A discrete event system specification (DEVS)-based model of consanguinity

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A B S T R A C T

Consanguinity or inter-cousin marriage is a phenomenon quite prevalent in certain regions around the globe. Consanguineous parents have a higher risk of having offspring with congenital disorders. It is difficult to model large scale consanguineous parental populations because of disparate cultural issues unique to regions and cultures across the globe. Although consanguinity has previously been studied as a social problem, it has not been modeled from a biological perspective. Discrete event system specification (DEVS) is a powerful modeling formalism for the study of intricate details of real-world complex systems. In this paper, we have developed a DEVS model to get an insight into the role of consanguineous marriages in the evolution of congenital disorders in a population. As proof-of-concept, we further developed a consanguinity simulation model in Simio simulation software. Simulation results validated using population growth data show the effectiveness of this approach in the modeling of consanguinity in populations.

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1. Introduction

A consanguineous or inter-cousin marriage is a cultural tradition in many societies around the world (Al-Awadi et al., 1985). A consanguineous marriage is formally defined as a marriage which is "solemnized among persons descending from the same stock or common ancestor with close biological relations" (Mehndiratta et al., 2007). Although consanguinity may have some positive effects such as increase in specific measures of population fitness (Denic et al., 2008), primarily, it has been known to lead to an increased rate of birth defects, manifesting as severe recessive disorders (Modell and Darr 2002; Strømme et al., 2010; Becker 2001; Rudan et al., 2003). Moreover, various studies have pointed out that consanguinity can lower many population fitness factors (Bittles, 2001; Amudha et al., 2005; Bener et al., 2007). Despite this, inter-cousin marriages are prevailing and in fact spreading because of their socioeconomic usefulness amongst diverse populations.

Outside its social and cultural context, consanguinity from a biological perspective has not been modeled in the past. Computational modeling and simulation techniques have previously proven useful in developing insights and understanding of the dynamics of complex biological systems (Meng et al., 2004; Cundiff and Agblevor 1998). Large-scale consanguineous parental population is in essence, a possible domain for the application of simulation. Socially consanguineous population patterns tend to emerge within large segments of geographic areas despite cultural, linguistic and religious heterogeneity (Denic and Nicholls 2007; Imaizumi 1986), thereby making consanguinity modeling a challenging problem. Discrete event system specification (DEVS) formalism (Kim et al., 2001), a formal modeling and simulation framework, has previously been successfully exploited as a framework for modeling complex computer systems and, at times, certain natural and biological systems (Wang 2009; Goldstein and Wainer 2010). However, to the best of our knowledge, DEVS has not been previously used to model consanguinity.

The goal of the present study was to examine the role of consanguineous marriages in causing congenital defects using a modeling and simulation approach. With a dearth of modeling and simulation studies in the domain of consanguinity, there is a need to develop a fundamental formalism for modeling the complex system associated with congenital defect spread due to consanguinity. In this paper, we develop a DEVS framework for the formal modeling of consanguinity. As proof-of-concept, we demonstrate conversion of the formal model into an actual simulation model using Simio simulation software (Pegden 2008). Validation of this model using real-world data shows that DEVS can be used effectively to model biological problems and Simio software can be useful for modeling complex biological and social problems.

2. Background

Consanguinity has been practiced in many cultures to secure certain family benefits such as dissemination of wealth among

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the same family, stability and better future (Modell et al., 1997; Khlat, 1997). However, it has also been well demonstrated that consanguineous unions result in an increased rate of genetic defects in their offsprings (El Mouzan et al., 2008; Tadmouri et al., 2009), including diabetes mellitus, cancers such as that of the cervix and the brain, and coronary artery disease (Rudan et al., 2003; Bener et al., 2007; Rudan, 2006; Denic, 2003). Consanguinity has even been considered to contribute to an increase in incidents of hypertension (Rudan et al., 2003; Charlesworth and Hughes, 1996). These negative health effects of consanguinity are due to single or multiple recessive genes expressed in the offspring (Mehndiratta et al., 2007). Therefore, medically it is suggested that consanguineous marriages should be discouraged to avoid social damages.

The degree of relationship involved in consanguineous marriages affects the rate of birth defects proportionally (Denic and Nicholls, 2007). Three relationship degrees are considered to have deleterious effects on human health that include first, second and third degree genetic associations, as shown in Fig. 1 (County, 1999). The first degree includes a person's parents and children. Siblings, grandparents and grandchildren come under second degree of genetic relatedness, while aunts/uncles, nephews/ nieces, great grandparents and great grandchildren come under the third degree (Fig. 1). First-cousin marriages constitutes higher rate of consanguineous union and share twice the consanguinity (four times the degree of consanguinity of second cousins) as any other degree relationship, and are used as prototypical examples in studies of consanguinity (Denic and Nicholls, 2007). First cousins share 50% genome, similar to their parents. That is why first cousin marriages are more discouraged than second or third degree unions. Carey (2003).

Due to population interactions complexities regarding consanguinity and large number of components involved, it is difficult to effectively study the behavior of consanguineous population along with congenital disorders. Many statistical studies have been conducted to study these interactions, but these studies have provided limited information regarding the resultant effects of consanguinity on a given population (Imaizumi, 1986; Hader et al., 2010; Jaber et al., 1994). A few

studies regarding simulation of consanguinity networks exist (White, 1999, 2004), but they have treated consanguinity as a social problem rather than a biological one. Since modeling and computer simulation techniques have previously proven useful for developing an understanding of the dynamics of complex biological systems (Ermentrout and Edelstein-Keshet, 1993; Saiz and Klein, 2002); therefore this approach has been used to examine consanguinity in this study.
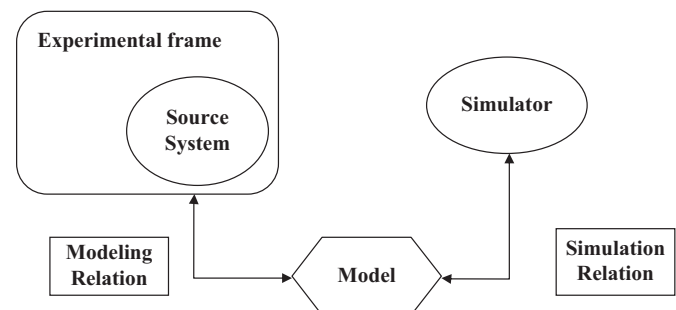
2.1. Modeling and simulation

Modeling is the process of producing models for a simulation study (Maria, 1997). The main focus of modeling is on the input and output signal relation instead of detailed dynamics within the system (Jauhiainen, 2005). Simulation is a tool which is used to simulate an abstract model or generate behavior of a particular system. Simulations are implemented with the help of a simulator software. If a model is a set of mathematical instructions, then simulator is a software which is used to execute these instructions and generate the behavior of the system of interest (Fig. 2) (Zeigler et al., 2000). The framework of modeling and simulation consists of four main entities (Zeigler et al., 2000):
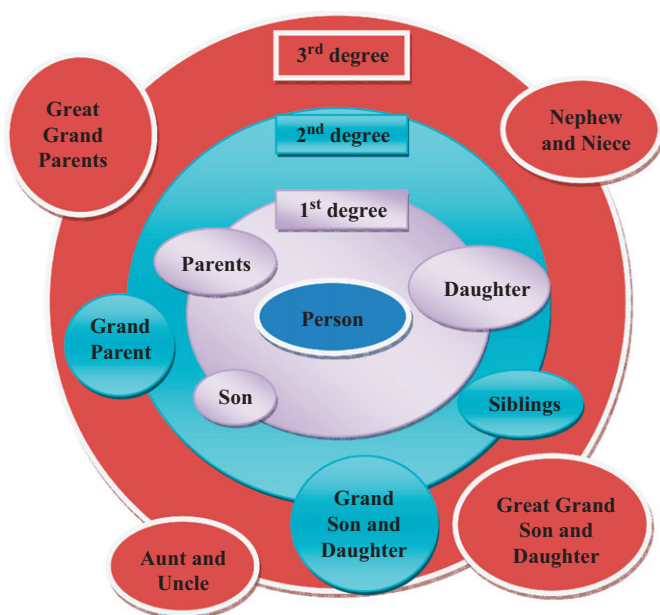
- Experimental frame
- Real/virtual source system to be simulated
- The model
- The simulator

The experimental frame specifies the environment under which the system is tested, while the source system is the environment (either real or virtual) to be modeled from which the data is gathered through observation. The model is a mathematical representation of a system or structure to represent the real world behavior. The simulator is that computational system/ software which obeys instructions of the model and generates behavior shown in Fig. 2 (Zeigler et al., 2000).

The modeling and simulation entities become significant only when they are properly related to each other. "Modeling Relation" shows the relationship between the behavior generated by the model, and how much it agrees with observed system behavior. On the other hand, "Simulation Relation" determines whether the simulator executes the model behavior correctly or not (Zeigler et al., 2000). The framework of modeling includes many system specification formalisms, such as discrete time system specification (DTSS), differential equation system specification (DSS) and discrete event system specification (DEVS). These formalisms help to model systems in the most appropriate and effective manner

Fig. 1. Degree relationships between family members. Each circle represents the degree of consanguinity (genetic relatedness) with the person in the middle of the figure. (Figure modified from County (1999).)

Fig. 2. The basic entities in modeling and simulation and their relationship to each other. Experimental frame specifies the conditions or environment in which system is experimented with, source system is the real or virtual system which is to be modeled, model is a mathematical representation of any system or structure, data is usually gathered by observing it and simulator is a software which follows model instructions and generate particular behavior of a real system.

during early development at the requirements and specification levels (Zeigler et al., 2000).

Modeling and computer simulation techniques have previously proven useful for understanding the dynamics of complex systems such as in *ad-hoc* and P2P networks (Niazi and Hussain, 2009), wireless sensor networks (Niazi and Hussain, 2011), detection of emergent behavior (Niazi and Hussain, in press), breast cancer research (Siddiqa et al., 2009; Mukhopadhyay et al., 2010), viral infections (Itakura et al., 2010), etc. Recently, DEVS formalism has been used as a specification framework to model natural or biological systems effectively, such as interactions in nerve cells and geographic distribution of adult Mediterranean fruit fly (Goldstein and Wainer, 2010; Bernardi et al., 2003). Therefore, in this study, we used the DEVS formalism to model potential effects of consanguinity in causing congenital defects.

2.2. Discrete event system specification

DEVS is a formal mathematical framework which is used to design models for discrete event simulation (Zeigler et al., 2000). DEVS models are usually described as either atomic or coupled models which are defined as tuples:

$(X, Y, S, \delta\text{ext}, \delta\text{int}, \lambda, \text{ta})$ [Atomic model]

$(X, Y, D, \{Mi\}, \{Ii\}, \{Zi, j\}, \text{select})$ [Coupled model]

Behavior specification of a component within a system is defined by the atomic DEVS model. Component's behavior specification is based on the time advance function ta(s), which keeps on changing after certain time period; therefore, it changes the initial state, s, of the component's behavior. During this constant time period, if any external event occurs and is received by the component as input, then a function, termed as "external transition", is implemented for the specific identification of the model's new transitioned state. Alternatively, if no external input enters in the component state and ta(s) defined time also passes by, then another function namely λ is called out which displays the output. After the display of output of the current state, the transition function is again executed to find the possible next component state of the generated model (Zeigler et al., 2000).

DEVS's coupled model is based on several small components (models), termed *Mi*. These small models are connected to each other in a way that the output of one model acts as an input of some other model module {*Ii*}. A defined function, *Zij*, reads and understand the output from a component i and then makes it compatible for another component j as an input. This is termed as the coupling mechanism of the DEVS coupled model. The transition functions of the embedded models actively participate in changing the state of events; therefore a tiebreaking selector is used which helps in maintaining the order so that only one transition function remains on, and when the coupling is over, then the other transition function is prompted. Thus, a general statement can be made that under the coupled DEVS model, several atomic DEVS models can be embedded (Zeigler et al., 2000).

The major strategy behind DEVS is that the model and simulator work separately and the simulator does not depend on the model in a sense that it can run simulations regardless of what DEVS model represents (Goldstein and Wainer, 2010). DEVS formalisms are developed to improve system reliability, design time and comprehensibility (Wasserman, 1977). Therefore, DEVS formalism provides a good framework to model consanguinity as a risk factor for many congenital disorders because it supports hierarchical and modular coupling construction for discrete events (Shang and Wainer, 2006). The impact of consanguinity as a genetic risk factor has not previously been modeled using formal methods. Therefore, our aim was to provide a DEVS framework to model consanguinity followed by conversion of DEVS model in simulation using Simio software and its validation.

2.3. DEVS in relation to other approaches

For the specification of model frameworks, various formalisms have been in use for decades. For example, Petri Nets (Kartson et al., 1994), Discrete Time Specification (Zeigler et al., 2000), Finite State Automata (Mohri, 1996) and Queuing Networks (Reiser and Kobayashi, 1975) have been widely used to specify system properties. In case of Discrete Time Specification (DTSS) formalism, inconsistency in the system state specifications is the major drawback because it treats time variable as a constant number, whereas in contrast, a real world system continuously changes with time. DEVS formal model specification framework, which uses mathematical notations to specify a system's behavioral characteristics, overcomes this problem by mainly focusing on the time "t" variable, whose value continuously changes like other variables in a system. It does so by separating the system states and constant states by using transition functions which calculate constant states from current system states. DEVS maintains separation between the simulators and models to handle system state and constant state complexity.

For the modeling of complex biological systems, various statistical and computational methods are in use, but the development of complex models that can be used to simulate data is not always intuitive. There are certain reasons why we used DEVS approach to model consanguinity instead of using statistical and other computational approaches which are elaborated below.

2.3.1. DEVS vs. statistical distributions

We used DEVS formalism to model consanguinity system. It is well known that statistical distributions cannot handle heterogeneities or micro behaviors of a system whose behavior and structure is not completely understood (Dutilleul and Legendre, 1993). DEVS applies mathematical modeling for handling heterogeneous data, as demonstrated by Zeigler et al. (2000). They reasoned that DEVS data is represented in the form of a model in which one can observe the system state at any point and at any given time (Zeigler et al., 2000). This is not the case with statistical tests since the intermediate values obtained through them do not provide any significant information as they are based on certain formulas (Lepetit et al., 2005). Hence, whole test statistical distributions provide results in the form of a concrete estimated value or percentage, and although they have proved effective, they are too slow for real-time use. Using DEVS, ongoing experiments can be viewed theoretically at any step of the integrated subsystems (Zeigler and Sarjoughian, 2002), while in case of statistical tests, it is difficult to estimate the value of states that are continuously changing with respect to time (Uther and Veloso, 1997). Beside these reasons, many algebraic notations do not include the time element that DEVS inherits from its system theoretic origins.

2.3.2. DEVS vs. genetic algorithms

Genetic algorithms (GA) are based on the theory of evolution (Mitchell, 1998). The basis of this approach is that evolution always leads towards the survival of the fittest, but in case of consanguinity, it does not always go towards fitness and in fact has many harmful effects. Thus, even though in the case of malaria, it has been shown that consanguinity provides benefits by congregating malarial resistant genes in offspring (Denic and Nicholls, 2007), a slew of other studies have shown the harmful effects of consanguinity in the form of inheritance of abnormalities which pass from generation to generation (Rudan et al., 2003; Bener et al., 2007). Additionally, genetic algorithms have difficulty in handling two different state spaces at the same time, whereas DEVS framework can handle many

scenarios of a system simultaneously by formally representing their structures (Close et al., 2002).

It is also unreasonable to use genetic algorithms to study consanguinity because GA works by its own internal rules which cannot predict system behavior without testing them first on a simulation model (Eoyang, 1996). On the other hand, DEVS framework can easily predict system behavior by changing its theoretical rules according to the particular system (Zeigler and Sarjoughian, 2002). Furthermore, GA uses many methods for selecting fittest populations (Bramlette, 1991), but in consanguinity the focus is not on the selection of the best population; rather, the aim is to determine that certain threshold of consanguinity which could be hazardous for a population depending upon the phenotype being studied.
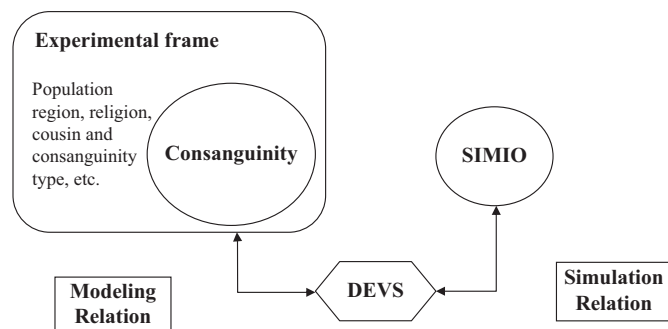
3. Development of the DEVS model of consanguinity

This section describes the DEVS model of consanguinity as a risk factor. As mentioned earlier, framework development of consanguinity system identifies key elements or entities and their relationships. Therefore, first we specified the basic entities of modeling and simulation of consanguinity, i.e., source/real system along with the experimental frame, model and simulator (Figs. 2 and 3). The experimental frame includes region, religion, arranged marriages or self-commitment, % consanguinity, allelic frequency, consanguinity type (i.e., 1st or 2nd degree) and co-efficient of inbreeding. With consanguinity as the source system, the DEVS model and Simio simulator are shown in Fig. 3.

After specifying the entities, the DEVS formalism of consanguinity was built which is described below:

$$M = (X, S, Y, \delta int, \delta ext, \lambda, ta)$$

where M is model representing the overall system; X is the set of input values, i.e., region, religion, arrange/self-commitment, % consanguinity, allelic frequency, consanguinity type and co-efficient of inbreeding; S is the set of states, i.e., Birth event→Marriage event→Birth event→Marriage event. Between these two events, the probability of congenital disorders and deaths are also included; Y is the set of output values, i.e., new populations with probability of congenital disorders due to consanguineous and non-consanguineous marriages; δint is the internal transition function, i.e., if birth event occurs in consanguineous union, then there is a probability of congenital disorder risk and death events; δext is the external transition function, i.e., if male and female populations are available, then consanguineous marriage event will occur; λ output function, i.e., S→Y; and ta is the time advance function, i.e., new births, deaths and marriages per year.

The model begins with a population growth submodel in order to understand how marriage and population growth events occurr, and then focuses on DEVS-based design of consanguinity to demonstrate its complexity. In the population growth model (Fig. 4), initially two populations are used, i.e., male (MP) and female (FP) rather than the whole population to simplify model development and analysis. After separating both populations, marriage events occur followed by population growth. Under population growth, another source of offspring is added to generate children from resulting marriages randomly. This leads to a new population consisting of the number of total marriages and offspring. To simplify its presentation, we focused on the handling of interactions between male and female populations.

The population growth submodel design helped us to expand the model of consanguinity as a risk factor. Next, DEVS-based consanguinity formal model was developed with an embedded population growth submodel (Fig. 5). In DEVS-based consanguinity formal model, initially the whole population (WP) is used and then separated into two groups, i.e., male (MP) and female (FP). This allows us to obtain male and female entities equally for marriage events. After combining both male and female populations, the group is split into two, i.e., consanguineous and non-consanguineous marriages. Consanguineous and non-consanguineous marriages event now occur separately followed by population growth (births). At the end, we obtain a new population with the probability of consanguineous and non-consanguineous marriage and their rate of offspring growth.

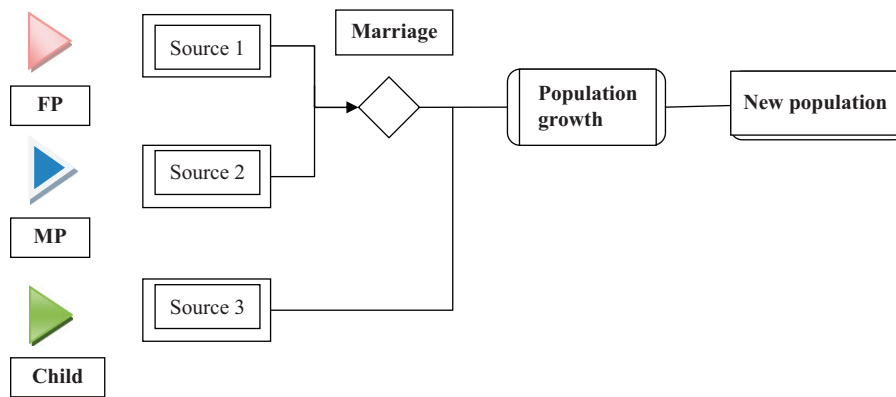Next, we chose a simulation approach to implement the DEVS-based consanguinity model to maximize its utility.

4. Simulation

In the previous sections, we presented basic entities and framework of consanguinity using DEVS formalism. This section will further describe the implementation of consanguinity using the simulation software Simio. Simio makes simulation easier for decision making and enables users to solve more problems, more easily than ever before. It is based on the model object-oriented framework and facilitates building of 3D models (Pegden, 2008). In Simio, the basic concept of object-oriented framework is that classes define the behavior of objects (Pegden, 2008). Those classes, when placed together in a model, result in the emergence of system behavior from previously defined object interactions. Objects can be user-defined and can easily be added and extended in Simio. The basic object types in Simio are (Pegden, 2008):

- Fixed→a fixed location.
- Source→generates entity objects
- Server→models a capacitated process.
- Sink→destroys entities that have finished processing in the model.
- Link→paths between objects.
- Node→intersection between links.
- Agent→unconstrained movement through free-space.
- Entity→an agent that moves across links and enters objects.
- Transporter→an entity that carries other entities.
- Combiner→attaches the batched members to a parent entity.
- Separator→separates batched members to a parent entity or makes copies of entity objects.

4.1. Simulation model of population growth

Model development in Simio begins with a population growth submodel, based on the flow diagram depicted in Fig. 4. Many

Fig. 3. Basic entities of modeling and simulation of consanguinity. This figure shows the main entities of consanguinity model which specifies experimental frame (population, allelic frequency, region, religion, cousin and consanguinity type, etc.), source system (consanguinity), model (DEVS-based) and simulator (Simio simulation software) for DEVS-based model of consanguinity.

Fig. 4. Flow diagram of population growth. This flow diagram shows population growth model which initialized with two populations, i.e., male (MP) and female (FP). After separating both populations, marriage events occur followed by population growth. Under population growth, another source of offspring (child) is added to generate children from resulting marriages randomly. This leads to a new population consisting of the number of total marriages and offspring.
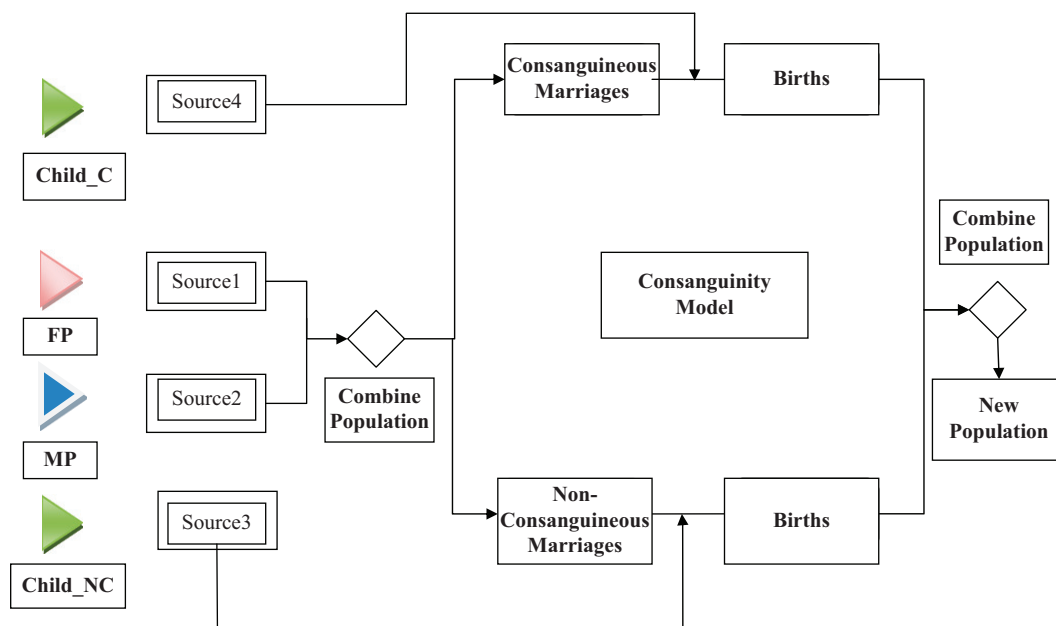

Fig. 5. DEVS-based consanguinity model. Flow diagram of DEVS-based consanguinity model. MP, male population; FP, female population; Children_C, children resulting from consanguineous union; Children_NC, children resulting from non-consanguineous union. This model initiates with male and female populations. After combining these two populations, the group is split into: consanguineous and non-consanguineous marriages. Consanguineous and non-consanguineous marriages event now occur separately followed by population growth (births) which include offspring source to generate children randomly. At the end, a new population with the probability of consanguineous and non-consanguineous populations with their rate of offspring growths are created.

objects are used in this simulation, such as model entities (here entities mean individuals or parents), source, server, combiner, paths and sink which destroy entities. Two source objects are used to create the male and female populations to facilitate the correct manner of handling male and female entities. Then both of the source populations are combined in a 'Combiner' object that takes one of each entity, combines them (marriage), and sends them to Server1 named "Population Growth". Connecting the female-population source to the top entry point of the Combiner and connecting the male-population source to the bottom entry point of the combiner takes a parent and member. In this case, the default batch quantity of '1' is used since we require only one male and one female entity to attach.

To execute "Population Growth" event, a server is used within the "Add-On Process Triggers" section of "Properties", which adds a new logic named a 'Processed'. This directs the user to the "Processes" window with a new process called "Server1_Processed".

Within this process, we can use a 'Create' step to create new entities (offspring) based on a distribution to determine the number of objects to create. When new entities are created, they are sent from the "Created Exit" of the "Create Step" and a "Transfer Step" step (Fig. 6) can be used to transfer them from "free space" (where they are created) to a particular node—in this case, they can be transferred either to the Output@Server1, where they can exit with the parents, or they can be transferred into a "sink" where they can be counted.

In the Simio simulation, for generating offsprings, a "children" entity object (similar to MP and FP) are added that are animated in such a manner that one can see the difference between children and parents. This is not required, but may be desirable at times. To create offsprings, within the "Processes" window, use the "Create Step" to change the "Object Instance Name" to "Children" and "Number of Objects" to "Random.Discrete" distribution based on information provided regarding how many

PopulationGrowth AddOn Processes_____

PopulationGrowth_Processed
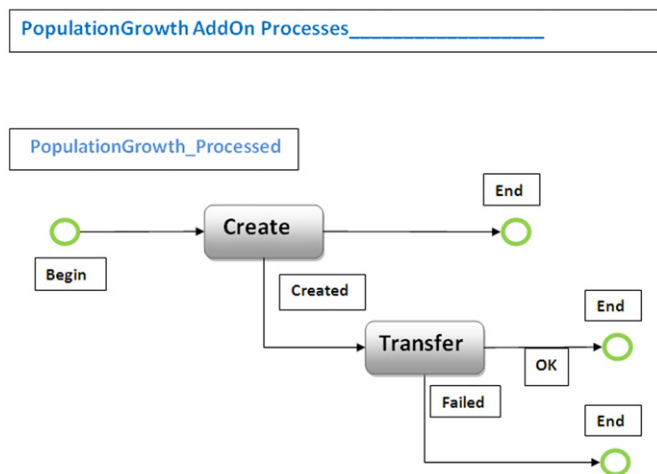
Fig. 6. Add-on process used in the population growth model to create offsprings randomly.
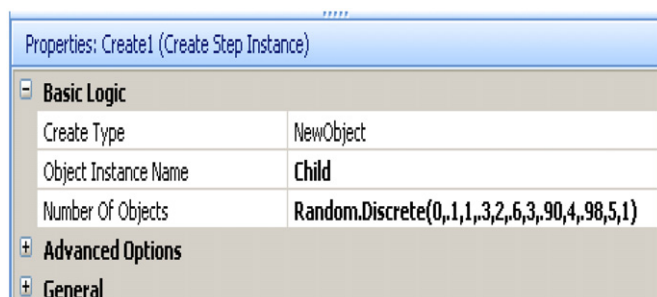
Fig. 7. Snapshot of "Create Step" for random offspring generation. This figure shows the properties for creating offspring randomly. To create offsprings, within the "Processes" window, use the "Create Step" to change the "Object Instance Name" to "Child" and "Number of Objects" to "Random.Discrete" distribution based on information provided regarding how many children per couple to create. For example, this figure shows that 10% of the population has 0 children, 20% has 1 child, 30% has 2 children, 30% has 3 children, 8% has 4 children and 2% has 5.

children per couple to create. For example, Fig. 7 shows that 10% of the population has 0 children, 20% has 1 child, 30% has 2 children, 30% has 3 children, 8% has 4 children and 2% have 5.

To graphically depict children leaving Server1 (population growth) with the parent (instead of them all leaving simultaneously on top of each other), one can change the "Path Allow Passing" property to "False" so they are shown in a line (Fig. 8). Data collected from simulations can provide information regarding the number of offsprings calculated. The parents are never split, as a separator object is not used—but stay together with the animated parent entity.

The population growth model generates male and female entities randomly and then these entities enter into a combiner object that triggers marriage events. The marriage events are followed by population growth (in which a random child population is created) and death event. After that this number is added into the new population (Fig. 9).

4.2. Simulation model of consanguinity

This population growth submodel is further used in an expanded consanguinity model by splitting it into two submodels: consanguineous marriages and non-consanguineous marriages (Fig. 10). In the same way as in the population growth model, the male (MP) and female (FP) population is used followed by the separation of this population into two groups based on

consanguinity. The first group has male (MP_C) and female (FP_C) populations for consanguineous marriages and the second group holds male (MP_NC) and female (FP_NC) population for non-consanguineous marriages. Path weights are used to distribute these population entities accordingly. Then a combiner is used to tie male and female entities together in marriage. After reaching the queue of server named "Population Growth", birth events occur and generate offsprings randomly. The same process takes place with non-consanguineous marriages with resulting birth events. The population is continuously updated based on marriages and generated offsprings (Fig. 10).

To differentiate offsprings which are generated randomly, an "Animation Property" is used which changes the appearance of the child entity. This dynamic property can be applied by using the "Additional Symbol" icon which generates multiple symbols of single entity until the desired number of symbols has been achieved. Two symbols of a single entity to represent male and female children were created in both population growth and consanguinity models (Fig. 11). After creating multiple desired symbols, the "Model Entity Properties > Animation > Random Symbol Property" was set to True, to allow each new object to be randomly assigned a symbol from the "Additional Symbol List".

5. Results and discussion

The consanguinity model thus developed was used to simulate real data for the validity of the model. Simulations were run at least 50 times and the results were exported into an Excel sheet with comprehensive data and statistics regarding the model behavior. Here, we will discuss results with the help of tables generated through Simio pivot grid or reports.

The first step towards testing our model was to validate the population growth model. This was done using data for Saudi Arabia available in the World Factbook (Central Intelligence Agency (CIA), 2006). Data from Saudi Arabia was chosen for the validation purposes since it is a society with high consanguinity rates for which a lot of data was available that we could use for the validation purposes.

5.1. Population growth model validation

We validated our population growth model by plotting the real data of Saudi population from the years 2005–2009 (Central Intelligence Agency (CIA), 2006) side by side with results from simulation of the same data using our population growth model. As can be seen, the predicted population came within 3% of the actual population (Table 1 and Fig. 12), precisely within the margin of error for actual Saudi Arabia population sampling that was ±3% (Central Intelligence Agency (CIA), 2006). Furthermore, plotting of the data with time showed that the growth curves of the predicted and expected populations were the same, revealing an excellent correlation of the expected growth rate with the actual one (Fig. 12).

Similarly, Simio was used to predict the number of male and female members of the Saudi population generated over the period from 2006–2009 using total population data, death rate, and male:female sex ratio from the year 2005 from the World Factbook (Central Intelligence Agency (CIA) 2006). As can be seen (Figs. 13 and 14), the actual and predicted gender-specific ratio observed for the year 2009 was similar in which the male population remained higher than the female population, a trend observed worldwide (Central Intelligence Agency (CIA), 2006). However, in terms of absolute numbers, there was a 14% difference between the predicted and actual gender-specific
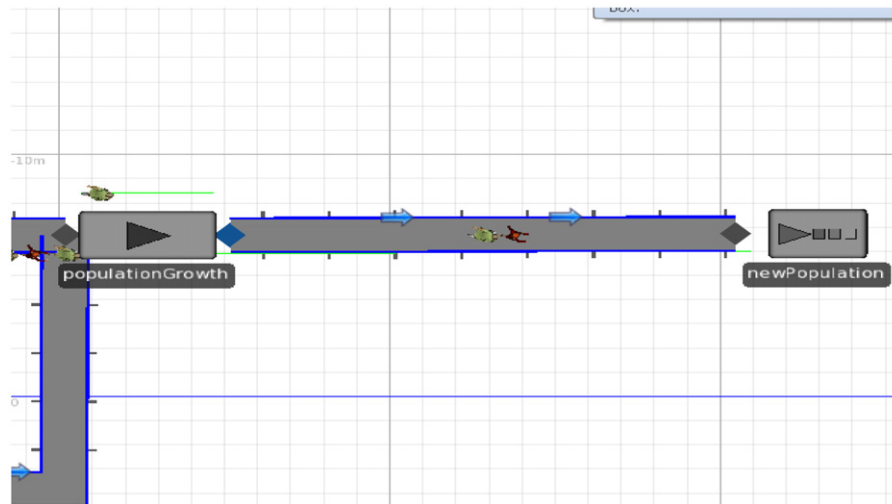
Fig. 8. Parent and offspring move together into a new population object as discrete entities in a line. This figure shows the children leaving the Server1 (population growth) with the parent graphically and then counted in sink object (new population).
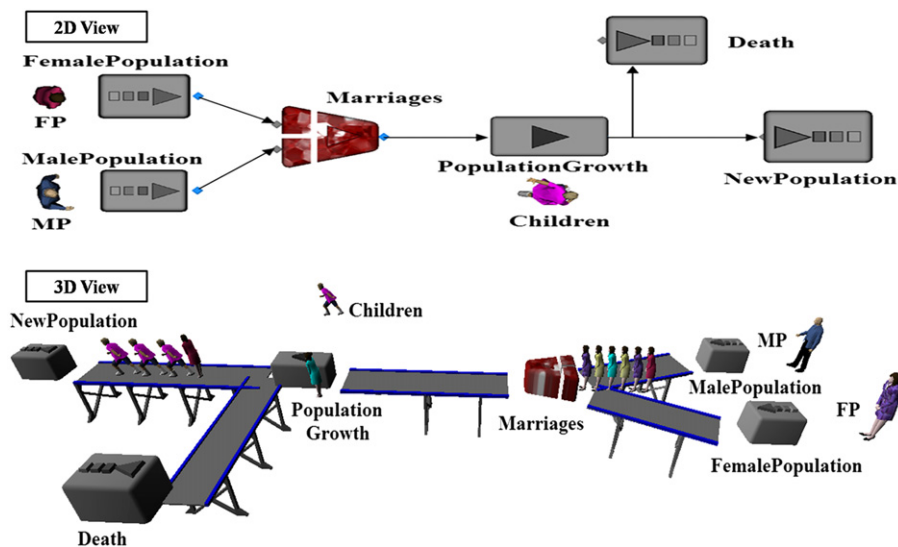
Fig. 9. Two and 3D view of the Simio complete population growth submodel. This figure shows the DEVS-based population growth submodel in 2 and 3D, using Simio simulation software.

population numbers for the year 2009 (UN Statistics Division, 2008), which probably reflects inaccuracies of reporting the actual numbers in the 2009 census, and/or use of sex ratio figures from different studies (World Factbook data (Central Intelligence Agency (CIA), 2006) vs. World Population Prospects (UN Statistics Division, 2008)).

Thus, test of our population growth model revealed that overall its simulation reflected real world data trends, and can be used for further simulation of consanguinity in a population.

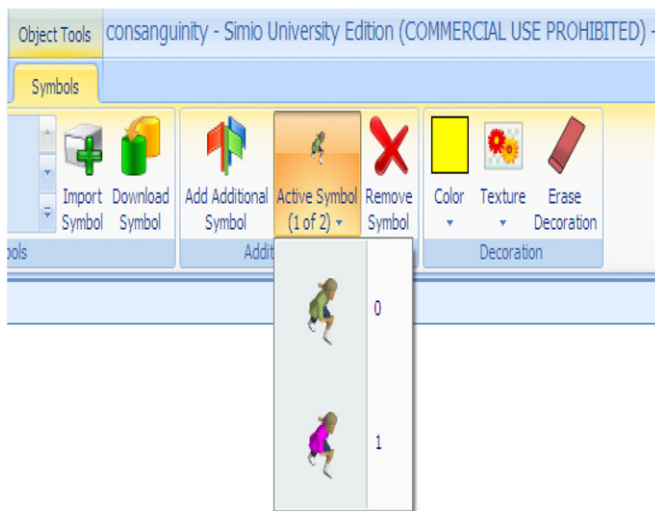### 5.2. Consanguinity model validation

To validate the consanguinity model, we needed specific data that was not available in the literature. Therefore, we used data available from different studies to determine whether our model could give us results as close to real life as possible. Towards this end, gender and death rate data for Saudi Arabia (2006) was used from the World Factbook (Central Intelligence Agency (CIA), 2006). The sex distribution of Saudi Arabia was 1.33 male(s)/female between the ages of 15–64 years (Central Intelligence Agency (CIA), 2006). We selected this defined age range since it

covers the reproductive time period of individuals which directly relates to consanguineous or non-consanguineous marriages. Our consanguinity model separates the male and female population into two groups (Fig. 10). The first group has male (MP_C) and female (FP_C) population for consanguineous marriages. Here, the distribution rate for consanguineous union was taken as 30% based on average rates of marriages between first cousins among Saudi populations (Al-Gazali et al., 2006). Conversely, for non-consanguineous marriages, the paths weights were assigned as 70 (Fig. 10). To correctly reflect the growth rate, a death rate of 2.58/1000 for the year 2006 was taken from the World Factbook for Saudi Arabia and assigned to accurately predict the population growth (Central Intelligence Agency (CIA) 2006). After assigning these parameters, comprehensive data was generated by our consanguinity model, shown in Table 2.

Table 2 demonstrates the total number of consanguineous and non-consanguineous marriages along with the population growth as a result of these marriages for the year 2006. Since the actual data of consanguineous and non-consanguineous population does not exist, in order to validate our model, we predicted the total population of Saudi Arabia for the year 2006 by adding both
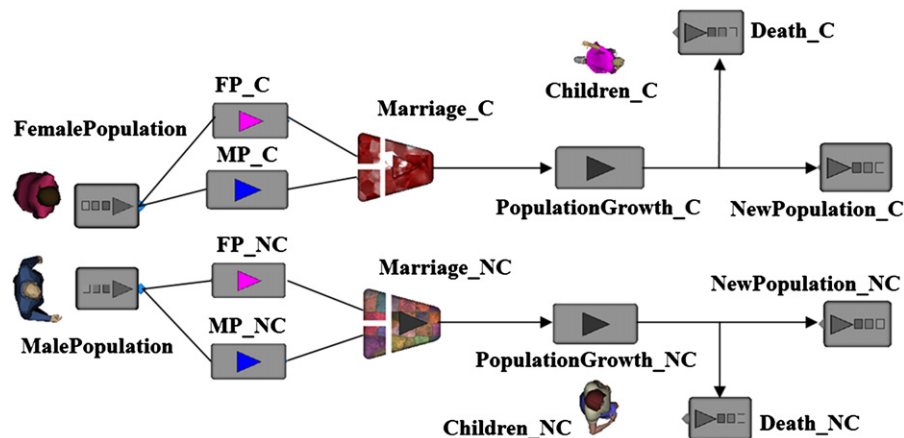
Fig. 10. Model of consanguinity. MP_C, male population for consanguineous marriages; FP_C, female population for consanguineous marriages; Children_C, children resulted from consanguineous union; Marriage_C, consanguineous union; PopulationG_C, consanguineous population growth; NewPopulation_C, new consanguineous population; MP_NC, male population for non-consanguineous marriages; FP_NC, female population for non-consanguineous marriages; Children_NC, children resulted from non-consanguineous union; Marriage_NC, non-consanguineous union; PopulationG_C, non-consanguineous population growth; NewPopulation_C, new non-consanguineous population.

Fig. 11. Adding additional symbols in Consanguinity Model. This property helps to create multiple desired symbols.
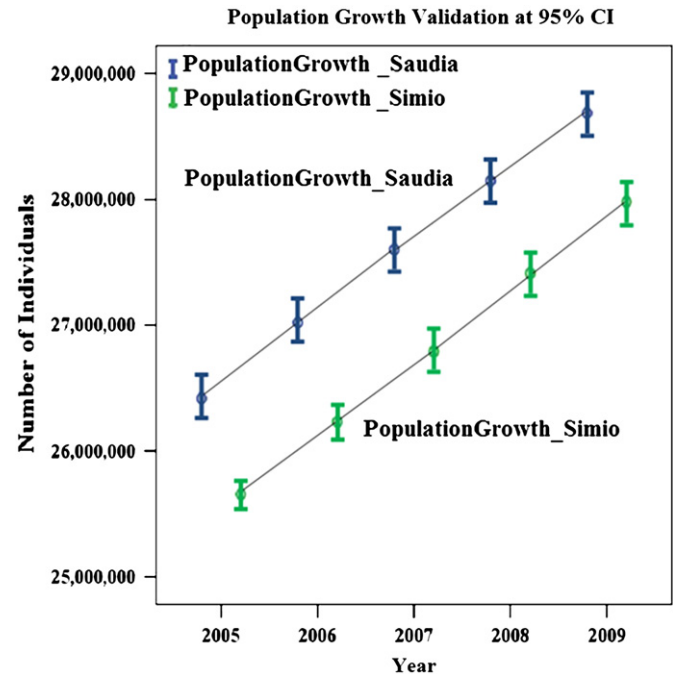
Table 1
Population growth statistics via Simio simulations. The year column shows the period over which female and male population data was generated along with the growth of the total population.

Year	Actual population growth of Saudi Arabia[a]	Predicted population growth rate of Saudi Arabia	% Difference between actual and predicted growth rates
2005	26417599	25655000	2.89
2006	27019731	26231000	2.92
2007	27601038	26790600	2.94
2008	28146656	27411500	2.61
2009	28686633	27980600	2.46

[a] Actual data available in CIA World Factbook (Central Intelligence Agency (CIA), 2006).

Fig. 12. Population growth model validation with Saudi population data. Graph comparing the original Saudi population growth data from the years 2005–2009 with the simulation data generated via Simio in SPSS.

consanguineous and non-consanguineous populations obtained through the simulation analysis and compared it to the total population of Saudia Arabia estimated actually for the year 2006 (Table 2). The two numbers came within 3.2%—the error rate of

the data collection (Central Intelligence Agency (CIA), 2006), revealing once again an excellent correlation of the predicted results with that of the actual data, though in an indirect manner.

6. Conclusions and future work

In this study, we have developed a DEVS model of population growth and used it to study the *in silico* emergence of consanguinity in the offsprings. The main idea of this study was to take the first steps towards answering questions such as what are the rates of consanguinity, which can impact the emergence of birth
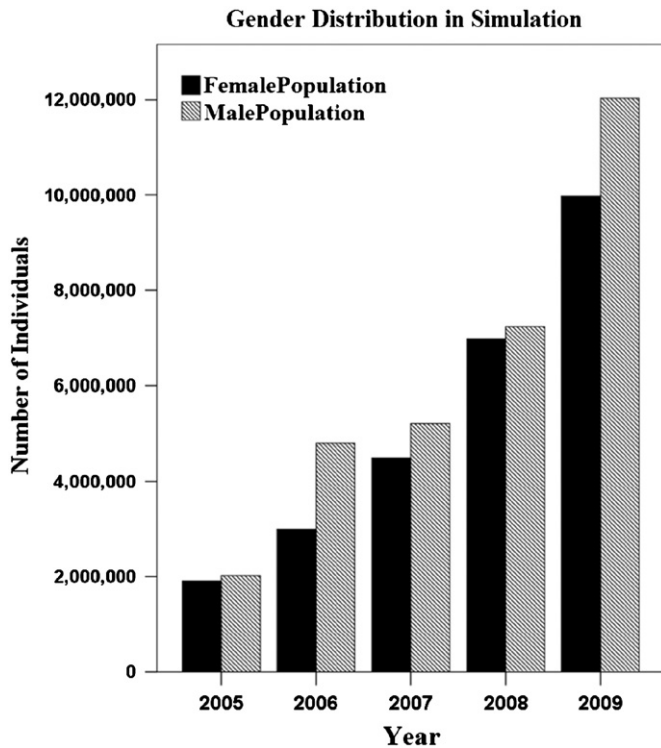
Gender Distribution in Simulation

Fig. 13. Male and female statistics from 2005–2009, generated using Simio simulation software generated using SPSS.
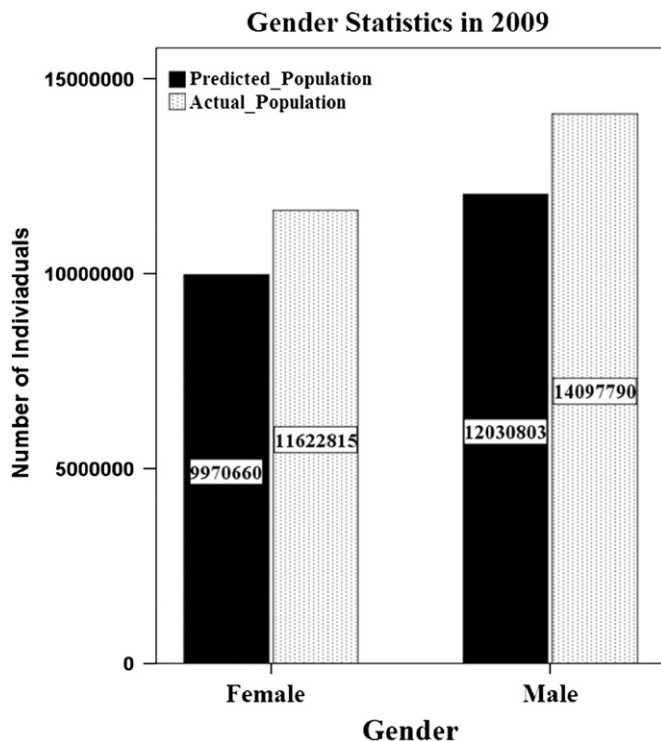
Gender Statistics in 2009

Fig. 14. Gender-specific distribution of the Saudi population in 2009 predicted by means of Simio using population growth data from 2006 generated using SPSS.

defects in a population. It is important to model consanguinity in order to acquire a complete picture of congenital defect trends. Our contribution is a DEVS-based model of consanguinity, which

Table 2
Statistics on total number of consanguinity model entities created using Simio simulation and comparison with real data.

Objects name	Actual statistics of Saudi Arabia from year 2006[a]	Predicted statistics from consanguinity model	% Difference
Consanguineous marriage(s)	–	3154352	
Non-consanguineous marriage(s)	–	9898900	
Consanguineous population growth	–	9628005	
Non-consanguineous population growth	–	18290500	
Total population growth	27019731	27918505	3.22

[a] Actual data available in CIA World Factbook (Central Intelligence Agency (CIA), 2006).

can predict the level of consanguinity in a population followed by simulation using the Simio simulation software. Validation of our model using real-world data shows that DEVS can be used effectively to model biological problems. In future, we plan on applying the DEVS formalism to specific congenital disorders due to consanguinity to evaluate the probability of congenital defects due to consanguineous and non-consanguineous marriages.

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