolean networks and has been used to predict the steady states of genetic networks in cancer cells, [28]. For other mathematical models see [12].

If we assume that a gene has more than two levels of possibilities which are determined by the environment and the concentration of a particular substance in the network, then the activity of a gene $i$ is taken from the set of natural numbers $\{0, 1, \ldots, m - 1\}$, where $m > 1$, [23, 24]. One of the problem to study genetic networks with more than two possibilities for each gene is to find a good way to describe the functions in the net. There are polynomial representations for this functions over a finite field and one of the most important results using the techniques of Computer Algebra is that we can find all the polynomial solutions. This ideas appeared for a first time in the Seminar of Reinhard Laubenbacher in Virginia Bioinformatic Tech [17, 18]. In [2], these functions are called partially
defined functions and study over a finite field of \( p^n \) elements. In [9, 10], it is proved that there exist polynomials solutions.

The theory of sequential dynamical systems (SDS) was first introduced in [6, 7, 8] as a mathematical abstraction of a simulated system by a computer. In [15, 16], Laubenbacher and Pareigis introduced a categorical framework for the study of SDS. In this paper, we describe a particular SDS for genetic networks. In addition, we present a mathematical background to use in the study of the Finite State Linear Model introduced by Brazma and Schlitt, [4]. Using partially defined function and the polynomial solutions we present a mathematical particular example over a finite field of three elements.

This paper is organized as follow, in section 2, we describe the ideas of the Finite State Linear Model for Gene Regulation Networks introduced by Alvis Brazma in [3, 4], and introduce a notation slightly different from the one used in [3, 4]. In section 3, we compare the definitions of SDS ([16]), and the definition of parallel dynamical systems. In section 4, we define two different models: the first describes the mathematical aspects of the Brazma Model and the second (genetic sequential dynamical system) generalizes the Brazma model.

2. Finite state linear model

Gene expression is a two-step process: first, a single stranded messenger RNA (mRNA) is copied (transcribed) from the strand of a duplex DNA molecule that encodes genetic information. In the second step, the mRNA moves to the cytoplasm, is complexed to ribosomes, and its genetic information is translated into the amino acid sequence of a polypeptide.

The model (FSLM) in [4] considers the following definitions of a gene (Section 3.3, [5]) and gene regulation networks (Section 4.3, [5]).

**Definition 2.1.** A gene is a continuous stretch of a genomic DNA molecule, from which a complex molecular machinery can read information (encoded as a string of A, T, G, and C) and make a particular type of a protein or a few different proteins.

Transcription factors control a gene expression by binding the gene’s promoter and either activating (switching on) the gene’s transcription, or repressing it (switching off). Transcription factors are gene products themselves, and therefore in turn can be controlled by other transcription factors. Transcription factors can control many genes, and some (probably most) genes are controlled by combinations of transcription factors. Feedback loops are possible. Therefore we can talk about gene regulation networks. Understanding, describing and modelling such gene regulation networks are one of the most challenging problems in functional genomics.

Now, we introduce the notation that we use in this paper. The network has \( n \) genes \( G_1, \ldots, G_n \). The binding sites are stages of the processes of transcription of a particular gene \( G_j \), denoted by \( B_{j1}, \ldots, B_{jm_j} \). Each binding site \( B_{jk} \) is determined by the concentration \( c_j(t) \) at time \( t \), of a particular substance \( i_j \) associated with or generated by a gene \( G_j \). There are two constants for each state of the binding site \( B_{jk} \), \( a_{jk} \) and \( d_{jk} \), called association and dissociation constants respectively. That is, taking the real number \( c_{jk}(t) \) and depending on its relation to \( a_{jk} \) and \( d_{jk} \), we give a state for the binding sites \( B_{jk} \). Each binding site \( B_{jk} \) can take a finite number of possibilities. For understanding the problem, \( B_{jk} \) is taking as a
finite subset of the set of the integers \( \mathbb{Z} \). Let denote by \( b_{jk} \in \mathbb{R} \) a state of \( B_{jk} \). In FSLM, they called \( B_{jk} \) a multistate binding site, and the vector \( b_j = (b_{j1}, \ldots, b_{jm}) \) a binding site vector. The set of all possible vectors \( b_j \) is the environment of the gene \( G_j \), that is

\[
B_j = B_{j1} \times \cdots \times B_{jm_j} \subset \mathbb{Z}^{m_j}.
\]

For each gene, there is a function \( F_j \) (the control function). Its inputs are the states of the binding sites, \( B_j \). The function \( F_j \) takes one of the values of the binding sites, but the output is the production of a substance at a given rate which can act again over all the binding sites. Therefore we consider the control functions \( F_j : B_j \to B_j \), whose output, a vector of \( B_j \), changed by the production of a substance. The production of the substance is given by another function \( c_j : \mathbb{R} \to \mathbb{R} \).

They make the following assumptions:

1. The activity of a gene is determined by the state \( b_j \in B_j \) of transcription factor binding sites in its promoter regions.
2. Each binding site can be in one of a finite number of states, characterized by having or not having bound a particular transcription factor (\( B_j \) is a finite set).
3. The state \( b_{jk} \) of a binding site \( B_{jk} \) depends on the concentration \( c_{j}(t) \) of the respective transcription factors.
4. Depending on the state \( b_j \) of the binding site \( B_j \) a gene can either be silent or have a particular activity level.
5. If a gene \( G_j \) is active, the concentration \( c_{j}(t) \) of the substance \( i_j \) that it produces is linearly growing with a particular rate, otherwise it is decreasing (or stays at 0).

Their multistate generalization is the following:

(a) A binding site can competitively bind more than one substance and therefore can have more than two states.
(b) A gene can have more than two levels of activity.
(c) A control function is not a boolean function, but a mapping which maps a vector of integers into an integer.

In FSLM model, multiple transcription factors can act on several binding sites to produce a finite output state for a gene. The finite output state translates to a particular growth or decrease rate (real valued) for a gene product. Transcription factors are gene products like any other gene product, and are measured with a real-valued concentration \( (c_{j}(t)) \). The concentration of transcription factors determines the finite state of each binding site. Time in the model is continuous, but measurements are made at a finite number of discrete intervals. The measurements that are performed is of the concentration of the gene products.

This model is a simplification of the true biological process in which the RNA produced by transcription is later translated into proteins which have their own rate of decay. Proteins and other cellular species can also interact and activate or deactivate each other besides interacting with the binding sites.

This model has two aspects. One is discrete, given by the control functions. But, the production of the substance at a given rate is continuous.
3. Sequential Dynamical Systems

For better understanding the next section we recall some definitions of graphs and sequential dynamical systems [16].

Let \( X \) be a set. Let \( \mathcal{P}^2(X) \) be the set of all two-element subsets of \( X \).

**Definition 3.1.** A (loop free, undirected, finite) graph \( G = (V_G, E_G) \) consists of a finite set \( V_G \) of vertices and a subset \( E_G \subseteq \mathcal{P}^2(X) \) of edges.

Let \( G \) be a graph. A 1-neighborhood \( N(a) \) of a vertex \( a \in V_G \) is the set \( N(a) := \{ b \in V_G | \{a, b\} \in E_G \text{ or } a = b \} \).

Let \( V_G = \{ a_1, \ldots, a_n \} \). Let \( (k[a_i], a_i \in V_G) \) be a family of sets. Define \( k^n := k[a_1] \times \cdots \times k[a_n] = \prod_{a_i \in V_G} k[a_i] \), the set of global states of \( G \).

**Definition 3.2.** A function \( f : k^n \to k^n \) is called local at \( a_i \in V_G \) if \( f(x_1, \ldots, x_n) = (x_1, \ldots, x_i-1, f^i(x_1, \ldots, x_n), x_{i+1}, \ldots, x_n) \), where \( f^i(x_1, \ldots, x_n) \in k[a_i] \) depends only on the variables in the 1-neighborhood \( N(a_i) \) of the vertex \( a_i \).

**Definition 3.3.** A sequential dynamical system (SDS), \( F = (Y, (k[a_i]), (f_i), \alpha) \) consists of

1. a finite graph \( Y \) with \( n \) vertices,
2. a family of sets \( (k[a_i], a_i \in V_Y) \) in \( Z \),
3. a family of local functions \( (f_i : k^n \to k^n, \text{ where } f_i \text{ local at } a_i) \),
4. and a word \( \alpha = \alpha_Y = (\alpha_1, \ldots, \alpha_r) \in V_Y^* \) in the Kleene closure of the set of vertices \( V_Y \), called an update schedule (i.e. a map \( \alpha : \{1, \ldots, r\} \to V_Y \)).

The world \( \alpha \) is used to define the global update function of an SDS as the function \( F = f_{\alpha_r} \circ \cdots \circ f_{\alpha_1} : k^n \to k^n \).

The length of the update schedule \( \alpha = (\alpha_1, \ldots, \alpha_r) \) is \( r \). The global update function of an SDS defines its dynamical behavior, properties of limit cycles, transients, etc..

**Definition 3.4.** A parallel dynamical system or a finite dynamical system is a function \( F : k^n \to k^n \).

**Remark 3.5.** Every parallel system can be represented as a sequential system by doubling the number of nodes and first copying the old states to the new variables. Conversely, after compose all the local update functions in a sequential system, then the global update function \( F : k^n \to k^n \) has coordinate functions (different from the local update functions in general), and we can think of the system as being a parallel system given by the coordinate functions. So the two representations are equivalent. If the system one wants to model is naturally sequential, then the representation as an SDS is generally better because it makes important system properties explicit.
4. Two models

In this section we define two models for genetics networks. First we introduce the definition of a translated function.

**Definition 4.1.** A vector function $\delta_{fg} = (\delta_1, \ldots, \delta_n) : \mathbb{R}^n \to \mathbb{Z}^n$ is a translated function between two vector functions $g = (g_1, \ldots, g_n) : \mathbb{R}^n \to \mathbb{R}^n$, and $f = (f_1, \ldots, f_n) : \mathbb{Z}^n \to \mathbb{Z}^n$ if:

$$\delta_i \circ g_i = f_i \circ \delta_i, \text{ for all } i = 1, \ldots, n.$$ 

That is, if the following diagram commute

$$\mathbb{R}^n \to g \mathbb{R}^n \delta \downarrow \delta \downarrow \mathbb{Z}^n \to f \mathbb{Z}^n$$

**Definition 4.2.** A finite state model (FSM) $\Gamma = \{Y, (B_j), (F_j), (c_j), \delta_{Fc}\}$, consists of

1. a finite graph $Y$ with $n$ vertices, $Y$ is the supported graph of relations between the $n$ genes $G_j$ with vertices $V_Y = \{g_1, \ldots, g_n\}$,
2. a family of finite sets $B_j$ (binding sites), for each $g_j \in V_Y$,
3. a vector function $F = (F_1, \ldots, F_n) : \prod_{j=1}^n B_j \to \prod_{j=1}^n B_j$ such that $F_j : \prod_{j=1}^n B_j \to B_j$,
4. a vector function $c = (c_1, \ldots, c_n) : \mathbb{R}^n \to \mathbb{R}^n$, where $\mathbb{R}$ is the set of real number,
5. a translated function $\delta_{Fc}$ between the two vector functions.

**Definition 4.3.** Let $\{t_0, t_1, \cdots, t_n\}$ be a set of real numbers, such that $t_0 < t_1 < \cdots < t_n$. Let $(a_0, b_0), (a_1, b_1), \ldots, (a_n, b_n)$ be $n + 1$ pair of real numbers. Suppose that

$$a_0 t_1 + b_0 = a_1 t_1 + b_1$$
$$a_1 t_2 + b_1 = a_2 t_1 + b_2$$
$$\ldots$$
$$a_{n-2} t_{n-1} + b_{n-2} = a_{n-1} t_{n-1} + b_{n-1}$$

We call the function

$$c(t) = \begin{cases} 
0 & \text{if } t < t_0 \text{ or } t > t_n \\
 a_i t + b_i & \text{for } t \in [t_i, t_{i+1}], i = 0, 1, \ldots, n-1
\end{cases}$$

a sectional linear function.

As a consequence of section 2 we have proved part of the following theorem.

**Theorem 4.4.** Brazma-Schillt Model is a finite state model, where the functions $c_j$ are sectional linear functions.

**Proof.** Here, we only need to see that the functions $c_j$ give the concentration of the substance. $\square$

We assume the following:

1. there are $n$ genes in the network $N$,
2. for each $1 \leq j \leq n$ we have $m_j \in \mathbb{Z}^+$ binding sites $\{B_{j1}, \ldots, B_{jm_j}\}$,
3. $B_{jk}$ is a finite set, and $B_{jk} \subset \mathbb{Z}$, for all $j$, and $k$. 


(4) one gene can be interact with another gene, and we describe this situation by a graph $Y$, with set of vertices $V_Y = \{g_1, \ldots, g_n\}$.

(5) the environment of the network $N$ is the set

$$B = \prod_{j=1}^{n} B_j,$$

where $B_j = B_{j1} \times \cdots \times B_{jm_j}$.

(6) for each gene $g_j$ we have a local function, $F_j : B \rightarrow B$, in the sense of Definition 3.2.

For all function $F : \mathbb{Z}^n \rightarrow \mathbb{Z}^n$, we define the coordinated functions $F_i$ as follows:

$$F(x_1, \ldots, x_n) = (F_1(x_1, \ldots, x_n), \ldots, F_n(x_1, \ldots, x_n)).$$

**Definition 4.5.** A genetic sequential dynamical system (GSDS) consists of $\mathcal{F} = (Y, (B_j), (f_j), (c_j), \alpha, \delta)$, where

1. $Y$ is the support graph of relations between genes with vertices $V_Y = \{g_1, \ldots, g_n\}$,
2. $B_j$ is a finite set, for all $j$, and $B = \prod_{j=1}^{n} B_j$,
3. a family of local functions $f_j : B \rightarrow B$, (genetic functions),
4. a word $\alpha$ with the order of interaction of functions, that is a function $F = f_{\alpha(n)} \circ \cdots \circ f_{\alpha(1)} = (F_1, \ldots, F_n) : \mathbb{Z}^n \rightarrow \mathbb{Z}^n$
5. a vector function $c = (c_1, \ldots, c_n) : \mathbb{R}^n \rightarrow \mathbb{R}^n$,
6. a translated function $\delta_F c$.

**Definition 4.6.** A genetic network is a pair $\Gamma = (F, c)$. A genetic network is compatible if there exists a translated function $\delta_F c$.

**Theorem 4.7.** The genetic sequential dynamical system is a generalization of the Brazma-Schlitt model.

**Proof.** In order to prove the theorem, we see how all the considerations of Brazma-Schlitt (BS) model are included in the definition of GSDS.

The interaction between genes is given by a graph $Y$ with $n$ vertices $g_1, \ldots, g_n$ and an edge $\{g_i, g_k\}$ if the gene $i$ has any relation with the gene $k$. So, we have the first condition of Definition 4.5.

We can observe that in Definition 2.1 a gene in action is a complex molecular machinery. So a gene is a function that can read information and make a particular type of protein. Where does a gene read the information? In the binding sites $B_j$ and the protein again changes the environment $B_j$. The Brazma model considers functions $F_j$ from $B_j$ to $B_j$. Since the protein can make changes in the 1-neighborhood, the genetic function $F_j$ is from $B$ to $B$, and it is a local function.

In the BS model, the binding sites are finite sets. So, we have conditions 2, and 3.

The genes act in an order, which implies an order in the composition of those genetic functions. Thus condition 4 holds.

The inclusion of a family of functions $(c_j)$ and the translated functions in the definition of GSDS gives the possibility to see the continuous and discrete sides of the genetic networks.

Then our claim holds.
5. Examples

In all the examples, we obtained the functions using partially defined functions and polynomial representation, see [2].

Example 5.1. We describe the Boolean model presented in [11, 21] using a GSDS. In this example the data is given with discrete values: 0 and 1.

\[ g_1 \rightarrow g_3 \]

(1) The digraph: \( Y \) \( \searrow \) \( \swarrow \) \( g_0 \rightarrow g_2 \)

(2) \( X = \mathbb{Z}_2 = \{0, 1\} \).

\[ f_0(x_0, x_1, x_2, x_3) = (1, x_1, x_2, x_3) \]

\[ f_1(x_0, x_1, x_2, x_3) = (x_0, 1, x_2, x_3) \]

\[ f_2(x_0, x_1, x_2, x_3) = (x_0, x_1, x_0 x_1, x_3) \]

\[ f_3(x_0, x_1, x_2, x_3) = (x_0, x_1, x_2, x_1(x_2 + 1)) \]

(3) The functions are the following:

(4) The schedule \( \alpha = \begin{pmatrix} 0 & 1 & 2 & 3 \\ 3 & 2 & 1 & 0 \end{pmatrix} \).

(5) The global function \( f = f_0 \circ f_1 \circ f_2 \circ f_3 : X^4 \rightarrow X^4 \),

\[ f(x_0, x_1, x_2, x_3) = (1, 1, x_0 x_1, x_1(x_2 + 1)) \].

We can observe that if we change the order we can not obtain the same function.

Remark 5.2. If we have only three states for genes we have the finite field \( \mathbb{Z}_3 = \{-1, 0, 1\} \), that is the integers modulo 3, with \( 1 + 1 = -1 \). If we have four possible states for genes we can use a finite field with 4 elements. A finite field \( GF(4) \) can be represented as: \( GF(4) = \{0, 1, \alpha, \alpha^2\} \), where \( \alpha \) is a root of the polynomial \( z^2 + z + 1 \), that is \( \alpha^2 = \alpha + 1 \) (with coefficients in \( \mathbb{Z}_2 = \{0, 1\} \)). We denote \( 0 = 00, 1 = 01, \alpha = 10, \alpha^2 = 11 \), then the operations + and \( \times \) are the follows:

| + | 00 | 01 | 10 | 11 |
|---|---|---|---|---|
| 00 | 00 | 01 | 10 | 11 |
| 01 | 01 | 10 | 11 | 00 |
| 10 | 10 | 11 | 00 | 01 |
| 11 | 11 | 10 | 01 | 00 |

| \( \times \) | 00 | 01 | 10 | 11 |
|---|---|---|---|---|
| 00 | 00 | 00 | 00 | 00 |
| 01 | 01 | 01 | 01 | 11 |
| 10 | 10 | 11 | 00 | 01 |
| 11 | 11 | 10 | 01 | 00 |

Example 5.3. We describe the example which appear in [12] of the generalized logical method developed by Thomas and colleagues [23]. Here we use the FSM and in this case it is not linear and we have the data with two or three values in the integers. We have three genes, and the regulatory network is the following:

\[ g_3 \circ \]

(1) The digraph: \( Y \) \( \searrow \) \( \swarrow \) \( g_1 = g_2 \)

(2) For genes \( g_1 \) and \( g_3 \) we have \( Z_3 = \{0, 1, 2\} \), and for gene \( g_2 \) we have \( X_2 = \{0, 1\} \).

(3) The functions are:

\[ f_1(x_1, x_2, x_3) = -x_2 \]

\[ f_2(x_1, x_2, x_3) = 1 + x_1^2 x_3^2 \]

\[ f_3(x_1, x_2, x_3) = 2 + x_1 + 2x_3 + x_1 x_3 + 2x_1^2 + x_3^2 + 2x_1^2 x_3 + 2x_1 x_3^2 + x_3^2 x_3^2 \]

(4) The global function

\[ F = (f_1, f_2, f_3) : Z_3 \times X_2 \times Z_3 \rightarrow Z_3 \times X_2 \times Z_3 \]
On the other hand, we will assume that the average concentration level of each gene $j$ by $c_j(t)$:

\[
\begin{array}{ccc}
t & G_1 & G_2 & G_3 \\
0 & c_1(0) = 0.5 & c_2(0) = 1.2 & c_3(0) = 0.5 \\
1 & c_1(1) = 0.78 & c_2(1) = 1.2 & c_3(1) = 1.25 \\
2 & c_1(2) = 1.5 & c_2(2) = 1.2 & c_3(2) = 1.5 \\
3 & c_1(3) = 0.5 & c_2(3) = 1.2 & c_3(3) = 0.5 \\
\end{array}
\]

The vector of concentrations is $c(t) = (c_1(t), c_2(t), c_3(t))$, and if we suppose that the functions $c_j$ are sectional linear functions then

\[
c(t) = \begin{cases} (0.28t + 0.5, 1.2, 0.75t + 0.5), & \text{when } t \in [0, 1] \subset \mathbb{R} \\ (0.72t + 0.06, 1.2, 0.25t + 1), & \text{when } t \in [1, 2] \subset \mathbb{R} \\ (-t + 3.5, 1.2, -t + 3.5), & \text{when } t \in [2, \infty) \subset \mathbb{R} \end{cases}
\]

On the other hand, we will assume that the average concentration level of $G_1$ is 0.78, $G_2$ is 0.75, and $G_3$ is 1.5. So, we give values to the states of genes $G_1$, $G_2$, and $G_3$.

\[
\delta_1 : \{ \text{less than } 0.78 \mapsto -1, \ 0.78 \mapsto 0, \ \text{more than } 0.78 \mapsto 1 \} \\
\delta_2 : \{ \text{less than } 0.75 \mapsto -1, \ 0.75 \mapsto 0, \ \text{more than } 0.75 \mapsto 1 \} \\
\delta_3 : \{ \text{less than } 1.25 \mapsto -1, \ 1.25 \mapsto 0, \ \text{more than } 1.25 \mapsto 1 \}
\]

We suppose that we have for each gene $G_j$ a binding site $B_j = X = \{-1, 0, 1\}$, and we consider the operations in the finite field $X = \mathbb{Z}_3$. Our problem is the following: we know $c(t)$ by microarray experiment, we suppose the vector $c(t)$ is a vector of sectional affine functions, but we want to obtain a function $f$ such that $f(-1, 1, -1) = (0, 1, 0)$ for $t = 1$, $f(0, 1, 0) = (1, 1, 1)$ for $t = 2$, and $f(1, 1, 1) = (-1, 1, -1)$ for $t = 3$. In this case, one of the possible functions is $f(x_1, x_2, x_3) = (x_1 + x_2, x_2, x_3 + x_2)$. In addition, we can obtain a graph $Y$ if we observe how the genes change with the action of $F$.

\[
Y \xrightarrow{g_3 \circ} \\
\xrightarrow{g_1 \rightarrow} g_2 \circ
\]

Now, we have a GS$\mathcal{F} = (Y, \mathbb{Z}_3; \{f_j\}, (\delta_j), (c_j), \alpha)$ for this dataset:

1. a collection $x_1, x_2, x_3$ of variables, which take on values in a finite field $X = \mathbb{Z}_3$.
2. $Y$ is the support directed graph of relations between genes with vertices $\{g_1, g_2, g_3\}$.
3. for each $j = 1, 2, 3$, the local update functions $f_1(x_1, x_2, x_3) = (x_1 + x_2, x_2, x_3)$, $f_2(x_1, x_2, x_3) = (x_1, x_2, x_3)$, and $f_3(x_1, x_2, x_3) = (x_1, x_2, x_2 + x_3)$.
4. a schedule $\alpha = \begin{pmatrix} 1 & 2 & 3 \\ 1 & 2 & 3 \end{pmatrix}$,
5. the global function $f = f_3 \circ f_2 \circ f_1 : X^3 \rightarrow X^3$ obtained by the schedule $\alpha$,
6. a vector function $c(t) = (c_1(t), c_2(t), c_3(t))$,
7. the translated functions $\delta_j$. 
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Department of Physics-Mathematics, University of Puerto Rico, Cayey, PR 00736

*E-mail address: m_avino@cayey1.upr.clu.edu*

Programmer-Archaeologist High Performance Computing Facility, University of Puerto Rico, [http://www.hpcf.upr.edu/~humberto/](http://www.hpcf.upr.edu/~humberto/)

*E-mail address: humberto@hpcf.upr.edu*

Department of Mathematics, and Computer Sciences, University of Puerto Rico

*E-mail address: moreno@uprr.pr*