Department of Mathematics

Master's degree: Study of Mathematics

Thesis name:

Various Techniques for the study of Epidemic Models

ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΙΓΑΙΟΥ

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October 2021

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1. Introduction

At the beginning of the 20th century, the Russian mathematician A. A. Markov, in an attempt to explain the "uncertainty" in the alternation of vowel and consonant letters in Pushkin's poem "Onegin", introduced the theory of Markovian processes. In 1957, Bellman introduced the theory of dynamic programming. He developed a retrospective procedure that calculates optimal values of profit or cost functions through an appropriate function equation. Dynamic programming is used in finite or infinite time horizon problems in which a stochastic process is controlled by a sequence of actions.

The main goal is to find a rule of selection of actions that controls the process in the optimal way. Markovian decision processes were introduced by Bellman and were the result of a combination of Markovian process theory and dynamic programming.

Over the last four decades they have been the subject of research by many researchers. They have found application in various fields of science, such as Business Research, Biology, Ecology and Informatics. In particular, they have been proved very useful in problems of optimal inventory control, optimal control of queues and biological populations, optimal maintenance and replacement of machinery, optimal management of networks and telecommunications.

Systems that evolve over time with "randomness" as the main feature of their evolution, are called stochastic dynamic systems.

In this chapter the basic elements of the theory of stochastic programming potential are presented, by introducing the Markovian decision processes at a

discrete time. Various models in finite time horizon problems will be described and analyzed.

1.1.Epidemics in the history of mankind

The history of epidemics is very fascinating and must be taught. The earliest reference to a possible epidemic, probably a plague epidemic, is found in the Bible. The plague is described as a plague that struck the Philistines because they had stolen the ark of the covenant from the people of Israel. So the Philistines were punished for their sin. These events date to about the second half of the 11th century BC.

1.1.1. The Black Death

The most well-known case of an epidemic is Black Death. It was one of the most devastating pandemics in human history. The first official records of the pandemic began in October 1347, when Genoese merchant ships from the port of Kafa on the Black Sea, which approached the port of Messina in Sicily full of the dead and dead, transmitted the disease to Europe. This disease had two forms: inguinal (or septic) and pulmonary. It was transmitted instantly and aided by poor hygiene, lack of medical knowledge of the time and the ensuing superstitious preventions, at the beginning of 1348 it had already spread from Italy, throughout central France, until the winter of the same year in southern England and, then to the Netherlands. The epidemic resulted in the loss of almost a third of Europe's population. Its total human toll is estimated at 75 to 100 million dead in Europe

and Asia. The epidemic struck again in the following years of the 14th century, with short breaks, thus completely reversing the demographic growth that had occurred in the middle of the 13th century. The world population returned to the levels before 1347 only in the 17th century.

1.1.2. The plague of Athens

An epidemic that many researchers have been dealing with for a very long time is the plague of Athens (430-428 BC) which is described in great detail by Thucydides. It reports the symptoms and the progression of the disease that resulted in the death of 1050 of the 4000 soldiers in a campaign. A plague so great (like this) and with such catastrophic consequences that it had no equal in human history. This is how Thucydides described -in the history of the Peloponnesian War- the epidemic that broke out in Athens and changed the military balances in the long Athens-Sparta war. Historians argue about the nature of the disease, with some arguing that it was typhus or chickenpox, and we may never know what really struck the people of Athens. Thucydides traced the roots of the plague to Ethiopia and estimated that the epidemic wiped out about one-third of the population of Athens, with the city's troops receiving an irreparable blow.

1.1.3. The plague of Justinian

At a time when the armies of the almighty Byzantine emperor Justinian were reviving the old glory of the Roman Empire by reclaiming lost lands, an internal enemy was showing its scary teeth: circa 540 AD. an unknown disease

born of the rodents of Egypt was transported by ships to Constantinople. The plague is estimated to have killed 5,000 people a day, wiping out about half the city's population. The pandemic, however, was not limited to the walls of Constantinople, but spread to Europe and Asia and was the deadliest epidemic of antiquity. Fifty years after its first manifestation, 25-100 million people had lost their lives.

1.1.4. The third plague pandemic

In the 1850s, China's Yunnan Province was set to become the gloomy setting for the third (and last) plague pandemic to hit the world. Infectious fever affected the inhabitants of the area, killing tens of thousands, while around the end of the 19th century the epidemic spread to the surrounding areas (Hong Kong, India, South Africa, Ecuador, San Francisco, etc.), with devastating consequences. : 12 million people would lose their lives. However, the scientific knowledge developed by the doctors' fight against the disease ensured that the world would never see a fourth plague pandemic in its history.

1.1.5. The first cholera pandemic

Cholera has plagued humanity for centuries, with Hippocrates implying it in his medicine, but it was for a time limited to the Ganges Delta in India. In 1817, however, travelers transmitted the disease, through trade routes, throughout the country and the neighboring areas now occupied by Burma and Sri Lanka. "Asian cholera", as it was called in the West (which had not been hit by cholera until 1830)

claimed the lives of thousands, and eventually hit the Philippines and Iraq, where 18,000 people died in the first three weeks of the epidemic. "Asian cholera" was the first of the 7 cholera pandemics that would break out on the planet.

1.1.6. The polio epidemic of 1916

Paralytic disease has infected thousands in America, killing more than 6,000 people. The 1916 polio pandemic counted 9,000 cases in New York alone, which led to quarantine throughout the United States. Polio, however, was to haunt America for decades, with 25% of patients dying. And people had to wait until the 1950s for the vaccine to be developed by Jonas Salk.

1.1.7. The yellow fever of Memphis

In 1878 thousands of Cubans fled their homeland as a result of the country's ten-year war for independence from Spain. On their trip to America, however, they inadvertently carried the yellow fever. New Orleans was the victim of the first yellow fever epidemic known to the New World, with the disease ascending the Mississippi River and spreading to Memphis. By the end of the year, more than 5,000 Memphis residents had lost their lives, and the total loss in the Mississippi Valley was 20,000.

1.1.8. The flu pandemic of 1918-1919

World War I had a serious contender for lethality: the "Spanish flu," as it goes down in history. The flu crisis has killed tens of millions and infected about 1/3 of the world's population. The victims of the virus died quickly and painfully. Even the law on mandatory masks in public places failed to curb its deadly action. Autopsies of the corpses struck by the "Spanish flu" showed that the lungs of the dead were full of fluid. Patients actually died from drowning.

1.1.9. The COVID-19 pandemic

For a year now, COVID-19 has been sweeping the globe, causing more than 1.89 new deaths. Greece until the night of Thursday 14.01.2020 counted 5,387 human losses. On the occasion of the pandemic, the interdisciplinary collaboration contributed to the timely emergence of the large clinical study "Solidarity", conducted under the auspices of the World Health Organization (WHO), that hydroxychloroquine and the combination of lopinavir / ritonavir efficacy, were of no benefit to inpatients. Similarly, other clinical studies have shown that only dexamethasone and secondarily remedisivir have been shown to be effective against severe COVID-19 disease. In addition, ongoing clinical trials are evaluating the efficacy and safety of innovative therapies, such as plasma delivery from recovering patients with active COVID-19, as well as specific monoclonal antibodies. In November, the US Food and Drug Administration (FDA) approved emergency use of the monoclonal antibody vamlanivimab in the treatment of mild to moderate COVID-19 infection in adult and pediatric patients, as well as a

combination of monoclonal antimicrobials and treatment of mild to moderate infection. Monoclonal antibodies appear to be effective in the early stages of the disease, in untreated patients, especially those over 65 years of age and those with comorbidities, in order to prevent serious disease and complications.

Although COVID-19 is a mild disease in over 85% of cases, with a total mortality of 0.2% -1%, in 5% of patients with severe disease, causes an attack on many organs. In the envelope of the virus there are spikes (protein S) which attach to the receptors of the angiotensin converting enzyme type 2 (ACE 2) and in this way the virus enters the body and causes the corresponding symptoms. ACE 2 receptors are present in the cells of the respiratory tract (sore throat, cough, dyspnea, pneumonia), myocardium (heart failure, myocardial damage), kidneys (acute renal failure), upper and lower digestive tract (nausea), nausea, nasal mucosa (anosmia) and other tissues. In severely ill patients, however, what causes the collapse of all vital systems and organs occurs suddenly, while the patient is hospitalized, is the "cytokine storm syndrome", an overreaction of the body's defense systems that inexplicably turns indistinguishably against the virus, but also against the organism itself, resulting in severe damage to vital organs. The body produces and mobilizes cytokines when it is in a state of war. Inadequate and excessive, however, their overproduction and overactivation causes toxicity and damage to vital organs and systems.

The safe and effective vaccine is only one way to provide effective immunity to the general population against COVID-19. That is why the Pfizer / BioNTech and Moderna vaccines have received an emergency authorization (EUA) from the FDA. These vaccines have gone through all the testing stages done for each vaccine before they get marketing authorization. Specifically, they have been tested in the so-called Phase 3 placebo trials (placebo). These tests were

performed on a group of 30,000 to 60,000 people, the more groups being tested with each vaccine. Indicatively, human papillomavirus vaccine trials were performed on 30,000 people and pneumococcal vaccine trials on 35,000 people. Therefore, similar procedures were initiated quickly, COVID-19 vaccines have been tested in as many individuals as any other vaccine. And what these tests have shown is that there is no such thing as an unusual, serious side effect. Obviously, someone cannot know for sure if there are any new rare, serious side effects until after the release of these vaccines. Exactly the same, however, applies to any medical product! It is understandable that people are hesitant about the vaccine now that it is available. But safety is a top priority and reinforces the many reasons why they should trust vaccination.

Effective response to the pandemic must focus on controlling the spread of the virus beyond treatment protocols and safe and effective vaccines. Control of the spread of the virus is based on the basic observance of the usual public health measures with social distancing, the extensive and correct use of a mask and the observance of hygiene measures. At the same time, the extensive use of diagnostic tools (molecular and antigenic tests) contributes to the rapid diagnosis of patients, their isolation and the investigation and quarantine of contacts, while their sampling application to the public provides epidemiological evidence for community dispersal and reception control measures. At this stage, efforts to treat SARS-CoV-2 infection aim to stop the virus from multiplying and the immune response, which is often excessive and self-destructive. The treatment strategy of the disease has been based on these pillars, with the search for an effective antiviral drug and the appropriate immunomodulatory intervention in the necessary time. However, the most important moment for the final treatment of the pandemic will

be the universal application of vaccination, aiming to cover 60% -70% of the total population.

Until the beginning of August 2021, more than 4.5 million deaths have been confirmed worldwide. There is considered to be an incomplete report of cases, especially in cases with milder symptoms (Li et al.,2020; Sun et al.,2020).

The epidemiological analysis of the event showed a possible pattern of a "mixed outbreak" - there was probably a continuous common outbreak in the Juan Seafood Market in December 2019, possibly due to various zoonotic events (China CDC Weekly,2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team,2020). After that, epidemiologists determined that the outbreak was most likely a source (transmitted from person to person), possibly due to the virus's ability to mutate (Wang et al.,2020;Li et al.,2020).Therefore, as the number of cases has increased, the importance of the market has decreased (Li et al.,2020).

Until March 13th, more than 5,300 deaths had been attributed to COVID-19. According to the China National Health Center, most of those who died were elderly patients - about 80% of the deaths recorded were over the age of 60 and 75% had pre-existing health conditions such as cardiovascular disease and diabetes (The New York Times ,2020).The mortality rate of cases is estimated at about 2-3% (World Health Organization,2020).

The first confirmed death was in Uhan (Holm et al.,2020). The first death outside China occurred in the Philippines (Ramzy et al.,2020; NBC News,2020), and the first death outside Asia was in Paris.

The ability to predict the evolution of an epidemic is based on the use of mathematical models. Perhaps the most popular concept in this science is the key

reproduction number, the Rt index, which tells how many people each virus carries. If it is more than 1, then the epidemic spreads because more cases are produced than are treated. If it is below 1, then the epidemic is eradicated because more cases are treated than those infected. Mathematical epidemiological models estimate this number from many sources, such as numbers of diagnoses, hospitalizations, intubations, and deaths, but also how long it takes for the infection to show symptoms. But there is another category of epidemiological models that aims to draw conclusions about the course of the epidemic in the long run, for example in 3 weeks or 3 months. These crown models fail in the case of coronavirus. This is due to several factors, the main one of which is the phenomenon of over-transmission: most infections are due to a small number of people and under very specific conditions. Thus, the epidemic course does not behave in a homogeneous way, as the models assume, but depends significantly on the fulfillment of over-transmission conditions. Simply put, the epidemic behaves in the long run like meteorological phenomena, chaotic. Therefore, good short-term forecasts can be made, but long-term forecasts fail.

Last March the world forcibly entered a new daily routine in hospitals and had to change the way they are organized and operate. Doctors had to get acquainted with the personal protection measures and be strict in their implementation, to devise ways of remote monitoring of patients. It all happened thanks to their ingenuity and donations of appropriate equipment. It was very difficult because they did not know how the disease behaves. They succeeded by applying the "good clinical practice" that they have been following for so many years in the treatment of the seriously ill. They now have experience, organization and knowledge about the course of the disease, although it never ceases to amaze them. Unfortunately, however, there is accumulated staff fatigue.

The pandemic has tragically highlighted the shortcomings in the NSS. The country was found with many young doctors working abroad and the region's hospitals understaffed, especially in front-line specialties such as Pulmonology, Pathology and nursing staff. Hundreds of patients with respiratory failure were treated in hospitals. The few physicians and the few pulmonologists and intensive care physicians heroically undertook the difficult task of supporting these patients. However, the pulmonology clinics in the country's hospitals are minimal and the pulmonologists are almost completely absent from the lists of auxiliary curators. A constant request of the Hellenic Pulmonary Society in recent decades has been the creation of pulmonology clinics in all hospitals in the country. The pandemic has violently shown the priorities that need to be addressed immediately, so that new doctors stay in the health system permanently and old students return to an attractive academic and health environment. The pandemic must leave a staffed and structured health system.

Nurses all these months experienced situations unprecedented. It was very positive that there was timely information from the competent bodies regarding the characteristics of the virus and the ways of its transmission. Thus, there was the possibility of preparing the medical staff, in a way that ensured the protection and safety of both themselves and the patients. They were called to follow the rapid spatial adjustment, in order to create clinics and units for patients with coronavirus, but also the urgent need for reorganization of staff as well as training in order to ensure the proper staffing of the newly established nursing departments. Loss of human life is a painful situation, whether for patients or the medical staff. Of course, in the second case, the management may be more difficult, due to the intense emotional charge. Nurses as human beings can bend, but as health professionals stand up and fight for all those who need them.

Chronic patients, most of whom belong to vulnerable groups, were naturally more affected by all social groups, experiencing fear, insecurity, anxiety and uncertainty. 78% of the patients who participated (a total of 2,354 people) in the study conducted by the Hellenic Patients 'Association on the effect of the pandemic on patients' access to the health system stated that they experienced stress or anxiety. 65% said they had a problem accessing the health system, 29% canceled an appointment and 26% had trouble communicating with their doctor. 19% of patients did not seek medical attention at all, fearing possible exposure and infection with the virus. It is certain that late care will affect the outcome of most chronic diseases and should be treated as an additional burden on the health system. The Patients' Association of Greece very quickly adapted its actions to the new conditions. The "TOGETHER" helpline started operating at the beginning of April, which has so far served more than 2,600 beneficiaries. At the heart of its actions is the defense of patients' rights, such as safe access and supply of medicines, prescriptions, special purpose licenses, as well as the submission of proposals for the upgrade of the health system.

The more the pandemic hit the body, the more it hit the human soul. According to statistics from the operation of the Psychosocial Support Line 10306, in lockdown conditions stress and fear for the coronavirus (82%), insecurity for tomorrow financially and personally (70%) and the feeling of isolation and fatigue (65%). There is growing anger and sadness about rising deaths. One in 3 report some form of depression and 31% increased anxiety, while 10% of callers suffer from a mental disorder. The government acted swiftly and decisively to provide psychological support to those affected by the pandemic. In addition to Line 10306, which operates as a free communication channel, anonymously and confidentially, staffed by trained and experienced mental health professionals,

psychological and psychosocial support programs are being developed through a telemedicine and teleconsultation platform. There is also a system being created for the protection and empowerment of addicts who are at risk due to a pandemic with the contribution of KETHEA and OKANA. A parallel goal of this initiative is to inform and raise awareness of drug addicts about coronavirus protection through streetworkers networks.

The Coronavirus Epidemic 2019 (COVID-19) is a current pandemic caused by the SARS-CoV-2 coronavirus and was first identified in Wuhan, the capital of China's Hubei Province, in December 2019. (World Health Organization,2020). To date, more than 113 million cases have been confirmed in 215 countries and regions, more than 2.51 million deaths from the disease have occurred, and more than 89 million people have recovered.

The virus is transmitted between people through droplets produced when they sneeze or cough. The time between exposure and onset of symptoms is usually 2 to 14 days. Symptoms may include fever, cough, and difficulty breathing (Rothan et al.,2020), while scientific research suggests that possible loss of taste and smell are complementary signs of viral infection. Complications may include pneumonia and acute respiratory distress syndrome.

1.2.Markovian decision-making processes at discrete time

Let a stochastic process X_n, n=0,1,2,… where the random variable X_n represents the state of a system at a time n. All the states of the system are finite or infinite numbered. Assume that it is the sum of the non-negative integers 0,1,2,... The system is inspected at the time points of t=0,1,2… which we consider to be

equidistant from each other. The state of the system is observed at each time of inspection and an action is selected from a set of alternative actions. If there is a fixed integer $N \geq 1$ such that the actions for the control of the system are selected at the time points 0,1,2,…N-1 and the process stops at the time point, N then it is said that a system of finite time horizon of N steps is examined. Otherwise, if the total action selection time points set is infinite, then the system is considered to be a system over an infinite time horizon.

Suppose the ongoing stochastic process, X_n, n=0,1,2…, is observed at the time points t =0, t=1,… t=N-1, t=N. Suppose that at some time of inspection t, the system is in state i and action a is selected from a set of alternative actions A(i). It is assumed that the set A(i)) for each state i is finite.

The system described above is a Markov decision process in discrete time if:

(a) There is a cost C(i,a) which depends only on state i and action a as an economic consequence of the choice of action a the time at which the system is in state i.

(b) The next time point the system's state is j with probability $p_{ij}(a)$ which depends only on action a and states i and j.

The term "Markovian" is justified by the fact that the cost C(i,a) and the probability of transition $p_{ij}(a)$ depend on the "past" of the process only through the current state i of the process and the action a selected in state i.

A policy π is a rule by which actions are selected at time points n = 0,1,2…. There are different types of policies. Their classification depends on whether or not they are "randomized" as well as on whether they depend on the "history" of the process. By "random" we mean that policy according to which, when the process is in state i, an action a is selected with probability, $P_{\alpha}, \alpha \in A(i)$ at some point in

time of action selection. Stationary policies are of particular interest due to the simplicity of their definition. A stationary policy is a policy according to which the choice of an action at any time point t=0,1,2,… depends only on the state of the process at that time point. Therefore a stationary policy f is completely determined by a sequence $\{f_i\}$, i=0,1,2,… where $f_i \in A(i)$ is the selected action whenever the procedure is in state i at an time point of an action's selection.

The real problem is to find the policy that, for each initial state of the process, minimizes a predetermined cost function. The cost function defines the optimality criterion of the problem. The most commonly used optimization criteria are the minimization of total expected (deflated) cost and the minimization of long-term expected average costs per time unit.

The interest is focused in a finite time model using the criterion of minimizing the total expected cost.

1.3.Finite time horizon models

Suppose we observe and inspect a system at the times t =0, t=1,…,t=N-1, t=N. Assume that if at some time point the system is, for example, in state i, then an action (decision) $\alpha \in A(i)$ can be chosen and that, under the influence of this action, the state of the process at the next time point of its inspection is the state j with a probability of $p_{ij}(\alpha)$. This transition entails a cost, the average (expected) value of which is equal to $C(i,\alpha,)$. For each state i, the total A(i) of actions (or decisions) is considered finite.

The problem is to find the policy, ie a rule of actions choice, which minimizes the expected cost which is received from the time point t=0 to t=N. Let V(i,t), t=0,…,N

minimum cost from time point t to N, if the system at time t is in state i. If t=N it is obviously true that:

If t=N-1,

$$V(i, N-1) = \min_{a \in A(i)} C(i, a)$$

Which means that at the time point t=N-1 the optimal policy selects that action that minimizes the right part of the forementioned relation.

Suppose that at time t the system is in state i and an action α is selected. Then the cost is C(i,α) and the next state is j with probability $p_{ij}(\alpha)$. The best that can be achieved in terms of expected cost if at time t an action α is chosen the best cost achieved is : $C(i, a) + \sum_j p_{ij}(a)V(j, t+1)$. Since V(i,t) is the best to be achieved it holds that:

$$V(i, t) = \min_{a \in A(i)} \left[C(i, a) + \sum_j p_{ij}(a)V(j, t+1) \right]$$

The forementioned Equation is known as the dynamic programming equation or optimization equation and provides a method for calculating the V(i,0) reductive.

First the quantity V(i,N-1) is calculated using the relation $V(i, N-1) = \min_{a \in A(i)} C(i, a)$. Then for t=N-2, the V(i,N-2) can be calculated and repeating the same process (N-2) times the calculation of V(i,0) is achieved.

The optimal policy is as follows: When the procedure is at time t=N, N-1,…,1, in state i, then the action that maximizes its right part of the forementioned relation is selected. The above claim can be proved by induction with respect to t.

1.4.Some examples of finite time horizon models

Let a population of people who can be infected with two communicable diseases. Assume that the total population size is N and that at most one person can be affected by one of the two diseases. Consider the two diseases to be in competition in the sense that if one person is infected with disease r (r=1,2) remains infected with this disease and cannot be infected by the other.

Disease transmission stops when the total number of people infected with diseases 1 and 2 equals with N, which is believed to certainly happen in finite time. The transitions of the epidemic process are:

$$(x,y) \to (x+1,y)\ with\ propability\ \frac{c_1 x^{\alpha}}{c_1 x^{\alpha} + c_2 y^{\beta}}$$

$$(x,y) \to (x,y+1)\ with\ propability\ \frac{c_2 y^{\beta}}{c_1 x^{\alpha} + c_2 y^{\beta}}$$

Where c_1, c_2, α, β, positive constants. The variable x represents the number of people infected with the disease 1 and the variable y represents the number of people infected with the disease 2. The positive real numbers α and β can be attributed to the term "infectious power" 1 and 2, respectively, and justify it as follows.

If the spread of a communicable disease in a population of susceptible individuals depends more on whether a susceptible person is susceptible to the disease and less on whether a person infected with the disease can transmit it to the rest of the population, then the rate at which new people will be infected with the disease does not particularly depend on the number of people who have already been infected with the disease.

In this case it can be assumed that the "infectious power" of diseases 1 and 2 is low and the positive real numbers α and β take values close to Zero. In the opposite case, in which the infectious power of diseases 1 and 2 is high, it can be considered that parameters α and β take values >1. In this case the epidemics spread to the population at a very fast pace.

Suppose that disease 1 causes serious symptoms in a person who has been infected with it and reduces his productivity. The presence of a person infected with the disease 1 brings some costs to society which is considered to be stable and equal to the unit. Assume that disease 2, compared to disease 1, is less harmful to a person infected with it. It is believed that the presence of a person infected with the disease 2 does not bring any cost to society.

The control of the epidemiological process at any time can be carried out by selecting an action. Consider that one action, which can control the process at any time, is to vaccinate against the mild disease 2 any number of susceptible individuals that have remained in the population and have not been affected by either disease. It is considered that vaccinating a person with mild illness 2 incurs a cost that is equal to $K> 0$.

Another action that is also considered to be able to control the epidemic process at any time is to isolate some or all of the people who have been infected with the

serious disease 1. It was assumed that isolating a person with a serious illness 1 incurs a cost equal to L>0.

We are concerned with finding that policy which, for any initial state of the epidemic process, minimizes the total expected cost. Because the procedure considered that stops when the total number of people affected by diseases 1 and 2 equals to N, the problem of finding the optimal policy is a finite horizon problem.

The epidemic procedure described above finds possible application in the case of the well-known spinal cord disease, polio. Disease 1 can be considered as the severe form of polio while disease 2 can be considered as its mild form.

The following ecological interpretation can also be attributed to the epidemic process. Consider two species of living organisms that grow in a habitat that has a maximum capacity of N. Type 1 is considered to be a parasite whose presence is harmful. The presence of a parasite incurs a cost that is constant and equal to the unit. Type 2 is considered to be a mild species, the presence of which is harmless. The presence of a mild species does not incur any costs. Consider policies that control the growth of living organisms in the habitat at all times, either by intentionally introducing mild species or by isolating or removing any number of pests from the habitat. Intentionally introducing a mild species incurs a cost equal to K> 0 while isolating or removing a parasite incurs a cost equal to L> 0.

For each situation (x,y) of the epidemic procedure, let V(x,y) be the minimum expected cost and W(x,y) the minimum expected cost when the process takes place according to the probabilities given in the forementioned relations and then the best policy is adopted.

As far as the process stops when x+y=N, the optimization equation for the problem of minimizing the total expected cost over a finite time horizon takes the following form:

$$V(x,y) = min\{K + V(x,y+1), W(x,y)\}, 0 < x + y < N$$

where

$$W(x,y) = \frac{c_1 x^{\alpha}}{c_1 x^{\alpha} + c_2 y^{\beta}}[1 + V(x+1,y)] + \frac{c_2 y^{\beta}}{c_1 x^{\alpha} + c_2 y^{\beta}} V(x,y+1), 0 < x + y < N$$

And

$$V(x, N-x) = 0, 0 \leq x \leq N$$

When the procedure is in the (x,y) state and the inequality $K + V(x,y+1) < W(x,y)$ is valid, then the optimal policy is to choose action (ii), ie to vaccinate in mild illness 2 one of the susceptible individuals who have been remained in the population and have not been affected by either of the two diseases. In this case the procedure goes to the state, (x, y+1).

When the process is in the state (x,y) and the inequality $W(x,y) \leq K + V(x,y+1)$is valid then the optimal policy selects action (i), ie it does not proceed in the development of the epidemic process.

The forementioned equations allow to calculate numerically the minimum expected cost V(x,y) for each state (x,y) of the process for which 0 <x + y <N. In addition, they determine the action chosen by optimal policy for each situation (x,y),0<x+y<N.

The minimum expected cost is calculated sequentially for the states (1,N-2), (2,N-3),…(N-1,0), (1,N-3),…(N-2,0),…,(1,0) from the equations referred above retrospectively.

A numerical example is shown below. Consider the case in which N=10, K=1, α=2, β=1, c_1=1.5 and c_2=1.

2. Basic Epidemiological Models

2.1. Modelization in Epidimiology

Modelization an epidemic is a complex phenomenon. The creation and spread of an infection is determined by various factors such as the environment in which the virus is located and grows, the population exposed to it, and the dynamics of the population being studied. The role of mathematics in epidemiology is to model the creation and spread of a virus.

To achieve this, scientists follow a method by which the population is divided into smaller groups or compartments depending on individuals' vulnerability to the virus that develops in the system. These models are called dividing models in epidemiology and contribute to the understanding of the systems by which the virus operates. The most well-known compartments in each epidemic model are the susceptible S, the infectious I and the recovered R. For example in models containing only compartments S and I, the population N is initially divided only into these compartments. S represents people who are healthy but susceptible to infection and I represents people who are infected but able to recover. From this separation of the two groups S and I in the population comes the simplest epidemic model SI. Then of course the segregation can become particularly rich and there may be additional groups of the population.

In different models, individuals can move randomly from one compartment to another at a certain rate rather than in a deterministic way, as stochastic models can better capture the dynamics of the spread of an infection. Studying the SI model it is observed that healthy individuals can move randomly

from compartment S to I at a rate of infection resulting from interactions with infected individuals. Accordingly, infected individuals can move from compartment I to S at some rate of recovery and this is a result of recovery from infection. As mentioned above, in addition to the models with only two compartments, there are other epidemic models that record more features of a disease. This is achieved by adding more compartments, such as R representing individuals who are no longer prone to infection. This compartment can symbolize the dead, the vaccinated or the immunized individuals. Next the focus is done on epidemic models, susceptible-infected-sensitive SIS and susceptible-infected-recovered SIR models.

2.2.Introduction to Epidemic Models

Epidemic models aim to predict the evolution of epidemics. Mathematical models of this kind are particularly important, as epidemics are the leading cause of death worldwide. Infections cause millions of deaths each year, mainly in developing countries (Zhou & Liu 2003). Thus, these models play an important role in predicting the effect of infectious diseases. Mathematical modelization can contribute to a better understanding of the spread of infectious disease and of control policies testing (Meyers, 2007; Kao, 2002).

Moving on to the historical development of mathematical epidemiology, in 1911 Ross's simple epidemic model was presented and followed in 1927 Kermack-McKendrick's simplest epidemic SIR model proposed to explain the rapid rise and fall in the number of infectious diseases observed in epidemics such as the plague (London 1665-1666, Bombay 1906) and cholera (London 1865).

Although vaccination can be given for many infectious diseases, they will continue to plague many people and cause death, especially in developing countries. In developed countries, chronic diseases such as cancer and heart disease receive more attention than infectious diseases, which however cause the most deaths in the world. Recently, the HIV virus that causes AIDS has become a very important infectious disease in developing as well as in developed countries.

The mechanism of transmission of an infectious disease from one infected person to another susceptible person is understood for almost all infectious diseases and it is also known how diseases spread through a chain of transmission of infections. The interaction of transmission in a population is quite complex and so it is very difficult to understand the dynamics of the spread of an infectious disease without knowing the typical structure of the corresponding mathematical model. An epidemiological model uses the microscopic description, that is, the role of an infected person, to predict the macroscopic behavior of the spread of the disease across the population.

In many sciences it is possible to conduct experiments to obtain information and to test hypotheses. Experiments with infectious diseases that spread to human populations are usually impossible, immoral, or very expensive. The information available is usually from epidemics that occur naturally without human intent and are usually inadequate due to lack of information. This lack of reliable information makes accurate estimation of the displayed parameters difficult and therefore only a range of values can be estimated for some parameters.

Since repetitive experiments and reliable data are not available in epidemiology, mathematical models and computer simulations will be used to conduct the necessary theoretical experiments. Thus, calculations can be made for a variety of values of variables and initial conditions.

Mathematical models have some limitations but also possibilities that must be taken into account. Many times the questions cannot be answered using epidemiological models, but other times the researcher can achieve the right combination of available data, interesting questions and a mathematical model and, thus, lead to answers.

Comparisons and comparisons can lead to a better understanding of the process of transmitting an infectious disease. Modeling can be used to compare different diseases in the same population or the same disease in different populations or the same disease in different time periods.

Epidemiological models are also useful for comparing the effects of a possible outbreak prevention attempt or control of the disease transmission process. These models are usually the only practical approach to answering the question of which prevention or control process is most effective.

Quantitative predictions of epidemiological models involve uncertainty as the models are usually ideal, with many simplifications and assumptions, since many parameter values can only be estimated and not accurately measured. However, the predictions for the relative validity of the various control methods are usually reliable and strong in the sense that we come to the same conclusions for a wide range of parameter values but also for a variety of models. Optimal vaccination strategies can theoretically be found using models.

Longini et al., (1978) used an epidemiological model to decide which age group to be vaccinated first to minimize the cost or number of deaths in a flu epidemic. Certainly, more information about the effectiveness of the vaccine as a function of time will be needed to be able to estimate the age at which the vaccine should be given to achieve optimal results. So epidemiological models can help to get this useful information.

An underestimated value of epidemiological models is that they lead to clear assumptions about the biological and social mechanisms by which the disease spreads. The values of the parameters used in the epidemiological models must have a clear correlation with indisputable physical quantities, such as the rate of interface or reproduction of the disease, ie the rate at which an infected person transmits the disease to another susceptible person. the duration of the disease, the incubation time of the disease coke.

The models can be used to estimate many quantitative assumptions. For example, one model could test the hypothesis that AIDS would be reduced if a large percentage of the heterosexual, sexually active population used systemic condoms. Models can also predict the spread or eradication of a disease. For example, Heathcote (2000) predicted that rubella and congenital rubella syndrome would eventually disappear from the US because the level of vaccination (using the combination of measles - mumps and rubella vaccine) is well above the threshold required to acquired immunity to measles. An epidemiological model can also be used to determine the sensitivity of forecasts to changes in parameter values. Once the values of the parameters that have the greatest influence on the forecasts are determined, it will then be possible to carry out studies to better estimate these parameters.

In this chapter some types of epidemic models, which are analyzed by three different stochastic modeling processes, will be examined. The first model is described by the Discrete Time Markovian Chain (DTMC), the second model by the continuous time Markovian chain (CTMC) and the third model by the stochastic differential equation (SDE). These three models differ from each other in relation to the time and state of the variables.

In the DTMC model the time and the state variable are discrete random variables, in the CTMC model time is continuous, but the variable state is a distinct random variable and in the SDE model both temporal and state variables are continuous random variables. However, for the moment most models created by scientists have been relied on the continuous time Markovian chain according to Keeling and Ross (Keeling & Ross, 2008).

Also, the status of the process is determined by the number of susceptible individuals. For this reason, it is understood that a population of N- individuals will need a large number of differential equations to describe the ease of propagation. For example, in a population with N individuals, the modelization of a continuous time SIS model would require N + 1 differential equations, while for the SIR model (N + 1) (N + 2) / 2 differential equations (Keeling & Ross, 2008).

Finally, the three apartments into which the population is divided (vulnerable, infectious, recovered), represent its' different states.

2.3.Symbols of Models

Vulnerable people, i.e. those who can be more easily infected with a contagious disease, are denoted by S (susceptible). Infected people, i.e. those who have been infected with the disease and can transmit the disease, are symbolized by I (infective). People who are infected but for various reasons cannot transmit the disease (have acquired immunity or have been quarantined, etc.) are denoted by R (recovery). Individuals who are infected and are in the incubation phase are denoted by E.

The main types of models are:

- **S-I-S:** They are the models in which individuals do not acquire immunity after they get well and therefore, can be re-infected with the disease. Vulnerable- Infected- Vulnerable
- SIR: They are the models in which people, after getting well, acquire permanent immunity and cannot transmit the disease. Vulnerable-Infected-Immunity
- **SIRS:** They are the models in which people, after recovering, acquire temporary immunity and then can become infected again and transmit the disease. Vulnerable-Infected-Immunity-Vulnerable
- **SI:** They are the models in which people after being infected cannot be cured. Vulnerable-Infected
- **SEIR:** They are the models in which people after becoming infected can only become contagious when the incubation period of the disease is over.
-

2.4. Vulnerable-Incubation-Infected-Immunity

SIR models are generally more suitable for diseases caused by viruses such as measles, mumps and smallpox. SIS models are suitable for models with diseases caused by bacteria such as meningitis, plague and venereal diseases but also for diseases with protozoa such as malaria and trypanosomiasis (sleep disease or encephalitis). SI models are suitable for diseases such as AIDS where there is no cure yet.

A basic principle in epidemiology is the existence of limit values, i.e. critical values for quantities such as interface rate, population size, population density, mortality rate, etc., which play a decisive role in the birth of an epidemic or not and also determine the rate of its spread or elimination.

2.5.Simple Epidemic Model of an Epidemic in an Unstable Population

Assuming we have an unstable population where there are endemics, expatriates, births and deaths. Suppose we have:

- x Vulnerable people in the sense that they can be infected with a contagious disease
- y infected people who can transmit the disease

Assuming, in the time period dt the number of people who can infect is μ x y dt people and at the same time some infected people have either died, been isolated or have become well and have acquired immunity.

If one says that vy dt people have left like this. If during this period ϱ dt new vulnerable individuals are added then we have the following model:

$$x' = -\mu \times y + \rho$$
$$y' = \mu xy - vy$$

where μ, ν, ϱ are positive constants.

If (x0, y0) is a point of equilibrium such that x '= 0, y' = 0 then we have:

$$-\mu x_0 y_0 + \rho = 0$$
$$\mu x_0 y_0 - v y_0 = 0$$

With $x_0 = \frac{v}{\mu}, y_0 = \frac{\rho}{v}$

Seeing how the population will behave if one approaches the equilibrium point with a neighboring point, he linearizes close to the equilibrium point by applying perturbation theory. Poses for

$$x = x_0(1 + \xi)$$
$$\kappa\alpha\iota$$
$$y = y_0(1 + \eta)$$

where ξ and η are very small quantities, i.e. $\xi - 0$ and $\eta - 0$ and replacing in the system (deleting quantities that have product of ξ and η because they are too small) takes

$$\xi' = - \sigma (\xi + \eta)$$

$$\eta' = \nu\xi$$

where σ = μρ / ν.

Substitutes ξ in the second equation and takes

$$\eta'' + \sigma\eta' + \sigma\nu\eta = 0$$

with initial conditions η = η0, $\eta' = v\xi_0$ for t = 0.

The equation has a solution

$$\eta = e^{-\frac{\sigma t}{2}}\left\{\eta_0 \cos \omega t + \frac{1}{\omega}\left(v\xi_0 + \frac{1}{2}\sigma\eta_0\right)\sin \omega t\right\}$$

whereas ω2 = σ ν - σ 2/4.

This is how it turns out:

$$\xi = e^{-\frac{\sigma t}{2}}\left\{\xi_0 \cos \omega t + \frac{\sigma}{2\omega}(v\xi_0 + 2\eta_0)\sin \omega t\right\}$$

If ω 2> 0, ie 4ν> σ or 4ν2> μρ then the population after oscillating around the equilibrium point will return to it with exponential damping.

2.6.Simple epidemic model (SI) in a stable population

Assuming there is a closed society, that is, a stable N population where there are no endemics or expatriates, nor births and deaths, and that they are evenly mixed. It can also be assumed that the infectious disease has no incubation period and that there is no cure for the disease.

Let's say that:

- S-vulnerable individuals
- I-infected individuals

Suppose that the rate of transmission of the disease is proportional to the number of susceptible individuals and proportional to the number of infected individuals.

The equations that describe the model are:

$$S' = -\alpha SI$$
$$I' = \alpha SI$$

where α is a positive quantity.

If there is a fixed population, i.e. S (t) + I (t) = N then the equivalent system results by substitution:

$$S(t) = N - I(t)$$
$$I^{|'}(t) = \alpha[N - I(t)]I(t)$$

This non-linear SDC is known as the logistic growth equation and was named after Pierre François Verhulst in 1845, a Belgian mathematician and physician who studied population development models.

They are separable variables, so dividing by follows:

$$\frac{1}{[N - I(t)]I(t)} I'(t) = \alpha \quad . \quad or$$
$$\frac{1}{[N - I(t)]I(t)} \frac{dI}{dt} = \alpha$$

and concluding:

$$\int_0^t \frac{1}{[N-I(t)]I(t)}\frac{dI}{dt}dt = \int_0^t adt \Rightarrow$$

$$\int_{I(0)}^{I(t)} \frac{1}{(N-u)u}du = at \Rightarrow$$

$$\frac{1}{N}\int_{I(0)}^{I(t)} \left(\frac{1}{N-u}+\frac{1}{u}\right)du = at \Rightarrow$$

$$[\ln u - \ln (N-u)]_{I(0)}^{I(t)} = aNt \Rightarrow$$

$$[\ln I(t) - I(0)] - [\ln (N-I(t) - \ln (N-I(0)] = aNt \Rightarrow$$

$$I(t) = \frac{I(0)Ne^{aNt}}{N-I(0)+I(0)e^{aNt}} \Rightarrow$$

$$I(t) = \frac{I(0)N}{I(0)+[N-I(0)]e^{-aNt}}$$

Concluding the accounting curve, one observes that as it turns out $t \to \infty$ eventually everyone $I \to N$, will be infected.

2.7. Deterministic SIS and SIR models

2.7.1. SIS model

In the SIS epidemic model, a susceptible person will become ill when it comes in contact with an infectious one. Then it will infect the people with whom it will associate. After treatment, infected people do not become immune to the disease and rejoin the vulnerable group. The SIS model expresses in some way the experience that in some diseases individuals do not acquire a long immunity time after the disease and therefore become immediately vulnerable after healing. Some hypotheses related to this model are that, all individuals belong to the vulnerable

group and there are no deaths from the epidemic. Such models have been applied to sexually transmitted diseases.

The following figure shows the evolution of an epidemic SIS model. There are two groups of the population in the figure, the group with the susceptible individuals S and the group with the infectious individuals I. The dashed arrows indicate the transition from one group to another and vice versa.

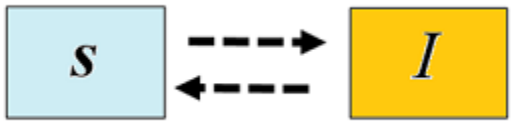

Figure 1. Representation of the SIS epidemic model

The system of differential equations used to describe the SIS epidemic model is:

$$\frac{dS}{dt} = \frac{-\beta}{N} + (\beta + \gamma)I$$

$$\frac{dI}{dt} = \frac{\beta}{N}SI - (\beta + \gamma)I$$

where $\beta > 0$ denotes the average number of contacts per person per year, with $\gamma > 0$ the rate of recovery or mortality, i.e. the number of recovered or dead during a day, with $b \geq 0$ the rate of births and with $N = S(t) + I(t)$ the total size of the population.

As initial conditions, S(0)>0, I (0)>0 and N =S(0)+I(0). Also, the initial assumption is that the birth and death rates are equal, so that the population size dN/dt =0 remains constant.

Next, the basic reproduction rate will be defined, which consists of the expected number of new infections, these new infections are sometimes called secondary infections, from a single infection in a population where all individuals are susceptible and given by the relationship:

$$R_0 = \frac{\beta}{b + \gamma}$$

When R_0>1 the infection will be able to start spreading to a population, but not if R_0<1. Therefore, if R_0>1, there is more than one transmission from an infectious person and then there is an epidemic.

In general, the higher the value of R_0, the more difficult it is to control an epidemic. In this case the epidemic can be avoided by reducing R_0. This can happen by vaccinating the population and thus reducing the initial vulnerable population.

The length of the infectious period is defined as the fraction 1/(b + γ). According to the following theorem the asymptotic solution of the SIS model of the relations mentioned above is as follows:

Theorem 2.1: If S(t) and I(t) are a solution of the aforementioned model then

i. If $R_0 \leq 1$, then $\lim_{t\to\infty}(S(t), I(t)) = (N, 0)$ (disease-free equilibrium state).

ii. ii. If $R_0 > 1$, then $\lim_{t\to\infty}(S(t), I(t)) = (\frac{N}{R_0}, N(1-\frac{1}{R_0})$ (endemic equilibrium state).

The term "disease-free equilibrium" defines the state in which there is no disease in the population. On the other hand, the term "endemic equilibrium state", defines the state in which the disease cannot be completely eliminated, but remains in the population.

2.7.2. SIR model

The SIR model is an epidemic model that estimates the theoretical number of people infected with a contagious disease in a closed population during the infectious period. Kermack and McKendrick define the deterministic epidemic model with a stable population of N individuals and three states S, I, and R.

In this epidemic model, infected people have the potential to develop immunity, unlike the previous model, and thus pass on to the R (recovered) group of the population. The epidemic is noted to end when I(t)=0, i.e. there are no infectious individuals. The SIR model has been applied to childhood diseases such as chickenpox, measles and mumps. Therefore, the features that govern the SIR model are:

1. the population is considered stable and is divided into three groups-departments

2. the set of susceptible S or S(t) (if the abundance of the set depends on time)

3. the set of patients I or I(t)

4. the set of recovered R or R(t)

In the figure Below the epidemic SIR model is represented.

Figure 2. Representation of the SIR Epidemic Model

The differential equations used to describe the epidemic SIR model are as follows

$$\frac{dS}{dt} = \frac{-\beta}{N} SI + b(I + R)$$

$$\frac{dI}{dt} = \frac{\beta}{N} SI - (\beta + \gamma)I$$

$$\frac{dR}{dt} = \gamma I + bR$$

where $\beta>0$, $\gamma>0$, $b\geq 0$ and the total population size satisfies the relation $N=S(t)+I(t)+R(t)$. The initial conditions are $S(0)>0$, $I(0)>0$, $R(0)\geq 0$ and $N=S(0)+I(0)+R(0)$ or otherwise the initial condition of the susceptible, infectious and deleted is equal to the population. Also, in this model it is assumed that the percentage of births and deaths is equal to keep the population size constant $dN/dt=0$. The following theorem gives the asymptotic solution of the deterministic SIR model of the aforementioned relation.

Theorem 2.2: If S(t), I(t) and R(t) are a solution of the aforementioned model, then:

i. If $R_0 \leq 1$, then $\lim_{t\to\infty}(I(t)) = 0$ (disease-free equilibrium state).

ii. If $R_0 > 1$, then $\lim_{t\to\infty}(S(t), I(t), R(t)) = (\frac{N}{N_0}, \frac{bN}{b+\gamma}\left(1 - \frac{1}{R_0}\right), \frac{\gamma N}{b+\gamma}(1 - \frac{1}{R_0}))$ (endemic equilibrium state).

iii. Assuming b=0. If $R_0 \frac{S(0)}{N} > 1$, there is an initial increase in the number of patients I(t) (epidemic), if $R_0 \frac{S(0)}{N} \leq 1$, then it decreases monotonically to zero (disease-free equilibrium).

Let define as initial replacement number the quantity $R_0 \frac{S(0)}{N}$ which indicates the average number of secondary infections produced by an infectious person at the beginning of the epidemic. In case (iii) it is observed that the disease disappears from the population, but if the initial replacement number is greater than one, the population is subject to an "epidemic outbreak".

If $R_0 < 1$, the person affected by the disease will infect less than a person before recovering, so the outbreak of the epidemic will be gradually extinguished, i.e. dI/dt <0. The number of susceptical individuals initially decreases and then becomes stable. Also, the number of infections is initially reduced and eventually zeroed, which indicates that the epidemic is not spreading. The number of recovered R(t) first increases and then stabilizes. These conclusions are reflected in following figure

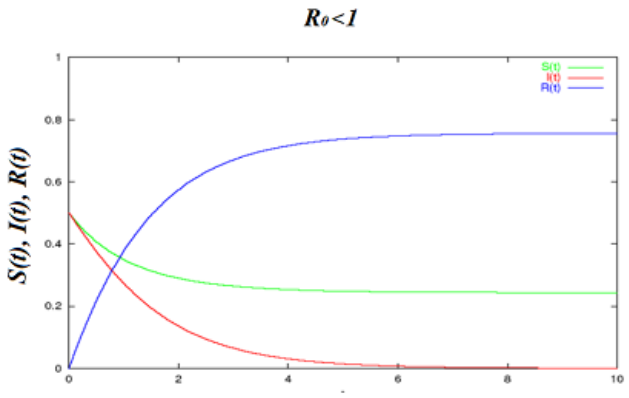

Figure 3. States of the model for R0<1

On the other hand, when R_0>1, the infected person will infect more than one persons, so the epidemic will spread, i.e. dI/dt>0. The number of susceptible individuals decreases initially and then stabilizes while at the same time the number of infectious people increases over the same period of time, which indicates the spread of the epidemic. The number of deleted increases at a slower rate and eventually stabilizes. In contrast, when R_0<1, the increase is at a higher rate. Then following figure is given in case R_0> 1.

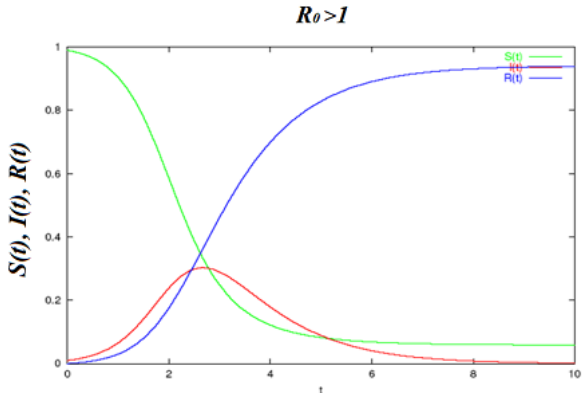

Figure 4. States of the model for R0>1

2.8.DTMC-Discrete TimeMarkov Chain Models

Discrete-time Markov models are commonly used for the study of pathogens with relatively short and constant durations infectivity. Usually, in these models the timeline step Δt determines the duration of the infectious period.

However, it is required a time step Δt that represents the interval between two consecutive decision time points, which is determined by the decision maker and will depend on the context of the under consideration problem. Therefore, disease transmission models that will support the reception of dynamic decisions need to be flexible enough to integrate th different Δt, which vary within a reasonable range and are determined by the receiver decisions.

As mentioned in the introduction, the DTMC model consists of distinct random variables. These variables are S(t), I(t) and R(t) ∈{{0, 1, 2, ..., N} in time t∈{0, Δt, 2Δt, ...} and symbolize the susceptible, the infectious and the recovered individuals of the population, respectively. Below the DTMC SIS and DTMC SIR models are analyzed.

2.8.1. Discrete Time Epidemic Model SIS (DTMC SIS)

In the DTMC SIS epidemic model, there is only one independent random variable, I(t) which symbolizes the new infectious individuals, because S(t) = N-I(t), where N is the constant total population size. As far as the stochastic procedure is concerned $\{I(t)\}_{t=0}^{\infty}$, each random process variable has the following probability function:

$$p_i(t) = P\{I(t) = i\}$$

with i = 0,1,2,…, N and t = 0, Δt, 2Δt, ..., where $\sum_{i=0}^{N} p_i(t) = 1$ and $p(t) = (p_0(t), p_1(t), \dots p_N(t))^T$ the probability vector associated with I(t). Also, the stochastic process $\{I(t)\}_{t=0}^{\infty}$ has the Markov feature:

$$P\{I(t + \Delta t) \mid I(0), I(\Delta t), \dots, I(t)\} = P\{I(t + \Delta t) \mid I(t)\}$$

that is, the process at time t+Δt depends only on the process at the previous step of time t.

Next the relationship between I(t) and I (t+Δt) will be determined. The probability transition from state I(t)=i to state I(t+Δt) = j, i → j, at time Δt, is defined as follows:

$$p_{ij}(t + \Delta t, t) = P\{I(t + \Delta t) = j \mid I(t) = i\}$$

When the probability of transition $p_{ji}(t+\Delta t,t)$ does not depend on t and $p_{ji}(\Delta t)$, the process is said to be temporally homogeneous. In addition, to reduce it number of time transitions Δt another assumption is made for time step Δt selecting it small enough so that the number of infectious individuals changes by at most one person in the time interval Δt, ie i → i + 1, i → i-1 or i → i.

However, there may be new infection, death or recovery during of the time interval Δt. The latter hypothesis can be modified if the time step cannot be arbitrarily chosen small enough. In that case the transition probabilities must be

defined for all possible transitions that may occur, i→ i+2, i→ i+3, etc. In the simple case of three transitions, the transition probabilities are calculated using the coefficients, multiplied by Δt.

The transition probabilities for the epidemic model DTMC are:

$$p_{ji}(\Delta t) = \begin{cases} \frac{\beta i(N-i)}{N}\Delta t, & j = i+1 \\ (b+\gamma)i\Delta t, & j = i-1 \\ 1 - \left[\frac{\beta i(N-i)}{N} + (b+\gamma)i\right]\Delta t, & j = i \\ 0, & j \neq i+1, i, i-1 \end{cases}$$

where, the probability of a new infection from i→i+1 is $p_{i+1,i}(\Delta t)= \beta i(N-i)\Delta t/N$ and the probability of death or recovery from i→i-1, is $p_{i-1,i}(\Delta t)=(b+\gamma)i\Delta t$. Finally, the probability that there is no state change, ie from i→i, is $p_{i,i}(\Delta t) = 1-[\beta i (N-i)/N + (b+\gamma)i]/\Delta t$. It has to be emphasized that neither in the determinist, but nor in the stochastic model is it necessary to assume that the number of births is equal to the number of deaths in order not to affect the constant sample size, N.

In order to simplify the possibility of transition the following symbols can be used, a new infection will be denoted by $b(i)\Delta t$ and death or recovery will be denoted by $d(i)\Delta t$, so:

$$p_{ji}(\Delta t) = \begin{cases} b(i)\Delta t j = i+1 \\ d(i)\Delta t, j = i-1 \\ 1 - [b(i) + d(i)]\Delta t, j = i \\ 0, j \neq i+1, i, i-1 \end{cases}$$

The sum of the three transitions is equal to one, because these transitions represent all possible changes in state i during time interval Δt. To ensure that these probabilities of transition are in the interval [0,1], the time step Δt must be selected small enough

$$\max_{i\in\{1,2,\dots N\}}\{[b(i)+d(i)]\Delta t\}\leq 1$$

From the Markov capacity and the previous probabilities of transition, the transition probabilities $p_i(t+\Delta t)$ can be expressed based on the probabilities transition time t. Thus, in time t+Δt:

$$p_i(t+\Delta t)=p_{i-1}(t)b(i-1)\Delta t+p_{i+1}(t)d(i+1)\Delta t+p_i(t)(1-[b(i)+d(i)]\Delta t)$$

where $i=1,2,\dots,N$ and $b(i)=\beta i(N-i)/N$, $d(i)=(b+\gamma)i$.

The transition probabilities from one situation to another can be expressed as an Array format. Each entry in the Array is a probability of transition, the array is called a transition array and is denoted as P(Δt). Then for the forming of a stochastic transition array the states from 0 to N have to be in order. The array P(Δt) is an array of dimensions (N+1)x(N+1) with the same sum of columns and is given below

$$\begin{pmatrix} 1 & d(1)\Delta t & 0 & \cdots & 0 & 0 \\ 0 & 1-(b+d)(1)\Delta t & d(2)\Delta t & \cdots & 0 & 0 \\ 0 & b(1)\Delta t & 1-(b+d)(2)\Delta t & \cdots & 0 & 0 \\ 0 & 0 & b(2)\Delta t & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & d(N-1)\Delta t & 0 \\ 0 & 0 & 0 & \cdots & 1-(b+d)(N-1)\Delta t & d(N)\Delta t \\ 0 & 0 & 0 & \cdots & b(N-1)\Delta t & 1-d(N)\Delta t \end{pmatrix}$$

Therefore, the DTMC SIS epidemic procedure has been fully defined, $\{I(t)\}_{t=0}^{\infty}$. From the initial probability vector p(0), it follows that p(Δt) = P(Δt) p(0). The aforementioned relation expressed through the stochastic array and vector gets:

$p(t+\Delta t) = P(\Delta t)p(t) = P^{n+1}(\Delta t)p(0)$ where $t=n\Delta t$.

The mean value of the epidemic process for time t is given by:

$$E\big(I(t)\big) = \sum_{i=0}^{N} i p_i(t)$$

Then, for t+Δt, multiplying and summing the above equations with i results:

$$E(I(t+\Delta t)) = \sum_{i=0}^{N} i p_i(t+\Delta t)$$

$$= \sum_{i=1}^{N} i p_{i-1}(t) b(i-1)\Delta t + \sum_{i=0}^{N-1} i p_{i+1}(t) d(1+i)\Delta t + \sum_{i=0}^{N} i p_i(t) - \sum_{i=0}^{N} i p_i(t) b(i)\Delta t - \sum_{i=0}^{N} i p_i(t) d(i)\Delta t$$

Replacing of *b(i)* and *d(i)* with the relations $\beta i(N-i)/N$ and $(b+\gamma)i$ respectively

$$E(I(t+\Delta t))$$

$$= E(I(t)) + \sum_{i=1}^{N} p_{i-1}(t) \frac{\beta(i-1)(N-(i-1))}{N}\Delta t - \sum_{i=0}^{N-1} p_{i+1}(t)(b+\gamma)(\iota+1)\Delta t$$

$$= E(I(t)) + [\beta - (b+\gamma)]\Delta t E(I(t)) - \frac{\beta}{N}\Delta t E(I^2(t))$$

where $E\left(I^2(t)\right) = \sum_{i=1}^{N} i^2 p_i(t)$. Because the relation is valid $E\left(I^2(t)\right) \geq E^2(I(t))$ the mean value satisfies the following inequality

$$\frac{E(I(t+\Delta t)) - E(I(t))}{\Delta t} \leq [\beta - (b+\gamma)]E(I(t)) - \frac{\beta}{N}E^2(I(t))$$

$\Delta t \to 0$,

$$\frac{dE\left(I(t)\right)}{dt} \leq [\beta - (b+\gamma)]E\left(I(t)\right) - \frac{\beta}{N}E^2\left(I(t)\right)$$

$$= \frac{\beta}{N}\left[N - E\left(I(t)\right)\right]E\left(I(t)\right) - (b+\gamma)E\left(I(t)\right)$$

The right side of Relation is the same as the differential equation for I(t). If I(t) and S(t) are replaced with E(I(t) and N-E(I(t)), respectively. Finally, from the inequality that exists in the relation above it is clear that the differential inequality shows that the mean value of random variable I(t) of the stochastic SIS epidemic model is less than solution of I (t) in the deterministic model of differential equations.

The following is a figure of a stochastic DTMC SIS epidemic model, where i = 0, 1, ..., N are the infectious states.

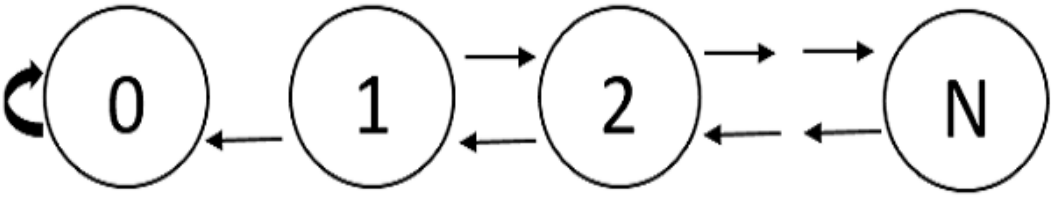

Figure 5. Representation of the Stochastic Epidemic Model DTMC SIS

The states {0,1 ..., N} present in the model can be divided into two sets consisting of the repeated zero state, {0} and the transitional situations, {1, ..., N}. The state {0}is called "absorbing state".

As it is observed in the Figure above, the state {0} is a closed set, however any situation from {1,2, ..., N} can be approached from any other situation as the situations {1 2, ..., N} are not closed sets because the relation $p_{01}(\Delta t) > 0$ is valid. For transitional situations it also applies that the elements of the stochastic array have the feature:

$$P^n = (p_{ij}^{(n)})$$

where $p_{ij}(n)$ is the *(i, j)* element of the n-th power of the stochastic array P^n Still, for every j and every transitional state i holds:

$$\lim_{n\to\infty} p_{ij}^{(n)} = 0$$

The limit of P^n with n → ∞ is a stochastic array with all rows being zero except the first one which has the unit everywhere. From Relation $p(t+\Delta t) = P(\Delta t)p(t) = P^{n+1}(\Delta t)p(0)$ and the theory of Markov chains:

$\lim_{t\to\infty} p(t) = (1,0,0,\dots,0)^T$ where t=nΔt.

The population is approaching equilibrium state without disease (disease-free equilibrium) with a probability of absorption per unit, regardless of size of the basic reproduction rate. The stochastic result is compared with the asymptotic effect of the deterministic epidemic SIS model, as the stochastic result is asymptomatic. Also, the convergence to disease-free equilibrium is achieved very slowly, while the average time to have a state of equilibrium disease-free equilibrium depends on the initial conditions and parameter values.

2.8.2. Discrete Time Epidemic Model SIR (DTMC SIR)

The DTMC SIR epidemic model, consists of distinct random variables S(t), I(t) and R(t) which indicate the number of susceptible, infectious and recovered individuals at time t, respectively. This model has as independent random variables S(t) and I(t) and dependent random variable R(t) given by the relation R(t) = N-S(t) -I(t). The common probability of the process $\{S(t), I(t)\}_{t=0}^{\infty}$ is given by the relation

$$p_{(s,i)}(t) = P\{S(t) = s, I(t) = i\}$$

The transition probabilities are given by:

$$p_{(s+k,i+j),(s,i)}(\Delta t) = \text{Prob}\,\{(\Delta S, \Delta I) = (k,j) \mid (S(t), I(t)) = (s,i)\}$$

where $\Delta S = S(t+\Delta t) - S(t)$.

So,

$$p_{(s+k,i+j),(s,i)}(\Delta t) = \begin{cases} \frac{\beta_{is}}{N\Delta t'} & (k,j) = (-1,1) \\ \gamma i \Delta t, & (k,j) = (0,-1) \\ bi\Delta t, & (k,j) = (0,-1) \\ b(N-s-i)\Delta t, & (k,j) = (1,0) \\ 1 - \frac{\beta is}{N\Delta t} - [\gamma i + b(N-s)]\Delta t & (k,j) = (0,0) \\ 0, & elsewhere \end{cases}$$

Δt is chosen to be quite small as the desired probabilities transition interval is [0,1]. The states are classified into pairs and so the calculation of the stochastic array becomes complex in relation with the SIS epidemic model and its form depends on their layout situations (s, i).

The Markov property is formulated as follows

$$p_{(s,i)}(t+\Delta t) = p_{(s+l,i-1)}(t)\frac{\beta}{N}(i-1)(s+1)\Delta t + p_{(s,i+l)}(t)\gamma(i+1)\Delta t + p_{(s-l,i+l)}(t)b(i+1)\Delta t$$
$$+ p_{(s-1,i)}(t)b(N-s+1-i)\Delta t + p_{(s,i)}(t)\left(1 - \left[\frac{\beta}{N}is + \gamma i + b(N-s)\right]\Delta t\right)$$

Finally, the mean values of the states S(t) and I(t) are:

$$E\big(S(t)\big) = \sum_{S=0}^{N} sp_{(s,i)}(t)$$

and

$$E\big(I(t)\big) = \sum_{i=0}^{N} ip_{(s,i)}(t)$$

3. Epidemic Model and Parameter Uncertainty

In this section we will look at the simple *SIR* epidemic model. The size of the population will be considered constant and the population at time t is assumed to consist of susceptible $S(t)$, infected $I(t)$ and recovered $R(t)$ individuals. If the population is constant, it holds that $N(t) = S(t) + I(t) + R(t)$ and the procedure is fully described by the state $\{(S(t), I(t)): t \geq 0\} = (s, i)$. Susceptible individuals $S(t)$ are vulnerable to infection. Infected individuals $I(t)$ are able to infect susceptible individuals and recovered $R(t)$ individuals have been removed and have no effect on the spread of infection (Panagiotidou & Dimitrakos, 2020). The situation of the population is evolving according to a continuous Markovian process

$$\begin{aligned} P((S(t+\Delta t), I(t+\Delta t)) = (s-1, i+1) |\ (S(t), I(t) = (s,i)) = \beta si\Delta t + o(\Delta t), \\ P((S(t+\Delta t), I(t+\Delta t)) = (s, i-1) |\ (S(t), I(t) = (s,i)) = \gamma i\Delta t + o(\Delta t) \end{aligned} \quad (1)$$

where $\beta > 0$ is the infection rate parameter and $\gamma > 0$ is the removal rate parameter, all other transitions have probability $o(\Delta t)$. For the relative removal rate parameter, $\rho = \gamma / \beta$ we determine the transition probabilities

$$p_{si} = \frac{s}{s+\rho}, \quad q_{si} = \frac{\rho}{s+\rho} \quad (2)$$

with p_{si} and q_{si} being independent of i.

The simplest cost function we will consider is the expected non-intervention cost function and the final expected size of the epidemic. The final size is the total number of susceptible people throughout the epidemic. The expected final size of the epidemic without intervention, $C_Q(s, i)$ is determined as

$$C\rho(s,i) = p_{si}(1+C\rho(s-1,i+1)) + qC\rho(s,i-1) \quad (3)$$

with $s, i \geq 1$ and $C_Q(s, 0) = 0$ with $s \geq 0$, $C_Q(0, i) = 0$ with $i \geq 0$.

The two interventions that we will consider are the isolation of infectious individuals from the population and the isolation of infectious individuals along with the immunization of the entire population.

As unit costs, we define the cost of an infected person. The policy we have adopted allows at any time to isolate infected individuals at a certain cost, L per person.

We define as $W_{L,Q}(s, i)$ the expected future cost for a single transition and then we can calculate the expected future cost $V_{L,Q}(s, i)$ for the adoption of an optimal policy starting from (s, i), so we have

$$\begin{aligned} W_{L,\rho}(S,i) &= p_{si}\left(1+V_{L_n\rho}(s-1,i+1)\right) + q_{si}V_{L,\rho}(S,i-1) \\ V_{L,\rho}(s,i) &= \min\left\{L+V_{L,\rho}(s,i-1), W_{L,\rho}(s,i)\right\} \end{aligned} \quad (4)$$

with $s, i \geq 1$ and boundary conditions $V_{L,Q}(s, 0) = 0$ for $s \geq 0$, $V_{L,Q}(0, i) = 0$ for $i \geq 0$.

In state (s, i) the best policy is to isolate an infectious person if $L + V_{L,Q}(s, i\text{-}1) \leq W_{L,Q}(s, i)$ and not to isolate if $L + V_{L,Q}(s, i\text{-}1) > W_{L,Q}(s, i)$. Also note that there is a positive

chance that at least one susceptible person will avoid infection and therefore $V_{L,\varrho}(s, i) \leq C_{\varrho}(s, i) < s$ applies. Next, we can set a limit $u_{L,\varrho}(s)$ such that for $1 \leq i \leq u_{L,\varrho}(s)$ we isolate all infectious individuals, while for $i > u_{L,\varrho}(s)$ there is no intervention in the population. The limit of isolation is given by the relation

$$u_{L,\rho}(s) = \max\left\{i : L + V_{L,\rho}(S, i-1) \leq W_{L,\rho}(s, i)\right\} = \max\left\{i : Li \leq WL_{,\rho}(S, i)\right\} \quad (5)$$

for $s \geq 1$, and given the optimal policy it follows that $V_{L,\varrho}(s, i) = \min\{Li: W_{L,\rho}(s, i)\}$ with $s, i \geq 1$. The function $V_{L,\varrho}(s, i)$ is a non-decreasing function for every s, i and holds that $u_{L,\rho}(s) \leq u_{L,\varrho}(s + 1)$ for $s \geq 0$ (Abakuks, 1974).

In addition, we will assume that we adopt a policy that allows the immunization of either all susceptible individuals or none of susceptible individuals. (Abakuks, 1974) proved that for this policy there is a limit of immunization and related properties. However, instead of studying the total immunization policy, we will look at a policy that allows the isolation of infectious individuals, while immunizing the entire population.

Therefore, at any time we can isolate any number of infectious individuals, each at cost $L > 0$, immunize the entire susceptible population at cost $A + sK$, where $A \geq 0$, $0 \leq K < 1$, $A + K > 0$, or otherwise there is no intervention in the population. Also, for $K \geq 1$ the cost of non-intervention is always less than the cost of immunization and we have the isolation policy.

In addition, we denote by $V_{L,A,K,\rho}(s, i)$ the expected future cost of adopting an optimal policy starting with (s, i) and by $W_{L,A,K,\rho}(s, i)$ the expected future cost of waiting to make a single transition and adopt an optimal policy. Then we have:

$$W_{L,A,K,\rho}(S,i) = p_{si}\left(1+V_{L,A,K,\rho}(S-1,i+1)\right)+q_{si}V_{L,A,K,\rho}(S,i-1)$$
$$VL_{v,A,K,\rho}(S,i) = \min\left\{A+sK, L+VL, A, K, \rho(S,i-1), W_{L,A,K,\rho}(S,i)\right\} \quad (6)$$

with $s, i \geq 1$ as well as $V_{L,A,K,\rho}(s, 0) = 0$ with $s \geq 0$, $V_{L,A,K,\rho}(0, i) = 0$ with $i \geq 0$.

In case for any state (s, i) it holds that $W_{L,A,K,\rho}(s, i) < \min\{A + sK, L + V_{L,A,K,\rho}(s, i-1)\}$ then intervention does not exist, if $L + V_{L,A,K,\rho}(s, i-1) < A + sK$ and if $L + V_{L,A,K,\rho}(s, i-1) \leq W_{L,A,K,\rho}(s, i)$ then isolate infectious individuals. In case $A + sK \leq \{L + V_{L,A,K,\rho}(s, i1), W_{L,A,K,Q}(s, i)\}$ we immunize the entire susceptible population. In addition, we conclude that when the costs are equal, total immunization prevails over isolation, which in turn prevails over non-intervention.

Furthermore, (Abakuks, 1974) proves the existence of the quantities $S_{L,A,K,Q}(s)$ and $R_{L,A,K,\rho}(s)$, so that the optimal policy in state (s, i) is to isolate all infectious individuals for $1 \leq s \leq S_{L,A,K,Q}(s)$, no intervention for $S_{L,A,K,\rho}(s) < i \leq R_{L,A,K,Q}(s)$ and immunize all susceptible individuals for $s > R_{L,A,K,\rho}(s)$. Finally, it proves that $V_{L,A,K,\rho}(s, i)$ is a non-decreasing function for every s and i, that $S_{L,A,K,\rho}(s)$ is non-decreasing in s and that $S_{L,A,K,\rho}(s) \leq u_{L,\rho}(s)$, where $u_{L,\rho}(s)$ is the isolation boundary.

3.1. Effect of changes in parameter values

In this section, we will examine the effects of changing the parameters of the epidemic model on expected costs and intervention policies, assuming that the parameter values are known. In the following sections we will first consider an optimal isolation policy and then give corresponding results when the

immunization of the entire susceptible population is allowed as well as the isolation of infectious individuals. (Panagiotidou & Dimitrakos, 2020).

Isolation policies

In the following we will mention some theorems on which the isolation policy is based. First, we consider the optimal cost function for the isolation policy. We consider the effect of changes in the value of the relative isolation rate, ρ on the optimal cost function $V_{L,\rho}(s, i)$ and the effect on the isolation boundary $u_{L,\rho}(s)$.

Theorem 1: Since s, i ≥ 0 then $V_{L,\rho}(s, i)$ is a non-increasing function of the relative isolation rate, ρ. In addition, $V_{L,\rho}(s, i) \to \min\{Li, s\}$ when $\rho \to 0$ and $V_{L,\rho}(s, i) \to 0$ when $\varrho \to 1$.

Proof:

We will first show by induction that $V_{L,\rho}(s, i)$ is a non-increasing function of the relative isolation rate, ρ. The result is true for s = 0, since $V_{L,\rho}(0, i) = 0$ for i ≥ 0, by definition. Assume that for a given s ≥ 1, $V_{L,\rho}(s\text{-}1, i)$ is a non-increasing function of the relative isolation rate, ρ for i ≥ 0. We know that for i = 0, $V_{L,\rho}(s, i) = 0$. Assume that for some i ≥ 1, $V_{L,\varrho}(s, i\text{-}1)$ is a non-increasing function of the relative isolation rate, ρ. From equations (4) and (2), for $\rho, \varepsilon \geq 0$ we have (Clancy & Green, 2007).

$$
\begin{aligned}
W_{L,\rho+\varepsilon}(s,i) &= \frac{s}{\rho+s+\varepsilon}\Big(1+V_{L,\rho+\varepsilon}(s-1,i+1)\Big)+\frac{\rho+\varepsilon}{\rho+\varepsilon+s}V_{L,\rho+\varepsilon}(s,i-1) \\
&= \frac{s}{\rho+s}\Big(1+V_{L,\rho+\varepsilon}(s-1,i+1)\Big)+\frac{\rho}{\rho+s}V_{L,\rho+\varepsilon}(s,i-1) \qquad (7) \\
&-\frac{\varepsilon s}{(\rho+\varepsilon+s)(s+\rho)}\Big(1+V_{L,\rho+\varepsilon}(s-1,i+1)\Big)+V_{L,\rho+\varepsilon}(s,i-1)
\end{aligned}
$$

We have $1 + V_{L,\rho+\varepsilon}(s\text{-}1, i + 1) + V_{L,\rho+\varepsilon}(s, i\text{-}1) \geq 0$ and yields:

$$W_{L,\rho+\varepsilon}(s,i) \leq \frac{s}{\rho+s}\left(1+V_{L,\rho+\varepsilon}(s-1,i+1)\right)+\frac{\rho}{\rho+s}V_{L,\rho+\varepsilon}(s,i-1) \quad (8)$$

Subtracting $W_{L,q}(s, i)$ we get

$$\begin{aligned} W_{L,\rho+\varepsilon}(S,i)-W_{L,\rho}(S,i) &\leq \frac{s}{\rho+s}\left(V_{L,\rho+\varepsilon}(S-1,i+1)-V_{L,\rho}(s-1,i+1)\right) \\ &+\frac{\rho}{\rho+s}\left(V_{L,\rho+\varepsilon}(S,i-1)-V_{L,\rho}(s,i-1)\right) \qquad (9) \\ &\leq 0 \end{aligned}$$

From expression (5) we have:

$$\begin{aligned} V_{L,\rho+\varepsilon}(S,i) &= \min\left\{L+V_{L,\rho+\varepsilon}(s,i-1), W_{L,\rho+\varepsilon}(s,i)\right\} \\ &\leq \min\left\{L+V_{L,\rho}(s,i-1), W_{L,\rho}(s,i)\right\} \qquad (10) \\ &= V_{L,\rho}(s,i) \end{aligned}$$

Thus, by induction at i and s, $V_{L,\rho}(s, i)$ is a non-increasing function of the relative isolation rate, ρ for $s, i \geq 0$. Then, to show that $V_{L,\rho}(s, i) \to \min\{Li, s\}$ with $\varrho \to 0$, we observe that the result holds for $s = 0$. From (2) we have $p_{si} \to 1$ and $q_{si} \to 0$ with $\varrho \to 0$. Assume that for a given $s \geq 1$, for all i, we have $V_{L,\rho}(s\text{-}1, i) \to \min\{Li, s\text{-}1\}$ with $\varrho \to 0$. After formula (4), as $V_{L,\rho}(s, i\text{-}1)$ is greater than s, we have $W_{L,\rho}(s, i) \to 1 + \min\{L (i + 1), s\text{-} 1\}$ with $p \to 0$. From the relation (5) $V_{L,\rho}(s, i) \to \min\{Li, L + s,$

Li + L + 1, s} = min {Li, s} with ϱ → 0. Finally, to show that $V_{L,\rho}(s, i) \to 0$ as ϱ → ∞, observe that the result holds for s = 0. From (2), $p_{si} \to 0$ and $q_{si} \to 1$ with ϱ → ∞. Assume that for a given i ≥ 1, for all s, $V_{L,\rho}(s, i- 1) \to 0$ with ϱ → ∞. Thus from (5) it follows that $V_{L,\rho}(s, i) \to 0$ with ϱ → ∞. By induction in i, we get the result.

Having considered the effect of changes in the value of the relative isolation rate, ρ on the optimal cost function $V_{L,\rho}(s, i)$ we then consider the effect on the isolation limit $u_{L,\rho}(s)$. (Panagiotidou & Dimitrakos, 2020).

Theorem 2: For s ≥ 0, the isolation boundary $u_{L,\rho}(s)$ does not increase in ρ. In addition, $u_{L,\rho}(s) \to \max\{i \in Z: i < s / L\}$ with ϱ → 0 and $u_{L,\varrho}(s) \to 0$ with ϱ → ∞.

Proof

We will assume that for some ϱ the s, i are such that $i \le u_{L,\rho}(s)$. That is, optimal policy requires isolating all infectious individuals in the condition (s, i). Then $V_{L,\rho}(s, i) = Li$ and for every ε > 0 with ε ≤ ϱ, from Theorem 1, $V_{L,\rho-\varepsilon}(s, i) \ge VL_{,\rho}(s, i) = Li$. Thus $V_{L,\rho-\varepsilon}(s, i) = Li$ which implies that $i \le u_{L,\rho-\varepsilon}(s)$, and implies that $u_{L,\rho}(s)$ does not increase in ϱ. (Clancy & Green, 2007).

(Abakuks, 1973) proved that $u_{L,\rho}(s) < s / L$ for ϱ > 0 holds. We get s, i ≥ 1 so that i < s / L. Then, from the proof of Theorem 1 we have, $W_{L,\varrho}(s, i) \to \min\{Ls + L + 1, s\}$ with ϱ → 0, so that for quite small ϱ → 0, $W_{L,\varrho}(s, i) > Li$. Therefore, for a fairly small ϱ> 0 we have $i \le u_{L,\rho}(s)$ and $u_{L,\rho}(s) \to \max\{i \epsilon Z: i < s / L\}$ with ϱ → 0. From Theorem 1, given s ≥ 0, $V_{L,\varrho}(s, 1) \to 0$ with ϱ → ∞. Because the intervention cost is constant in L then $u_{L,\varrho}(s) = 0$ for large ϱ.

If we assume, for example, that the infection is more serious than reality, that is, if we underestimate the value of ρ, from Theorem 2 we have that it is best to

intervene by isolating the infectious individuals. In addition, Theorem 1 shows that we may not underestimate, but may overestimate, the cost of the best policy. If we overestimate ρ, opposite conclusions apply.

On whether or not to intervene when the true value of ρ is unknown, knowing the state (s, i) of the population, then we intervene by isolating all infectious individuals if $\rho < \rho_0$ (s, i) when $0 \leq \varrho_0$ (s , i) $\leq \infty$, otherwise there is no intervention. Therefore, it is enough to know if ρ is above or below ρ_0 (s, i) and it is not necessary to know exactly the value of ρ. However, as the state (s, i) of the process evolves, its relative value ρ_0 will change and the process can go through states (s, i) so that the value ρ_0 (s, i) is within the range of reasonable values ρ.

Although our primary interest is the uncertainty about the epidemiological parameters β, γ or equivalents for ρ, it is possible that we do not know the cost of isolation, L. According to the above results on the effect of changes in ρ, we have the following with the effect of changes in L.

Theorem 3: Since s, i ≥ 0, then $V_{L,\rho}$ (s, i) is a non-decreasing function of L. In addition, $V_{L,\rho}$ (s, i) $\rightarrow 0$ with $L \rightarrow 0$ and $V_{L,\rho}$ (s , i) $\rightarrow C_{\varrho}$ (s, i) as $L \rightarrow \infty$.

Proof:

We will first show that $V_{L,\rho}$ (s, i) is a non-decreasing function of L, by induction. It holds for s = 0, with $V_{L,\varrho}$ (0, i) = 0. We assume that for a given s ≥ 1, $V_{L,\varrho}$ (s-1, i) is a non-increasing function of L for every s. We also know that $V_{L,\varrho}$ (s, 0) = 0 for s ≥ 0, $L \geq 0$. We will now assume that for some i $\geq V_{L,\varrho}$ (s, i-1) is a non-decreasing function of L. Then (Clancy & Green, 2007)

$$
\begin{aligned}
W_{L+\varepsilon,\rho}(S,i) - W_{L,\rho}(S,i) &= \frac{s}{\rho+s}\left(1+V_{L+\varepsilon,\rho}(s-1,i+1)\right) \\
&+\frac{\rho}{\rho+s}\Bigg(V_{L+\varepsilon,\rho}(s,i-1) - \frac{s}{\rho+s}\left(1+V_{L,\rho}(s-1,i+1)\right) \\
&-\frac{\rho}{\rho+s}\left(V_{L,\rho}(S,i-1)\right. \\
&\geq 0
\end{aligned}
\tag{11}
$$

Thus,

$$
\begin{aligned}
V_{L+\varepsilon,\rho} &= \min\left\{L+\varepsilon+V_{L+\varepsilon,\rho}(S,i-1), W_{L+\varepsilon,\rho}(s,i)\right\} \\
&\geq \min\left\{L+V_{L,\rho}(s,i-1), W_{L,\rho}(S,i)\right\} \\
&= V_{L,\rho}(S,i)
\end{aligned}
\tag{12}
$$

By induction, $V_{L,\varrho}(s, i)$ is a non-decreasing function of L for s, i ≥ 0. Moreover, since $V_{L,\varrho}(s, i) = \min\{Li, W_{L,\varrho}(s, i)\}$ we have that $V_{L,\varrho}(s, i) \to 0$ when $L \to 0$ for any s, i ≥ 0.

Finally, to show that $V_{L,\varrho}(s, i) \to C_{\varrho}(s, i)$ when $L \to \infty$, note that for L > s the cost of isolating a single infectious individual is greater than the cost of infecting all susceptible individuals and it is best not to isolate infectious individuals, so $V_{L,\rho}(s, i) = C_{\varrho}(s, i)$ for L > s. Next, we assume that the isolation threshold $u_{L,\varrho}(s)$ does not increase with respect to L for every s ≥ 0, L ≥ 0 and we have the following.

***Theorem 4**:* Given s ≥ 1, then $u_{L,\rho}(s) \to \infty$ when $L \to 0$ and $u_{L,\rho}(s) \to 0$ when $L \to \infty$.

Proof:

For s, i ≥1 from the relation (4) $W_{L,\rho}(s, i) \geq p_{si} = s / (s + \varrho) > 0$, so that for a fairly small *L* we have Li $<W_{L,\varrho}(s, i)$ and the best policy for the situation (s, i) is to isolate all infectious individuals. That is, for every s, i ≥ 1, $u_{L,\varrho}(s) \geq i$ for all small enough L, so that $u_{L,\varrho}(s) \to \infty$ when $L \to 0$. From Theorem 3 for s ≥ 1, $V_{L,\varrho}(s, 1) \to C_{\varrho}(s, 1)$ when $L \to \infty$, which means that for a large enough L, $V_{L,\varrho}(s, 1) < L$, so that $u_{L,\varrho}(s) = 0$ for every large enough L. (Clancy & Green, 2007).

3.2.Isolation or total immunization policies

In this section we will refer to results that correspond to the results of the previous section on isolation or total immunization policy, without giving evidence of these results. For proofs and more detailed information you can refer to (Green, 2005) for the best isolation policies.

Theorem 5: Given s, i ≥ 0 then the optimal cost function $V_{L,A,K,\rho}(s, i)$ satisfies the following

(i) $V_{L,A,K,\varrho}(s, i)$ is a non-increasing function of ϱ with $V_{L,A,K,\varrho}(s, i) \to \min\{Li, A + sK, s\}$ when $\varrho \to 0$ and $V_{L,A,K,\varrho}(s, i) \to 0$ when $\varrho \to \infty$.

(ii) $V_{L,A,K,\rho}(s, i)$ is a non-decreasing function of each of L, A and K with $V_{L,A,K,\rho}(s, i) \to 0$ when $\min\{L, A + K\} \to 0$ and $V_{L,A,K,\rho}(s, i) \to C_{\rho}(s, i)$ when $\min\{L, A + K\} \to \infty$.

As mentioned in the previous section, the form of optimal isolation policy or total immunization contains the quantities $S_{L,A,K,\rho}(s)$ and $R_{L,A,K,\rho}(s)$ so that the optimal

condition policy (s, i) isolates all infectious individuals when $1 \leq i \leq S_{L, A, K, \varrho}(s)$, does not intervene when $S_{L, A, K, \varrho}(s) < s \leq R_{L, A, K, \varrho}(s)$ and immunizes all susceptible individuals when $i > R_{L, A, K, \varrho}(s)$. It is also proved that $S_{L, A, K, \varrho}(s) = R_{L, A, K, \varrho}(s)$ (Abakuks, 1974) for large s, and it is given that

$$\varphi(s)=max\{i \epsilon Z: Li < A+sK\}$$

for $s \geq 1$. If $S_{L, A, K, \varrho}(s) = R_{L, A, K, \varrho}(s)$ holds then $S_{L, A, K, \varrho}(s) = \varphi(s) = R_{L, A, K, \varrho}(s)$. Note that for any $s \geq 1$, $\varphi(s)$ is a non-decreasing function of L and a non-increasing function of A, K. Also, similar to Theorem 2 we have in Theorem 6 the following results.

Theorem 6: Given $s \geq 0$,

i) $S_{L, A, K, \varrho}(s)$ is non-increasing in ρ.

ii) $R_{L, A, K, \varrho}(s)$ is non-decreasing in ρ.

iii) For $s < A / (1-K)$, we have $S_{L, A, K, \rho}(s) \rightarrow \max \{i \epsilon Z: i < s = L\}$ and $R_{L, A, K, \rho}(s) \rightarrow \infty$ when $\varrho \rightarrow 0$. For $s \geq A / (1-K)$, we have $S_{L, A, K, \varrho}(s) \rightarrow \varphi(s)$ and $R_{L, A, K, \varrho}(s) \rightarrow \varphi(s)$ when $\varrho \rightarrow 0$.

iv) $S_{L, A, K, \varrho}(s) \rightarrow 0$ and $R_{L, A, K, \varrho}(s) \rightarrow \infty$ when $\varrho \rightarrow \infty$

4. Models of Markovian Procedure Decisions in Epidemiology and Medical Treatments

4.1. Introduction to MDP Models

In this research, Markov Decision Process (MDP) will be studied and how they find application in Epidemiology and Medical Therapies. The Markovian Decision Process Theory (MDP) theory is based on a combination of two theories, the Markovian Processes and Dynamic Programming. Markovian Processes were introduced in the early 20th century by the Russian mathematician Markov, while Dynamic Programming theory was introduced by Bellman in 1957. Dynamic Programming develops a retrospective process that calculates optimal values of cost-benefit functions through an equation. It is also used in finite or infinite time horizon problems, in which a stochastic process is controlled by a sequence of actions. Bellman, continuing his research, combined the above two theories and introduced the Markov Decision Processes (MDP), which for the last four decades have been applied in various fields of science, such as, among others, Business Research, Epidemiology, Ecology. and Informatics. The problems faced by the application of this theory have as their main feature randomness. In the field of Epidemiology and Medical Therapy, most cases involve uncertainty and doctors have to carry out a difficult task as they judge the health of patients. Each patient responds differently to the treatment that will be given to him, the medical material that is available each time varies as well as the regimen of the treatment that is administered may be different depending on the judgment of the respective doctor. All of the above are sources of uncertainty and physicians should take

subjective action to address each incident. However, mathematical decision models provide information about the nature of optimal decisions and can assist in treatment decisions. Markovian Decision Procedures (MDPs) are an appropriate technique for certain types of treatment decisions. MDP models find optimal solutions to stochastic decision-making problems. An MDP model aims to provide the best policy which is a decision policy to optimize a specific criterion. This differentiates them from other stochastic modeling techniques. But MDPs also have drawbacks. As the size of the problem increases, their solution is not given accurately. However, there are many techniques that provide an approximate solution. Also, finding medical data is a problem for the application of MDP because it is very difficult and costly. More specifically, the analysis of an MDP model requires information on certain characteristics such as decision time horizons, situations, actions, costs and transition probabilities. In each decision period or time, the system provides us with the necessary information so that from the situation in which we find ourselves we choose the appropriate action through a set of actions. The chances of transition depend on the situation but also on the choice of energy. So at a certain point in time following a rule of decisions that can depend either only on the present situation or on the situations of the past one can choose an action. For future situations the policy to be followed is the one that will provide the necessary information for the choice of actions. A Markovian policy is a policy according to which the choice of an action at any time n = 0,1,2, ... depends only on the time n and on the state of the process at that time.

For the application of a Markovian decision process is considered a stochastic process X_n with n = 0,1,2…, N where the random variable X_n denotes the state of a system at time n. System states can have a finite or infinite number of counts. The

system is inspected at times $t = 0,1,2\ldots, N$ as well as its condition at this time. Finally, an action is selected from a set of actions.

The above system is called a finite time horizon system of N steps, if there is a fixed integer $N \geq 1$ such that the actions for controlling the system are selected at times $t = 0,1,\ldots, N-1$ and the process stops at time, N. In contrast, the system is called an infinite time horizon if the set of energy selection time points is infinite.

4.2. Usefulness of MDP Models in Medical Care

MDP models are very useful and are applied to solve medical problems. Their usefulness lies in the fact that medical problems are often complex and complicated. We also often observe that doctors are called upon to make treatment decisions at different times and this complicates the problem.

For a physician, for example, the life expectancy of a patient whose health progress follows an MDP model may be at stake. However, we understand that the path of the model until the answer to the patient's life expectancy is finally found is complex, as the patient may go into different health states from the initial point of decision to healing or death. Modeling these transitions requires a large number of status changes at multiple time points. This is why MDP models are popular in medical decision making as they allow a simpler representation of future conditions and possible transitions that may occur until the patient recovers or dies.

Therefore, MDP models have the advantage that through them decisions can be made at different time periods. Evaluation of the actions to be taken is not based on a one-time decision, as is the case with other decision models. For example,

organ transplantation can be formulated as an MDP model, in which when a donor organ is available the possible options are either for the patient to accept the organ, or to reject it and wait for a more appropriate one. Therefore, at different times and depending on the patient's condition there is the flexibility to choose different actions.

In conclusion, we conclude that in almost any case where one wants to optimize a process over multiple time periods one can use an MDP model.

4.3.MDPs Model Methodology

Stochastic Dynamic Programs and Markovian Decision Processes contribute to the modeling of dynamic systems under uncertainty. Their main goal is to develop models and make decisions in an optimal way so that there is a transition of the system to the expected state.

The discrete-time MDP model is applied as decisions are made sequentially to optimize a defined performance criterion. At the same time, the model is a link between the previous, current and future decisions of the system. This connection is made by defining the system states which are defined as variables and include the relevant information for future decision making.

Next, the system evolution methodology of an MDP model will be analyzed. The state of the system, the energy taken, the costs incurred, and the transition of the system to a new state follow a known probability distribution. Status variables need to be defined so that, given the current situation, future transitions and cost rewards are independent of the past, thus following the hypothesis of a Markov process. In addition, decisions are considered to occur sequentially.

4.4.MDPs in Discrete Time Models

This work will also develop finite-time MDP models. Initially, the Markov decision process in discrete time will be described. Let X_n be n = 0,1,2, .. the stochastic process that represents the state of the system. At the time of inspection t with t = 0,1,2,… the system is in state i and 73 the action a is selected, where a∈A (i). A (i) is the set of possible actions, even if it is finite.

At the next time, the system goes to state j with probability $p_{ij}(a)$ which depends only on energy a and states i and j. Also, for every possible action performed there is a cost C (i, a) which depends only on state i and action a as a consequence of the choice of action a the time at which the system is in state i.

Next, as policy π we call a rule μ by which actions are selected at time n = 0,1,2,…. The goal of an MDP model is to find a policy that minimizes costs. The cost function is defined by the optimality criterion. The criterion of minimizing the total expected cost will be used. Therefore, we consider V (i, t) with t = 0,…, N, the minimum cost when the system is in state i, the time interval [0, N].

For $t = N$ -1 it is valid

$$V(i, N-1) = \min_{a \in A(i)} C(i, a)$$

for $t = N$, has as boundary condition V (i, N) = 0.

Below is the relation, known as the dynamic programming equation or optimization equation, for the system which at time t is in state i and the action a is selected.

$$V(i,t) = \min_{a \in A(i)} \left[C(i,a) + \sum_{j} p_{ij}(a) V(j, t+1) \right]$$

At time t selecting action a results in the best possible cost in terms of expected cost. Through the dynamic programming equation it is possible to calculate V (i, 0). Initially, the quantity V (i, N -1) from Equation (1.1) has been calculated.

Then, by induction setting in the optimization equation $t = N$ -2 the quantity V (i, N -2) is calculated. The same procedure is followed and the quantity V (i, 0) is calculated. The optimal policy is the policy which at time t = 1,2,…, N -1, N is in state i and minimizes the right-hand side of the optimization equation. Finally, the same procedure is followed in case we are interested in maximizing the expected profit.

4.5.MDPs in Infinite Time Models

In the previous paragraph the theory of finite time horizon MDP models was developed. In this section, we will develop the theory of MDPs in Infinite Time Models following the same procedure and the same assumptions with the difference that it is in infinite time t, with t∈ (0, ∞). It is understood that the data required in these models is infinite and this is quite difficult to happen. For this reason it is considered that the data change slowly over time in order to achieve their homogeneity. In order to solve the problems that exist in the MDP models of infinite time horizon, the concept of stagnant policy is introduced. A policy is defined as stationary if it is non-random and the action selected by it at time n depends only on the state of the process at time n. Regarding the theorems applied

to such a model, it is observed that they do not differ much from those applied to the finite time horizon MDP model. It is assumed that there is a real positive number B, such that for every ADA action (i) and for every situation i of the procedure it holds ⏐ C (i, α) ⏐

$$V_{\pi}(i) = E_{\pi}\left[\sum_{t=0}^{\infty} \alpha^{t} C(X_t, a_t) \mid X_0 = i\right]$$

where α is constant, which is called the deflation factor and $\alpha \in$ (0,1). The deflationary factor is introduced as there is an economic incentive, since the cost to be paid in the future has a lower value than the present. Defined is the bound average price below the policy π. The quantity V_{π} (i) is well defined as the costs C (i, α) are blocked and α <1, and implies ⏐ V_{π} (i) ⏐ ≤B / 1 -a.

Demanded in this case, too, is the best policy that minimizes the total expected deflated costs. The α-optimal policy is the policy for which * applies

$$V_{\pi^*}(i) = \inf_{\pi} V_{\pi}(i)$$

for each initial state $i \geq 0$. It is considered as V_a (i) = $\inf_{\pi} V_{\pi}$ (i) and the policy π * is called α-optimal if Vπ * (i) = Vα (i), for each initial state $i \geq 0$. The optimality equation for the Infinite time horizon model is given by the relation

$$V_a(i) = \min_{\pi}\left\{C(i,a) + a\sum_{j=0}^{\infty} p_{ij}(a) V\alpha(j)\right\}$$

for each initial state $i \geq 0$.

Next, we consider B (I) the set of blocked real-time functions in the process state space and V$\pi \in$B (I) for each policy π. The stationary policy is a function f: I $\rightarrow$ A (i), where I is the state space of process f (i) is the energy selected in state i. For each stationary policy f the function Tf is defined: B (I) $\rightarrow$ B (I), such that

$$\left(T_f u\right)(i) = C(i, f(i)) + a \sum_{t=0}^{\infty} p_{ij}(f(i))u(j)$$

Therefore, from relation (1.6) for each function u$\in$B (I) the quantity $T_f u$ is a function whose value in state i is given by the above formula. The function $T_f u$ is a blocked function and holds that $T_f u \in$B (I). Finally, $T_f u$ is interpreted as the value (Tf u) (i) in condition i and is the expected cost if policy f is used first and after a period the process stops receiving a final cost equal to αu (j) if the final state is state j. Therefore, for the calculation of the recurring cost $T^n \ _f u$ for n ∞ ∞ steps the relation is used

$$T^n \ _f u(i) = C(i, f(i)) + a \sum_{j=0}^{\infty} p_{ij}(f(i))\left(T_f u\right)(j)$$

receiving a final cost equal to anu. Since α <1 and the function u is blocked it holds that $T_f u \rightarrow V_f$.

Next, an important theorem for stagnant fa policy is given.

Theorem 1.1: Let fa be a stationary policy which is in state i and the action that minimizes the right member of relation (1.1) is chosen, i.e. we have fa (i) to be

$$C(i, f_a(i)) + a\sum_{j=0}^{\infty} p_{ij}(f_a(i))V_\alpha(j) = \min_{\alpha \in A(t)} \{C(i,a) + a\sum_{j=0}^{\infty} p_{ij}(a)V_a(j)\}$$

then $Vfa\ (i) = V_\alpha(j)$ for every i≥0 and therefore the fa policy is α-optimal.

The above theorem proves that there is a stationary α-optimal policy determined by the 1st relation. Therefore, we can calculate the minimum total expected deflated cost $V_\alpha(j)$ with i≥0 and find the stagnant policy in state i, which selects the action that minimizes the quantity called the policy optimization quantity, $C(i,a) + a\sum_{j=0}^{\infty} p_{ij}(a)V_a(j)$.

A widely used technique used to find the best policy is the policy iteration algorithm. This algorithm works assuming that we have at our disposal a finite set of states. To begin with, there was an initial policy stance f. Calculate the quantities $V_f\ (i)\ i$ = 1,…, n through the graphical system of equations n to n unknown

$$V_f(i) = C(i, f(i)) + a\sum_{j=0}^{\infty} p_{ij}(f(i))V_f(j)$$

for i = 1,…, n.

The stationary policy f * is in state i by selecting the action α, a∈A (i) which minimizes the

quantity $C(i,a) + a\sum_{j=0}^{\infty} p_{ij}(a)V_f(j)$

The new policy f * is obtained by selecting f * (i) = ai provided that the action f * (i) is selected the same as the action of the previous f (i) when this action minimizes the above expression.

Because the number of possible policy stances is finite, since the number of stances is finite, one will arrive at a stagnant policy for which there is no further improvement. So the new f * policy will be the same as the previous f and the algorithm will terminate. Finally, f * is the non-optimal policy.

4.6.Partially Observed MDPs (POMDP) Models

Until now, for the finite and infinite time horizon MDP models studied, there was accurate information about their condition. But often no one has accurate data on their model. If, for example, the results of a patient's medical examination were given as data in an MDP model, they are subject to the error that may arise in the examination.

Therefore, Partially observed MDPs (Partially observed MDPsPOMDP), which are an extension of MDP models, were developed to address lack of information problems (Sondik ,-1978). In such models there is uncertainty in what state the system goes into. For this reason, the aim is to adopt an optimal policy based on the system's observations and the above. In this case, one can use an adequate statistical assessment of the situation instead of the partially observed situation, which can be interpreted as a probability of estimating the actual situation of the

system based on the observations. In this way, it has a complete model in terms of information (Streibel,1965).

Finally, to emphasize that even with this technique one can arrive at models that are difficult to calculate even for medium-sized systems of situations and factors. For this reason, approximate techniques must be used to effectively create realistic solutions to problems.

4.7.Semi-Markovian Decision Making Procedures (Semi-MDPs)

In healthcare and other applications, decisions can occur at regular intervals, such as how often treatments are given to patients depending on their state of health. The time between these transitions may depend on the action selected or may occur randomly. In these cases, an extension of MDPs is the Semi-Markovian Decision Processes (Semi-MDPs), which can be used effectively. Through transformations and redefinitions, technical and algorithmic solutions similar to those of discrete-time MDPs models have been developed.

4.8.Application of MDP SIR Epidemic Model in Seasonal Influenza

In this Section we chose to present an application of the Markov decision-making process, using a finite-time MPD model for seasonal influenza and highlighting the best health policies through the mathematical model of SIR disease spread.

For the study of seasonal flu, two health policies have been adopted, ie ways of intervention in order to control its transmission. The first way is the vaccination and administration of drugs, while the second way is some interventions to reduce the transmission, such as social exclusion (quarantine), the use of a mask and the closure of structures that will be implemented in the population.

However, the model of influenza is very simple and does not realistically approach the spread of the disease. Several hypotheses have been made to simplify the use of an MDP model to create optimal health policies. Initially, it is assumed that the number of new infections during each period can be observed by the decision maker and that an infected person comes in contact with the rest of the population over a period of time, transmits the virus and then removes (isolates) by the population. By relaxing these hypotheses, he can use the generalized Markov models for infectious diseases Yaesoubi & Cohen (2011) as well as the partially observed POMDP models to characterize optimal health policies (Sondik,1978).

More specifically, the best health policy adopted is to maximize the health of the general population during an epidemic, as opposed to other policies aimed at identifying optimal health policies for vaccine distribution prior to the onset of an epidemic without considering interventions. which can be used during the epidemic.

In addition, health policy is adopted in real time, allowing interventions at any time and responds to the changing 80 characteristics of the disease (infectivity, levels of antimicrobial resistance), to the characteristics of the population (prevalence of diseases, percentage of healthy individuals) and resource constraints (vaccines, antimicrobials, staff and budget).

In addition, the control of an epidemic such as seasonal flu is determined by the availability of effective vaccines and drugs and the availability of money and resources for the supply of vaccines, the diagnosis, treatment of new cases and the implementation of transmission reduction interventions during the epidemic. Thus, the best health policy to maximize the overall health of the population is, for example, minimizing the number of deaths or hospitalizations or maximizing other measures, such as quality-adjusted life years.

5. Summary

Uncertainty is a key feature in the day-to-day reality of various companies and organizations. For example, in a department store, customers' daily requirements for a particular product vary from day to day. In a private telephone company, customers' calls for help due to possible network failures reach the call center with unforeseen frequency.

In each of the above cases, the problems that arise and the exact times of their solution, can not be predicted in advance. Uncertainty seems to be an inevitable feature. The researcher is faced with a decision. The various stochastic models constructed are used to compare and evaluate researchers' decisions in cases where uncertainty is so significant that it cannot be ignored. In the case of the department store, the researchers will suggest to the owner alternative rules for ordering the product. In the case of a telephone company, the researcher must properly distribute the company's support staff to satisfy all complaining customers. He must therefore make a decision that will help the optimal operation of the company. In the case of the computer center the researcher should prevent the congestion of the system as much as possible by making critical decisions. For the product manufacturing company, the researcher is invited to propose optimal rules for preventive maintenance or repair of the Machinery. In all the above cases, it is observed that the uncertainty can be managed by the respective researcher.

The introduction of uncertainty into a mathematical model often increases its complexity. During the 20th century, the development of mathematical theory of stochastic models allowed for a more complete analysis. Business Research is one of the applied sciences in which stochastic models play a dominant role. Informatics, Economics, Biology, Ecology, Medicine are still some scientific fields

in which stochastic models are now central. The main objectives of the Stochastic Modeling Course are:

(a) To transmit the central ideas of Stochastic Modeling and to show how they can be used in various models at a mainly applied but also at a theoretical level.

(b) To reveal the interaction of two scientific areas that are usually presented as separate "clusters" of Science: Stochastic Processes and Stochastic Modelization.

(c) To highlight the importance of stochastic models through their construction and analysis in various scientific fields.

To summarize, in this thesis we have studied the effect of changes in parameter values on the optimal cost function and the optimal energy for Nonpharmaceutical Interventions (NPIs), first for an isolation policy and then for an isolation policy in parallel with the general immunization of the population. The results show that if the state (s, i) of the process is known, then to determine the optimal energy it is not necessary to know the exact value of the relative isolation rate, ρ but only to know if ρ is greater or less than the value ρ_0 (s, i). (Panagiotidou & Dimitrakos, 2020).

References

Abakuks, A. (1973). An optimal isolation policy for an epidemic. *Journal of Applied Probability*, 247-262.

Abakuks, A. (1974). Optimal immunisation policies for epidemics. *Advances in Applied Probability*, 494-511.

Clancy, D., & Green, N. (2007). Optimal intervention for an epidemic model under parameter uncertainty. *Mathematical biosciences*, *205*(2), 297-314.

Green N. (2005). Optimal Intervention for Epidemic Models under Uncertainty, Ph.D. Thesis, University of Liverpool.

Herbert W. Hethcote, The Mathematics of Infectius Diseases, SIAM Review, Vol. 42, No. 4 (Dec., 2000), pp. 599-653.

I.M. Longini, E. Ackerman, L.R. Elveback, An optimization model for influenza A epidemics, Mathematical Biosciences, Volume 38, Issue 1-2, pp. 141-157 (1978).

Kao, R. R. (2002). The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK. *Trends in microbiology*, *10*(6), 279-286.

Keeling, M. J., & Ross, J. V. (2008). On methods for studying stochastic disease dynamics. *Journal of the Royal Society Interface*, *5*(19), 171-181.

Meyers, L. (2007). Contact network epidemiology: Bond percolation applied to infectious disease prediction and control. *Bulletin of the American Mathematical Society*, *44*(1), 63-86.

Panagiotidou D., Dimitrakos T. (2020). Stochastic Modeling in Problems of Optimal Control of Susceptible Populations (*Master's thesis*), University of the Aegean, Department of Mathematics, Samos.

Sondik E (1978) The optimal control of partially observable Markov processes over the infinite horizon: Discounted costs. Operations Research 26: 282–304

Streibel, C.T. (1965). Sufficient statistics in the optimal control of stochastic systems. Journal of Mathematical Analysis and Applications, 12, 576-592.

Yaesoubi R, Cohen T (2011) (In Press) Generalized Markov models of infectious disease spread: A novel framework for developing dynamic health policies. European Journal of Operational Research

Zhou, Y., & Liu, H. (2003). Stability of periodic solutions for an SIS model with pulse vaccination. *Mathematical and Computer Modelling*, *38*(3-4), 299-308.