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Discrete Event Simulation to Evaluate Different Treatments of Diabetic Retinopathy Disease

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Abstract

Modeling approach using discrete event simulation has been proven to work well in modeling in health care. The aim of our paper is to propose a simulation approach which shows realistic models presenting different possible treatments in different stages of diabetic retinopathy. We have presented three models in order to choose the best treatment for diabetic retinopathy patients. The first model describes the flow of a patient through stages without any medical treatments. It takes 13 years to reach blindness. The second model which includes the laser photocoagulation treatments leads to blindness after 46 years. Then, the third model illustrates the involvement of vitrectomy operation and delays blindness by 23 years. To construct the models, data were taken from experienced doctors and professors of the ophthalmology department in the University hospital Habib Bourguiba and the endocrinology department in the University hospital Hedi Chaker in Sfax, Tunisia. Our objective is to delay reaching the blindness stage as late as possible. Three models were developed, verified and validated through many iterative implementations with ARENA simulation software.

Keywords

Diabetic Retinopathy, Modeling, Discrete Event Simulation, Health Care, ARENA Simulation Software

1. Introduction

Diabetic Mellitus (DM) is defined by a state of chronic hyperglycemia which follows an abnormal secretion of insulin or insulin action or both associated anomalies. This chronic disease is classified into two basic forms: Type I and Type II

diabetes [1]. DM is a severe disease which is frequent in developed countries and in developing ones as well. Diabetes is reaching epidemic proportions worldwide. In dead, there is a high number of world population affected [2]. Detection and treatment of diabetes is expensive. For this reason, and with resource constraints, there are more undiagnosed than diagnosed cases in developing countries.

Diabetic Retinopathy (DR) is a form of complication of DM which is asymptomatic in early stages of the disease [3]. This severe anomaly usually affects both eyes. If someone has DR, he may not notice changes to his vision at first. But over time, DR can get worse and cause vision loss [4]. Blindness is a major cause for concern in many developing countries. Hence, without his sight, a person can expect to be out of work and also unable to attend the fields in order to provide his family with income and food [3]. Detection and treatment of diabetes is an involved process; especially, in developing countries where there are resource constraints [5]. Indeed, there are more undiagnosed than diagnosed cases in these countries. Care of people with DR requires a multidisciplinary team with an active participation of the patient [6].

Many researchers of the literature have used simulation and modeling tools in their applications. Moreover, modeling and simulation have well results in healthcare decision making and have improved hospital performances.

Our work differs from published works since it incorporates a simulation modeling approach, which works well for modeling the onset of diabetic retinopathy disease. This approach shows real models incorporating different treatment strategies targeted at different stages of DR. We illustrate the approach using data taken from experimented doctors and professors of ophthalmology department in the University hospital Habib Bourguiba and endocrinology department in the University hospital Hedi Chaker in Sfax, Tunisia. This is because of the lack of official data in the register support of patients in that hospital. In our work, we have used discrete event simulation (DES). We show that the DES technique is able to model and resolve complex real problems with various resources.

In the first section, we discuss the diabetic mellitus disease with its two types, then its complications. In the second section, we focus on the use of modeling and simulation in health care. In Section 3, we present the problem statement. This is followed by model presentation in Section 4. Simulation of DR is discussed in detail as an application model in Section 5. Results and discussion are presented in Section 6. Finally, the last section provides conclusion and perspectives.

2. Literature Review

2.1. Diabetes and Its Complications

There are two main types of diabetes: diabetes mellitus type 1 (insulin dependent diabetes) is a form of DM that results from a near or complete lack of insulin

producing β-cells in the pancreas which causes an increase of glucose in blood, also in urine. It is an autoimmune. That disease causes the body to destroy insulin producing cells in the pancreas [1] and therefore insulin must be injected. Type 1 diabetes can occur at any age. However, it is most often diagnosed in children or young adults (whose ages are less than 35). Diabetes mellitus type 2 (no insulin dependent diabetes) is a very heterogeneous disease with insulin resistance associated to a relative deficiency of insulin. It has an essential clinical characteristic that has not a vital need to insulin treatment [7]. Patients suffering from this type of diabetes can produce some insulin themselves. They should be controlled by diet and drugs. Type 2 diabetes is common in individuals over 40 years of age. It is characterized by hyperglycemia and associated with micro vascular (retinal, renal, possibly neuropathic), macro vascular (coronary, peripheral vascular), and neuropathic (autonomic, peripheral) complications [1].

Many diabetes people are poorly controlled on existing therapies, and then they are faced with hard complications which may lead even to mortality [1]. Complications of poorly-managed diabetes mellitus may include diabetic nephropathy which is one of the main causes of end stage renal disease, the macro diabetic angiopathy which is a major etiology of cardiovascular diseases including gangrene and amputations lower limbs, diabetic neuropathy, and DR which can lead to blindness.

2.1.1. Diabetic Retinopathy Disease

DR is one of the complications of diabetes, which affects the microvasculature of retina. It is the leading cause of a visual impairment. All people with diabetes, both type 1 and type 2, are at risk. It is shown to cause visual impairment in more than 86% type 1 diabetic patients and in 33% type 2 diabetic patients [8] [9]. That's why everyone with diabetes should get a comprehensive dilated eye exam at least once a year. If signs are detected, the exam should be taken every 3 or 6 months according to the fundus. The longer someone has diabetes, the more likely he or she will get diabetic retinopathy. If someone has DR, his doctor can recommend treatment to help prevent its progression. In Tunisia, where the prevalence of diabetic exceeds 10% of the population aged more than 30 years, DR affects about one by three diabetic person [1].

DR is a progressive disease. With reference to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification, DR has 3 stages: Non Proliferative Retinopathy (NPR), Proliferative Retinopathy (PR) and Complicated Proliferative Retinopathy (CPR) or Intra Vitreaous Hemorrhage (VH). Maculopathy or Macular edema can occur at any stage (NPR or PR). About half of the people with PR have also macular edema [10].

2.1.2. How Are Diabetic Retinopathy and Macular Edema Treated?

During the first stage of DR, no treatment is needed, unless a macular edema is present. But prevention from progression of DR is possible. Hence, people with

diabetes should make regularly analysis of levels of blood sugar, blood pressure, and blood cholesterol and then follow a diet. Large clinical trials have emphasized that blood pressure control can help in reducing the risk of blindness in patients with diabetic retinopathy [11]. PR is treated with laser. This procedure is called laser photocoagulation treatment. The main purpose of this treatment is to remove the stimulus for neo vascular proliferation by destroying the ischemic areas. The number of laser sessions to complete treatment is determined by the ophthalmologist and the interruption may have bad effects. The patient may notice some loss of his side vision, but treatment by laser can save the rest of sight. Patient should follow the doctor's advices like the diet and reducing colors and the night visions.

The efficacy of treatment of PR by laser photocoagulation has been demonstrated by the conduct of a controlled therapeutic trial, the Diabetic Retinopathy Study (DRS). When laser photocoagulation treatment is compared with indefinite deferral of treatment, it was found to be beneficial to all subgroups of DRS patients, reducing occurrence of severe visual loss by approximately 50% [4]. The risk of vision loss is reduces by 50 percent if a laser photocoagulation treatment is followed [12].

If the bleeding is severe, or in case of recurrence of VH, the patient may need a surgical procedure called a vitrectomy. During a vitrectomy, blood is removed from the center of the eye. In a small number of cases, if vision is lost, it can be improved. If the patient has a lot of blood in the center of his eye (vitreous gel), he may need a vitrectomy to restore his sight. If he needs vitrectomies in both eyes, they are usually done several weeks apart. A vitrectomy is performed under either local or general anesthesia. Some people stay in the hospital overnight.

2.2. Discrete Event Simulation

Discrete event simulation (DES) is a form of computer based modeling used to represent complex systems that provides an intuitive and flexible approach. Several authors use the DES method. We can seat for example [13]. DES is used in a wide range of health care applications [14]. Therefore, it is an important technique used to solve healthcare problems in operations research. [15] uses the simulation in the outpatient appointment problem. [16] proposes simulation optimization to solve the problem of emergency department. The basic concepts of DES are entities, attributes, events, resources, queues, and time [17]. Entities are objects or persons that have attributes, experience events, consume resources, and enter queues, over time. The creation of entities can be at the start or even when a new entity arrives at the queue. Attribute shares features specific to each entity that allow it to carry information like age or sex [17]. Attribute values may be modified at any time during the simulation, may be aggregated with those of other entities, or analyzed further outside the simulation. Events are which can happen to an entity or the environment. A resource is an object or a person which offers a service to an entity [18]. In representing resources, DES can cap-

ture spatial factors, such as the number of available machines or distance between different rooms. Queues are formed because of a need for waiting by the entity if a resource is "occupied". Queues can have a maximum capacity. In DES, individuals possess given attributes, such as age, sex and disease complexity, which influence their way through the simulation and the time staying between events. DES has been used by many authors for the planning of future expansion and integration [19], and giving different paths to patients has good results to the hospital administration decision maker's in term of cost effectiveness [20] [21], also it gives best ways to saving patients' health.

3. Problem Statement

With the increasing number of patients suffering from diabetes and its complications particularly DR, the use of different techniques of operational research becomes a necessity to help decision makers in the domain of health care to solve such a problem.

If we focus on literature reviews, we see that many researchers in health care have used different techniques such as Markov and Semi Markov chain models, queuing models, deterministic models which are useful for examining patient flow in large population groups. The use of DES models has the advantage of permitting to patients to have individual attributes and to interact with the common resources.

4. Model Presentation

Arena is a powerful software tool used frequently in the field of modeling and simulation. In fact, it allows its user to create and run experiments on modeling, also to predict the future with confidence. Any process which can be described by means of a flowchart can be simulated with Arena software.

Arena software application is well used in different domains such us business, manufacturing, healthcare systems, ... It gives perfect performances for the evaluation and prediction of the impact of existing strategic and possible changes. This advanced software usually provides an easy to use and clear system for building, verifying, and analyzing simulation models. Due to Arena software, we can also graphically animating and designing a unique Arena template that is specific to a particular project, and which permits its user to create new simulation tools in a graphical. In Arena, there are two types of modules that define the process to be simulated: the flowchart modules and the data modules.

5. Application Model: Simulation of DR Disease

Our objective focuses on determining the extension in years of saved sights for patients suffering from DR disease if treatment is conducted. For this reason, we have built three models which will be compared to give the best solution for those patients.

Our models are built in Arena by placing modules (blocks of different shapes)

that represent the logic of DR disease. Objects that flow through the system are patients. These objects are known as entities. Connector lines are used to join modules together and specify the flow of entities over stages presented through process blocks.

At each stage, we should specify a processing time of its development, also probabilities of following stages. Data were taken from ophthalmologists working in the ophthalmology department of the university hospital Habib Bourguiba of Sfax. We have used the triangular distribution of Arena software. This distribution is commonly used in situations in which the exact form of the distribution is not known, but guesses for the minimum, maximum, and most likely values are available.

As we see bellow, we give successively the three constructed models. **Figure 1** presents the first model where the patients develop the different stages of the disease without any medical treatment. In the second model (shown in **Figure 2**), we added the Laser photocoagulation treatment when the patients develop NPR and maculopathy, only maculopathy, or PR. The third model (presented in **Figure 3**) differs from the first by adding vitrectomy treatment for entities (patient) which develop VH.

6. Results and Discussion

6.1. Arena Results

After presenting the model and the choice of number of replications, we select the run menu, then Fast-Forward. The model runs and a default report window appears.

The report window summarizes the results across all replications.

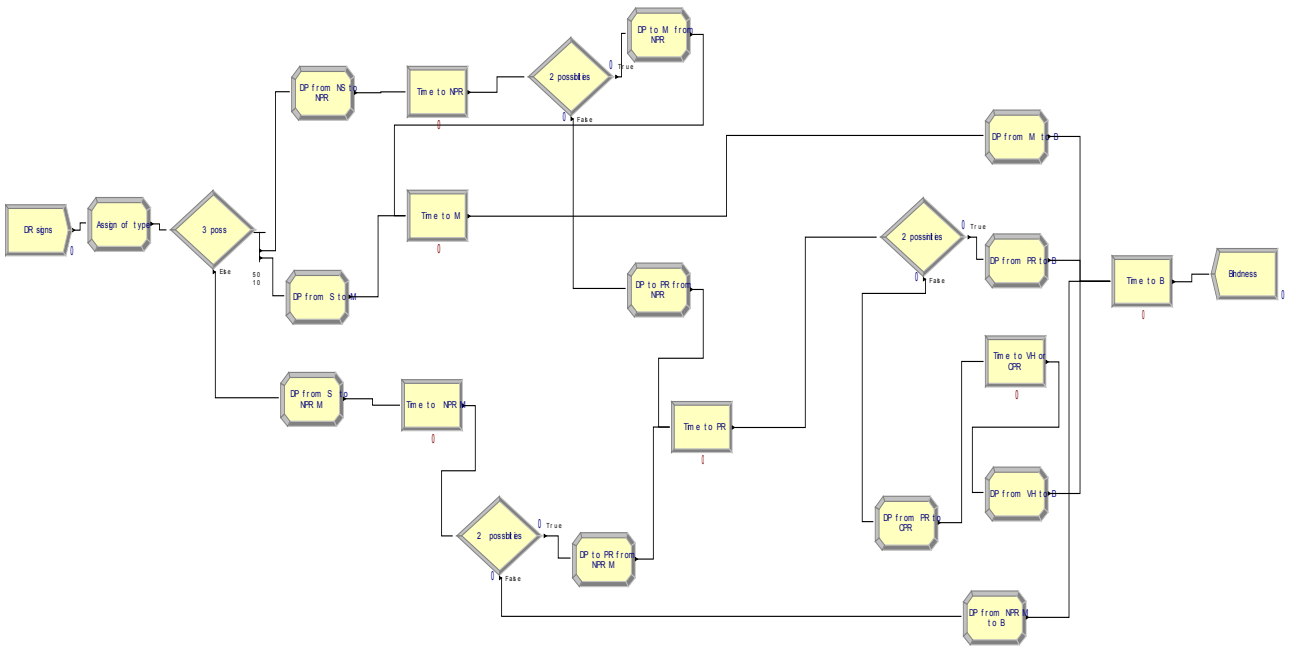

Figure 1. Patients' flow through the model without medical treatment.

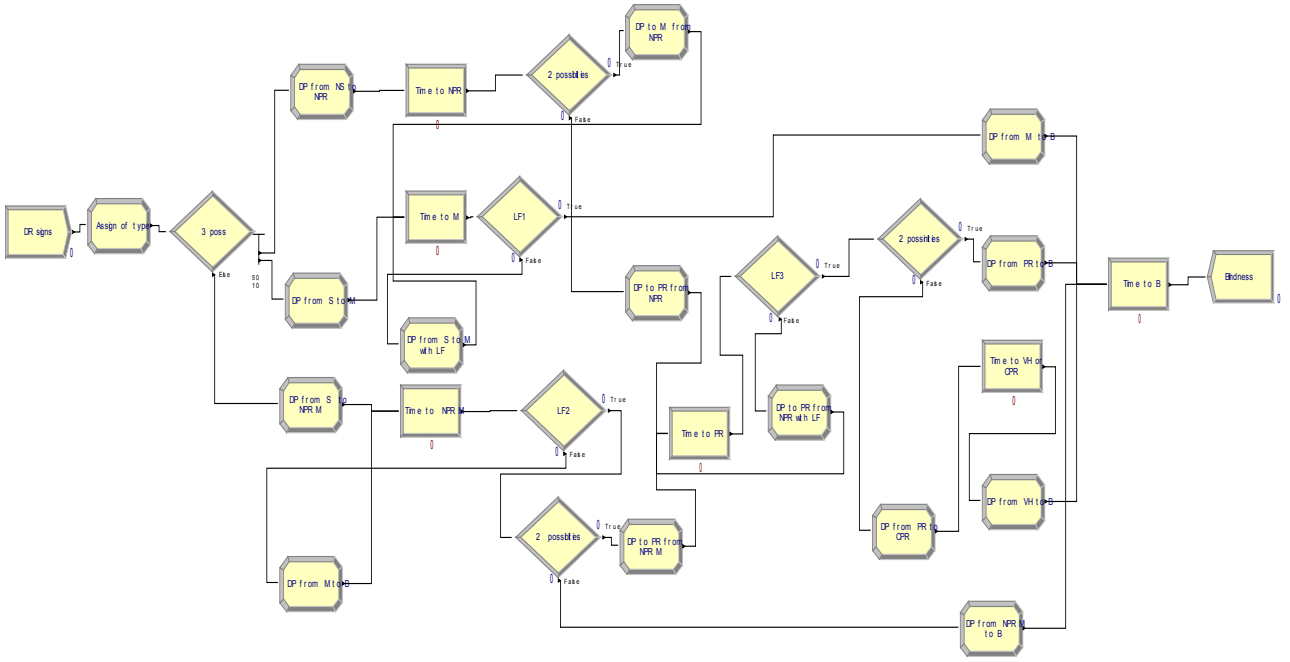

Figure 2. Patients' flow through the model with laser photocoagulation treatment.

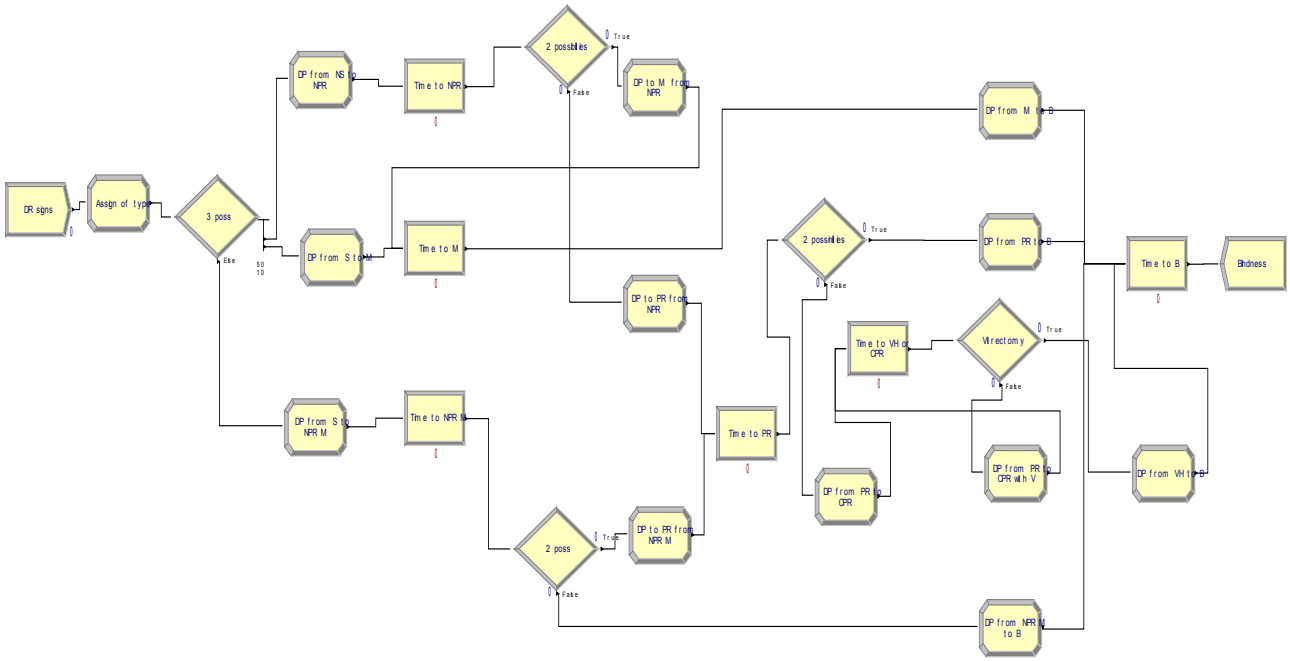

Figure 3. Patients' flow through the model with vitrectomy treatment. DR signs: a diabetic patient with signs of Retinopathy. 3 poss: 3 possible anomalies. DP from NS to NPR: distribution parameter from no signs to NPR. DP from S to M: distribution parameter from signs to Maculopathy. DP from S to NPR M: distribution parameter from signs to NPR and Maculopathy. Time to NPR: time to develop NPR. Time to M: time to develop Maculopathy. Time to NPR M: time to develop NPR and Maculopathy. DP to M from NPR: distribution parameter to develop Maculopathy from NPR. DP to PR from NPR: distribution parameter to develop PR from NPR. DP to PR from NPR M: distribution parameter to develop PR from NPR and Maculopathy. Time to PR: time to develop PR. DP from PR to CPR: distribution parameter from PR to CPR. Time to VH or CPR: time to develop VH or CPR. DP from PR to B: distribution parameter from PR to blindness. DP from M to B: distribution parameter from Maculopathy to blindness. DP from NPR M to B: distribution parameter from NPR and Maculopathy to blindness. DP from VH to B: distribution parameter from VH to blindness. Time to B: time to develop blindness. LF: lazer photocoagulation treatment.

As it is shown in the first page of the report presented in Figure 4, the number of replications is 1000. In fact, the input of 1 year was repeated 1000 times. The "Number In" of entities or patients entering in the system is 145. Indeed, there is a daily arrival of two patients and a half. The average of entities or patients going out of the system "Number Out" is 145, which is the total number of patients. It means that all patients will develop blindness at the end whatever their path.

Table 1 gives some information about the time between arriving to leaving any stage of DR disease. This information includes: the average, minimum average, maximum average, minimum value, and maximum value.

6.2. Differences between Constructed Models

Table 2 and Table 3 resume the differences between results given by Arena software of the three constructed models. We focus especially at the "total time per entity" and the "Number Out". The total time to develop blindness for a patient with signs of DR differs in the three models. It is about 13 years in the model without treatment. It is about 23 years in the model with vitrectomy treatment. It is about 46 years in the model with Laser photocoagulation. We can see that for the process block "Time to develop NPR", variables are unchangeable whatever the model is. Indeed, at this stage, there is no treatment. Also, for the number

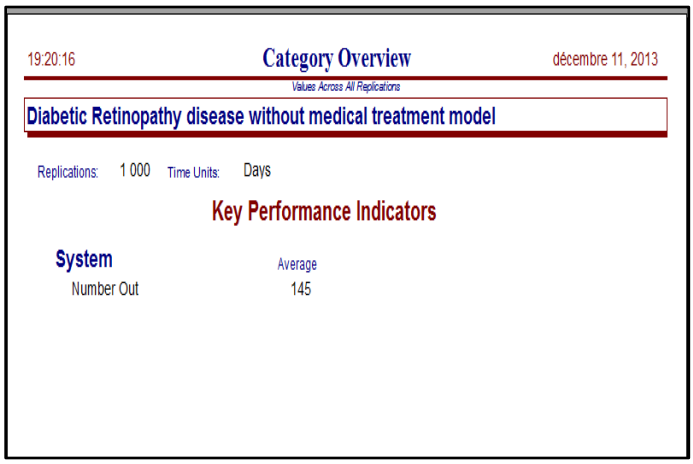

Figure 4. The category overview report of the Diabetic Retinopathy disease without medical treatment.

Table 1. Total time per entity results of the first simulated model.

Total time per entity	average	Half width	Minimum average	Maximum average	Minimum value	Maximum value
Time to develop M	3287.87	<7.61	2890.30	3653.71	1112.37	5460.7
Time to develop NPR	2127.13	<5.42	1815.74	2409.61	195.83	3642.4
Time to develop M and NPR	1002.17	<2.78	843.85	1145.45	185.78	1821.4
Time to develop PR	1124.63	<2.13	1013.45	1224.42	194.32	1823.9
Time to develop CPR	1004.80	<2.44	871.22	1147.76	185.28	1824.0
Time to develop blindness	1010.25	<0.73	974.64	1055.03	624.26	1816.7

Table 2. Differences between the three constructed models: total time per entity.

Model	Without treatment	With vitrectomy	With Lazer photocoagulation
Time to develop M	3287.871	3292.091	4743.857
Time to develop NPR and M	1002.170	1002.170	1455.987
Time to develop PR	1124.629	1124.918	1756.414
Time to develop CPR	1004.800	2592.049	547.678
Time to develop NPR	2127.129	2127.129	2127.242
Time to develop blindness	1010.246	2644.261	1009.681

Table 3. Differences between the three constructed models: number out.

Model	Without treatment	With vitrectomy	With Lazer photocoagulation
Time to develop M	50.703	50.507	253.340
Time to develop NPR and M	58.067	58.067	116.157
Time to develop PR	82.877	83.116	412.014
Time to develop CPR	74.649	74.649	74.547
Time to develop NPR	72.512	72.512	72.504
Time to develop blindness	145	145	145

out of the process block "Time to develop Blindness", we have always 145 which is the total number of entities that have to leave the system. As it is shown above, for the stage "Time to develop Maculopathy", the total time per entity for the model in which we add a Laser photocoagulation at this stage is larger. It become 13 years instead of 9 years. The number out of entities is bigger. It is 253 instead of 50 patients. This deduction is the same with the other stages treated by Laser photocoagulation ("Time to develop Maculopathy", "Time to develop PR"). The stage "Time to develop vitreous hemorrhage" is treated with vitrectomy. As a result of this treatment, the number out of entities becomes 149 instead of 74 patients. The total times per entity become 7 years instead of 3 years.

Our results are equivalent to doctors' suggestions but there are more precision in times and percentages. This is due to the use of Arena simulation software.

7. Conclusion and Perspectives

The work presented in this paper focuses on the study of three specific models, for diabetic patients with signs of Retinopathy, and determine the best way for those patients to decrease their suffering. As a tool of simulation, we used ARENA software. This has important prospects, for local health decision-makers dealing with planning for future prevention and treatment of this chronic disease.

Our contribution consists in adapting, for the first time in Tunisia, clear and

simple models in which we explain the flow of patients through different complicated stages of DR disease, possible treatments, and the efficiency of those treatments in extending the time to develop blindness for patients with signs of Retinopathy.

This project demonstrates, despite the complexity of both the data requirements and the simulation program itself, that DES technique can be successfully used in such a decision system.

In the light of this work, taking into account the importance of Laser treatment for DR patients, and knowing how much it is expensive to get the treatment in private sector in developing countries, we though as a perspective to develop mathematical models for the scheduling of patients to laser treatment in the ophthalmology department of Habib Bourguiba hospital in Sfax, Tunisia in order to encourage patients to get their treatment regularly

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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