Alma Mater Studiorum · Università di Bologna · Campus di Cesena

SCUOLA DI INGEGNERIA E ARCHITETTURA
Corso di Laurea Magistrale in Ingegneria e Scienze Informatiche

Managing Challenges of Non Communicable Diseases during Pregnancy: An Innovative Approach

Tesi in Sistemi Distribuiti

Relatore:
Prof. Andrea Omicini
Correlatore:
Dott.ssa Sara Montagna

Presentata da:
Valentina Intrusi

Sessione III
Anno Accademico 2016/2017

Contents

Introduction

In 2015, the number of maternal and fetal deaths is still too high. In particular, the 65% of maternal deaths is associated to problems related to *Non-Communicable Diseases* (NCDs) during pregnancy. Over 75% of these deaths are in underdeveloped and developing countries. Most of these deaths may have been *prevented.*
Generally speaking, pregnancy, in women with NCDs, implies the emerging of *high-risk pregnancy.* The best way to avoid serious complications is to *improve maternal health* before, during and after pregnancy.
Access to health-care facilities should be guaranteed to all women in order to achieve *continuous monitoring* of pregnancy progress. This leads to promptly complications detection and, consequently, in taking corrective actions and/or initiating recommended prophylaxis.
Information Technology plays a key role in this context. Mobile Health (M-Health) is the general term used to indicate medical support provided by mobile devices.
M-Health helps the monitoring process providing support for both physicians and patients. It represents a way to facilitate access to health-care services transcending time and space providing support to *everyone, everywhere and anytime.*
In environment permeated by sensors it is possible to collect information about the patient and his context. Such information, while correctly elaborated, describe potentially any kind of situations like real-world ones. In order to describe or predict events, data from environment could be elaborated by different *analysis techniques*, from statistics and mathematics to Artificial Intelligence algorithms.
These techniques may be exploited to *describe* a system through the patterns discover or *predict* the future values of specific systems attributes on the basis of other ones.
Among several studied approaches, the one that we choose is simulation. In par-

ticular we paid attention on Multi Agent-Based Modeling and Simulation (MABS) approach. Such kind of approaches is particularly related to complex systems because of nature: an agent is thought of as an autonomous entity with a behavior that interact with other agents creating real societies. Such behavior is described by *rules*. Based on their behavior, agents may be *reactive* or *proactive entities*. A reactive behavior describes how the agent has to react to external stimuli, a proactive behavior describes how it behaves in order to perform its goals. Agents may be capable to *evolve* by adapting to changing environment.
The main advantage of using simulation techniques is the capability of reproducing *evolution of the system* under controlled conditions. In this way is possible to understand which factors influence more the evolution of the system. These factors are usually difficult to evaluate in many real-world situations, one of them being the description of physiological processes in humans.
Considering the importance of factors influencing pregnancies, this thesis has as its goal the modeling of high-risk pregnancy condition starting from model described in [2]. Among the several pregnancy complications, we focused on the Gestational Diabetes Mellitus one.

This thesis is structured as follow:

- In the **first chapter** we will explore literature about the maternal and fetal mortality problem. The focus will be on main problems arising from pregnancy complications and which factors are connected to it. Among these risk factors particular attention will be paid for Non-Communicable Diseases and their influence on pregnancy outcome. Current challenges aim to improve maternal and fetal health will be shown in the later sections. Finally we will show the case of Emilia Romagna considering the data collected through CedAP, highlighting the statistics that emerged in this year with regards to pre-term births examinations and obesity complications.

- In the **second chapte**r we will explore literature about the use of technology in health-care area. In particular we will give an overview about terminology and its technological influence in medicine. Particular importance will be given to Mobile Health-care systems. We will describe ICT applications in health-care area and benefits and drawbacks arising from them. Finally we will describe current challenges affecting this area and the vision of Hospital 4.0.

- In the **third chapter** we will explore ICT applications in the specific field of pregnancy monitoring. We will describe which systems are used to support pregnant women achieving a healthy pregnancy. We will show the architecture of M-Health systems with particular attention given to data processing techniques such as Machine Learning and Simulation Techniques. Finally we will describe Agent-Based modeling and simulation approach showing characteristics of such systems.

- In the **fourth chapter** we will provide a physiological description to Gestational Diabetes Mellitus model. In particular we will describe glucose metabolism and the physiology of main organs involved in it. We will describe metabolic changes arising from pregnancy and its influence on metabolism. At the end of chapter we will introduce the Self-Management system model used to simulate a healthy and Type-1 diabetic patient metabolism.

- In the **fifth chapter** we will introduce case study of current Type-1 diabetes self-management system model. Before that, we will explain the experience about the initial decision to using machine learning techniques in order to predict future outcome of high-risk pregnancy. We will explain the changes made on the aforementioned system in order to simulate healthy pregnancy and Gestational Diabetes Mellitus complicated pregnancy. In particular, which improvements have been made on existing model and the addition of the placenta one to the system. We will show the changes introduced by the new organ on metabolism of the other ones. Results of simulation will be shown at the end of chapter.

- At the end of this thesis we will provide conclusions containing considerations about the actual systems and possible future works on it.

Chapter 1

Background

This chapter describes the background on maternal and fetal mortality world problem.
In particular we initially describe in details the problem of fetal mortality and morbidity and resulting consequences.
A great deal of attention is paid to describe the causes of this problem and which disorders are connected to it. About risk factors, particular attention is paid on Non-Communicable Diseases (NCDs) such as obesity, hyperglycaemia and hypertension. At the end of this section we present the results of recent studies related to it.
Later we describe current challenges to accept in order to improve maternal and fetal health.
Finally we show the specific case of Emilia Romagna considering the data collected through CedAP, highlighting the statistics that emerged during this year with regards to examinations in pregnancy, pre-term births and obesity complications.

1.1 The Problem

Over the past two decades, improving maternal health has became an increasingly important focus of the global development agenda [3]. Many pregnancies are lost during early gestation. Some studies report percentages of fetal loss in more than 50% of pregnancies [4].

At the moment European Commission is so much interested to improve healthcare systems, so they organize a call for paper about ”Implementation research for maternal and child health” topic [5].
Fetal mortality is closely related to maternal mortality, which is defined by the *World Health Organization* (WHO) as *the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.*
Even though between 1990 and 2015 maternal mortality worldwide dropped by about 44%, it remains unacceptably high: the WHO assesses that in 2015 about 303 000 women died during pregnancy and follow childbirth, and roughly 2.6 million of babies were stillbirth. It's important to note that most of these deaths could have been prevented.
The high number of deaths in low-resource countries reflects inequities in access to health services. The Maternal Mortality Ratio - MMR (the number of maternal deaths per 100'000 live births) in developing countries is 14 times higher than in developed countries ones [6].
”Ensure healthy lives and promote well-being for all at all ages” is the third of 17 Sustainable Development Goals (SDGs) for 2030 and it aims to reduce global MMR to less than 70 deaths per 100'000 live births. Achieving this global target requires a global annual maternal mortality rate reduction of at least 7.5%, more than double of the rate achieved between 2000 and 2015 [7].
The main cause of maternal and fetal mortality in underdeveloped and developing countries is *access to care.* There are no roads, transportation and health facilities in countries such as Burundi and Cameroon, in sub-Saharan Africa.
The low level of education, weak health systems, lack of skilled birth attendants and no capacity to deliver essential life-saving interventions helps make it difficult to receive the necessary medical care [8].
Non-Communicable Diseases (NCDs) such as diabetes, obesity and hypertensive disorders are strongly connected with maternal health. They have a significant adverse impact on pregnancy outcome and child health, as well as maternal health. Parents health, in particular metabolic and nutritional state of the mother during pregnancy, defines the environment in which the fetus grows. This environment

may lead to increased risk of developing NCDs later in life [9]. There are hypotheses regarding the predisposition to non-communicable diseases developed in adulthood. This would be the result of exposure to certain intrauterine conditions that influence the development of important tissues during critical stage of pregnancy.
Worldwide NCDs are responsible for about 65% of maternal deaths. Over 75% of these deaths are in underdeveloped and developing countries [10]. Diabetes, anaemia, hypertensive and thyroid disorders are also associated with preterm birth (also known as premature birth), that is the birth of a baby at fewer than 37th weeks gestational age.
NCDs such as denutrition, obesity, hypertension and hyperglycaemia are commonly associated with pregnancy as causes of maternal morbidity and mortality.

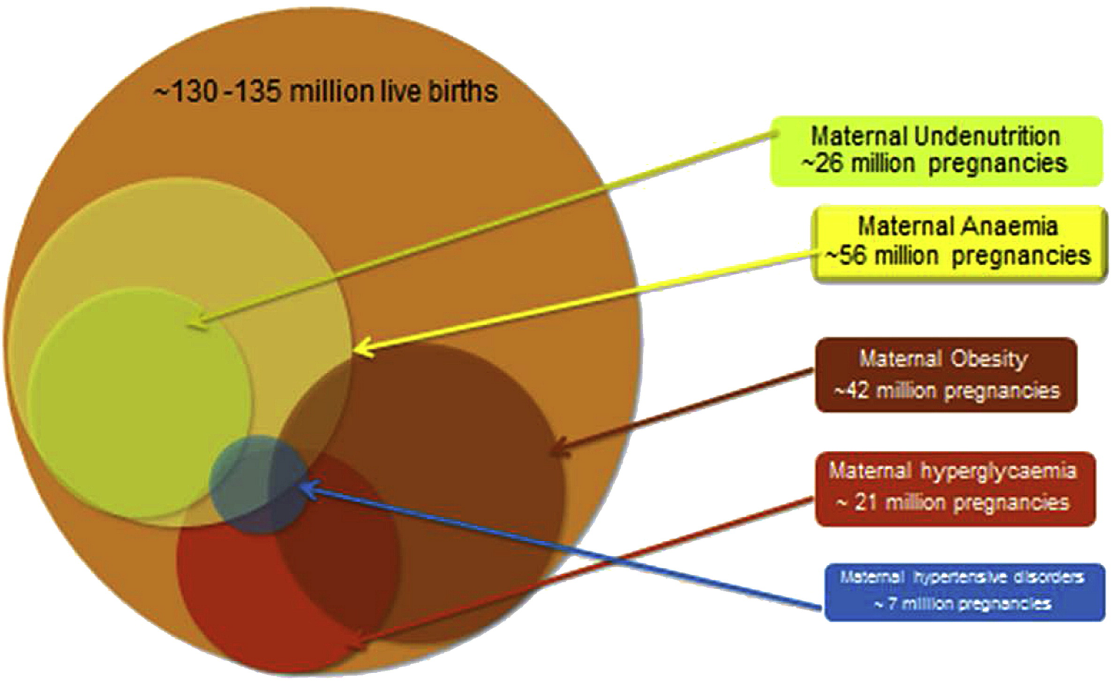


Figure 1.1: Global estimates of common NCDs affecting pregnancy [9]

1.2 Causes

Several studies show that countless factors contribute to determine the outcome of pregnancy. Many of them are strongly related with the socio-economic environment in which women live, such as lack of basic infrastructures, communicable diseases and undernutrition.
These factors will not be studied in deep in this work.

1.2.1 Risk factors

Maternal Nutrition Worldwide almost 870 million people suffer from chronic *malnutrition*, 60% of these are women and girls. Undernutrition affects the outcome of pregnancy because it can determine low birth weight (LBW) and subsequent childhood malnutrition and it contributes significantly to maternal morbidity and mortality and neonatal mortality.
Nutritional iron deficiency in maternal diet can lead to anaemia development, defined as haemoglobin concentration (Hb) < 110 g/L. In most cases it is associated with increment of maternal and perinatal morbidity and mortality and long-term adverse consequences involving the baby.
Women with serious forms of anemia have an higher risk to develop pre-eclampsia, with consequent onset of eclampsia, in comparison to non-anaemic women. In medical application eclampsia is defined as the direct and worst complication of pre-eclampsia, with onset of seizures (convulsions). Pre-eclampsia, in turn, is a pregnancy disorder characterized by the onset of edema (abnormal fluid accumulation in the interstitium, located under the skin, in the cavities of the body), hypertension (high blood pressure) and often proteinuria (significant amount of proteins in the urine).
The most serious cases of anaemia are associated with pre-term births, low birth weight (LBW) defined by the WHO as a birth weight of an infant of 2,499 g or less regardless of gestational age, and perinatal death.
Another factor linked to maternal nutrition is *vitamin B12 deficiency*. This deficiency in pregnancy causes on one hand an high risk of insuline resistance with consequent development of type 2 diabetes, on the other an increased incidence of

Gestational Diabetes Mellitus (GDM) [9].

Non-Communicable Diseases

Increase of Impaired Glucose Tolerance (IGT), diabetes and other NCDs in developing countries is not to be only attributed to genetic risk factors and onset of obesity. In low and middle-incoming countries individuals who are affected by such diseases are, in most cases, not obese.
The concept of "fetal programming" is related to predisposition to multiple NCDs and it is defined as "*a permanent structural or physiological function change in utero during development of organs as a result of defined stimulus. This change depends on type and timing of exposure*". When a malnourished mother's child introduces calories with diet in his/her early childhood, he/she develops anthropometric and biochemical markers of metabolic syndrome and consequently an high risk for developing diseases like IGT, diabetes, arterial hypertension, coronary heart diseases, lipid abnormalities and stroke later in life [11].
This concept leads to argue that the origin of *Non-Communicable Diseases* is to attribute not only to genetic factors, but also to many environmental ones acting early in life. These can lead to "developmental mismatch" defined as *"mismatch occurring between generation and within the life-course of the individual if the environment in which they live changes"* [12].
According to this model, components that critically influence the risk of NCDs has been established during early gestation. In this period informations about the current environment affect both tissues formation and settings process responsible of individual reactions based on changes of surrounding environment.
Such informations are handed down by the mother during pregnancy and nursing of the infant. This process is influenced by many factors such as mother's genetic makeup, her nutritional state, lifestyle, parity and external stressors. This mismatch between information biologically handed down and environment that evolves over time suggests an increased risk of developing NCDs, such as obesity and diabetes in the next generation.
NCDs during pregnancy increase the risk of miscarriage, stillbirth, congenital malformations, birth injuries, neonatal hypoglicaemia, infant respiratory distress syn-

drome and being Large for Gestational Age (LGA) which implies having weight that is above the 90th percentile for that gestational age [10].
Factors such as unhealthy diet, physical inactivity, tobacco use and abuse of alcohol contribute to the increase risk of developing NCDs.

Obesity Obese individuals are those who have a Body Mass Index (BMI) greater than 30 kg/m^2, those who have BMI between 25 and 30 kg/m^2 are overweight. Obesity and overweight are among the main risk factors of fetal mortality in high-income countries. The number of reproductive-aged women who are obese and overweight is growing.
Maternal obesity is linked to an increased risk of obesity in the offspring [12], birth complications such as induction of labour, caesarean section (C-section), post-partum haemorrhage, maternal infections and shoulder dystocia, and onset of pre-eclampsia, thrombosis and GDM. The pre-eclampsia risk grows as BMI increases [9].
A serious problem concerning overweight and obesity is the risk of Intrauterine Growth Restriction (IUGR) defined as poor fetal growth in the mother's womb.

Hyperglycaemia Hyperglycemia is a condition in which an excessive amount of glucose circulates in blood plasma. This condition arises in those who have diabetes.
At the moment, diabetes is a critical aspect of maternal health. 92% of diabetic women are in low and middle-income countries, where they have a limited access to health-care facilities. Health systems are often not structured and poorly organized to provide them appropriate cares [13].
Chronic medical condition such as diabetes may greatly affect the course of pregnancy because the high maternal glucose concentration crosses placenta and, with the normal levels of fetal insulin, allows a growth above average of the fetus. Diabetic women's babies are thus often large for gestational age.

Almost 90% of all cases of diabetes during pregnancy are gestational diabetes [11].
Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance of variable

severity with onset or first recognition during pregnancy. Worldwide, between 2 to 9% of all pregnancies are affected by GDM. This kind of diabetes is associated with fetal macrosomia and perinatal risks such as shoulder dystocia, bone fractures, nerve palsies and hypoglycaemia [14].
Babies born from a mother with Gestational Diabetes Mellitus risk to developing several complications including perinatal death. Other delivery problems, including haemorrhage, obstructed labour, infection and sepsis, hypertensive disorders and cardiovascular diseases (CVD) are directly or indirectly connected to GDM and leading causes of maternal mortality. Women which have been already diagnosed type-1 or 2 diabetes have the same risks and, beyond these, the problems linked to diabetes may get worse with the pregnancy [10]. Women with GDM and their offspring have an increased risk of developing type-2 diabetes, impaired glucose tolerance (IGT) and obesity later in life [13]: between 30% and 70% of women with GDM will develop type-2 diabetes and an increased risk of cardiovascular diseases [11].

Hypertension Hypertension is the widespread problem seen during pregnancy. This disorder complicates almost 10% of pregnancies. Hypertensive pregnancy disorders (HPD) are responsible for 10% of maternal deaths in underdeveloped and developing countries and they are the major contributors to prematurity [9]. Diabetes, low metabolic control and pregestational microalbuminuria or high blood pressure increase the risk of pre-eclampsia in gestational diabetic women [15].
HPDs are commonly classified as: gestational hypertension or pregnancy-induced hypertension that is hypertension without proteinuria; pre-eclampsia, hypertension with proteinuria; chronic hypertension or essential hypertension that is pre-existing hypertension; chronic hypertension with superimposed pre-eclampsia.
Pre-eclampsia and eclampsia may lead to an increased risk of renal/liver failure, clotting disorders, stroke, premature birth (that includes stillbirth and neonatal death) and C-section or emergency C-section. Women with previous hypertensive disorders potentially have risk of high glucose, insulin, triglycerides and total cholesterol concentration in blood after pregnancy.
HPD is associated with cardiovascular and metabolic disorders, including hyper-

tension, type-2 diabetes and dyslipidaemia (abnormal amount of lipids in the blood). Both, mother and offspring could have long-term consequences deriving from HPD [9].

1.2.2 Results

Improving maternal health implies decreasing fetal deaths, even if it is not always possible.
The study of maternal death cases is often not possible because of vital registration systems lack in most countries and inadequacy of databases. It is also true that informations about many causes of death are often subject to errors such as misclassification and misinterpretation of the incident or omissions because of the particular treated problem. Information data is also often incomplete.
Sometimes it is also difficult determine whether a pregnancy might be an high-risk pregnancy as result of aggravation of pre-existing medical disorders. Recording the correct sequence of events is essential [16].
In order to prevent NCDs, understanding the role of maternal hyperglycaemia and obesity is essential. Numerous studies do point out the association between maternal hyperglycaemia and child obesity [12]. It emphasizes how important maternal health is.
Pre-gestational and gestational diabetes may already be the leading cause of high-risk pregnancies in many countries. Fetal effects are dependent on duration and exposure to high blood glucose level [11].
The fetal environment is represented by mother health status, which determines if newborn will start his/her life with a health "advantage" or "handicap". Exactly this can determine whether someone is more vulnerable to disease development than those who are born with "health advantage" [9].
Preterm birth is closely connected to newborn long-term neurological disabilities and infant death. Priority is given to chronic diseases such as diabetes, hypertension, asthma and renal disease as risk factors of preterm births [17].
Other studies show that multple factors can predict possible miscarriage during first trimester. Among various factors involved, a strong correlation between high

maternal age, low BMI, high concentration of Corticotrophin-Releasing Hormone (CRH), low level of Progesterone-Induced Blocking Factor (PIBF) and fetal loss has been found [4].
Low BMI of the mother (less than 20 kg/m^2) proved to be a risk for miscarriage during first trimester of gestation (4-7 weeks) regardless of mother's age. Interesting to note is the association between progesterone and woman's age with no relation to gestational age. Low *progesterone* concentration (12 ng/ml) is linked to an increased risk of miscarriage in older women (more than 33 years old) for the duration of first trimester.
Early miscarriage would also be caused by high levels of *cortisol*, which is detected with an increased of stress perception.
Anterior pituitary gland releases CRH to regulate cortisol secretion, but placenta produces cortisol too. Adverse effects on uterus and fetus are registered by high levels of glucocorticoids that inhibit pituitary luteinizing hormone, ovarion estrogen and progesterone secretion. This could result in miscarriage. Pharmacological intervention is essential to keep the right concentration of progesterone, and it must be done as soon as the risk of miscarriage is suspected [4].
The risk of spontaneous abortion increases if some factors occur together.
The International Diabetes Federation's Diabetes Atlas estimates that about 76 million women in reproducible age suffer from diabetes or impaired glucose tolerance\pre-diabetes. This means that their pregnancies will be potentially affected by diabetes. This creates a "*vicious cycle of diabetes begetting diabetes*" [18].
The [13] study show that the most frequent pregnancy outcomes of women with GDM were C-section, macrosomia, stillbirth and newborn jaundice.
Several studies show that multiple kinds of phisical activities are associated with a lower risk of developing type-2 diabetes and a better management of this disease [19].
Treatment of GDM in the form of dietary advices, blood glucose monitoring and insulin therapy with an adjusted dose on the basis of glucose levels limits the onset of bone fracture, nerve palsy, shoulder dystocia and death without increasing the rate of c-section [14].
Diet plays an essential role in the treatment of GDM. As a 2017 study suggests,

rich feeding of probiotic, fruits and vegetables may protect against GDM with their antioxidant properties and micronutrients (such as magnesium and vitamin C). At the moment, adhere to Mediterranean diet could be the best way to prevent GDM [20].

Women with undiagnosed and uncontrolled gestational diabetes expose fetus to high levels of glucose and other circulating fuels that during the late part of pregnancy result in a large baby [11].

An increment of maternal and perinatal morbidity and mortality is relating to undiagnosed or mismanaged diabetes or hyperglycaemia during pregnancy. Hyperglicaemia and hypertensive disorders are clear indicators of possible high future risk for hypertension and diabetes that can be used to prevent serious complications such as adverse pregnancy outcome such as miscarriage, stillbirth, congenital anomalies, macrosomia and birth complication (including C-section and assisted delivery) [18].

1.3 Challenges

The imperative is improving maternal health-care through appropriate health facilities and basic infrastructures in low and middle-income countries.

First objective of [21] is, according to SDGs, "survive" with the meaning of ending preventable deaths within 2030. In order to achieve this goal it provides a roadmap. Firstly, research is essential to understand and overcome the barriers to health services for women and their children. Innovation is the beginning of transformation of powerful new ideas and scientific evidences into widely used interventions. Research can also leads to stronger systems and to improved service quality, efficiency and effectiveness. Data acquisition (such us monitoring) must be done in exhaustive and accurate way to improve accuracy of tools and information.

Dr. Babatunde Osotimehin, Executive Director from United Nations Population Fund in order to achieve goal 3 of SDGs, says that good nutritional advices are important to have a balanced diet with micronutrients (diet should be rich in fruit and vegetables) as well as comprehension of the body and access to health services is essential to prevent a wide range of diseases [22].

Considering the importance of in-depth analysis on causes of maternal death, registering good informations about that is essential: distinguishing between aggravation of pre-existing diseases and external actions, for example, is important to attribute the maternal death to the correct causes. Documentation of correct and accurate sequence of events needs to be improved [16].
Chronic disease managements is important to avoid pre-term births. Understanding complications that have occurred in previous adverse pregnancies it is the best way to handle upcoming pregnancies at best. Identifying high-risk pregnancies depends, among other things, on treatment options available to women. Improving the health-care systems is necessary to reduce poor birth outcomes [17].
Understanding every facet of how diabetes in pregnancy affects maternal and newborn health is important to promote cooperation among interventions to treat this disease. Intervention like screening for diabetes as a standard care for pregnant women, getting nutrition advices and taking physical activity could be the first step to improve future generation health [3].
Appropriate dietary modification and physical activity can be enough to control gestational diabetes. Choosing to use a better treatment such as close monitoring makes possible to achieve optimum metabolic control to normalize blood sugar level [11].
Estimates have shown that early detection and management of diabetes in pregnancy could help to reduce stillbirth up to 45% and maternal and newborn death too [10].
An integrated approach to maternal health and NCDs could provide benefits to both, considering the known enhanced risk of maternal and perinatal mortality and morbidity. The stress is on benefits for NCDs prevention rather than cure. Women with pre-existing diabetes have to access to preconception counseling for reducing risks for them and their offspring. These informations need to be integrated by supportive policies and suitable programs, that can have on one hand immediate effect on pregnancy outcome, and on the other long-term benefits to mother and future generation [10]. This initiative could have significant positive effects on the overall health of the family and community.
Pregnancy offers a ”window of opportunity” that allows to provide maternal care services for prevention of several chronic diseases through generations.

1.4 The Case of Emilia Romagna

The CedAP (Certificato di Assistenza al Parto, that is childbirth certificate) provides health, epidemiological and socio-demographic information about births, stillbirths and new-born babies suffering by malformations. These data are important for public health and necessary for national and regional health planning.
The [23] is the result of CedAP certificates processing and contains data coming from hospital discharge cards about 34.155 births, related to 34.790 babies occurred in Emilia Romagna.

1.4.1 Examinations in Pregnancy

This report shows, inter alia, that, average number of examinations in pregnancy is 6,7. 3,8% of women carries out less than 4 medical visits (or no-one) and 10,8% of women have first examination over 12 weeks of gestation (women with a low or medium level of education are more likely to perform their first visit later than women with high education) and these indicators are worsening in the last year.
For women who have late access to the first check during pregnancy the probability of making a lower total number of visits is higher. To identify possible high-risk pregnancies, multiple and timely examinations are essential.
The number of ultrasounds performed during pregnancy is on average 4.8, but it could be overestimated because it's still impossible distinguish between ultrasound screening for diagnostic purposes (formal ultrasound) and ultrasound to complete the visit.
According to data, women that carry out invasive prenatal investigations are decreasing, while those who decide to undergo the combined test (non-invasive) are increasing.
It seems that 17,4% of pregnancies have a pathological course and the remaining have physiological course.

1.4.2 Pre-Term Births

The [23] shows that pre-term births (less than 37 weeks of gestation) in Emilia Romagna are the 6,8% excluding c-section without labour, while delivery is induced in 26.7% of cases, and this data is increasing. Premature rupture of membranes (occurred in 30.0% of cases), maternal pathology (27.9%) and prolonged pregnancy (22.3%) are the most frequent reasons.
Pre-term births seem to be more frequently in:

- multiple pregnancies (57,4%) than the single ones,
- primiparous women compared to multiparous (7,5% vs 6,0%),
- women with low education (7.2% vs 5.9% of women whit high schooling)
- women with foreign citizenship (7.3% vs 6.5%),
- obese women (8.0% vs 6.5% of women with regular BMI).

Children born pre-term have a chance to get CPR (cardiopulmonary resuscitation) almost 8,5 times more than those born at gestational age over 37 weeks.
Women with low education have greater risk of serious SGA babies compared to those who have a university degree.

1.4.3 Obesity Complications

Obesity is universally recognized as a risk factor towards pregnancies. Emilia Romagna, where the population is suffering an increase in its impact as a factor of pre-gravidational BMI, confirms this claim too.
The audit revealed that in overweight/obese women stillbirth is strongly associated with hypertension, and almost half of these women have weight increase exceeding the recommended maximum limits. This fact exasperates cardiovascular and metabolic disorders.

Chapter 2

ICT for Health-Care

This chapter describes the use of telecommunication technology in health-care area.
In particular we give an overview about terminology used in this area, describing concepts like Health Information Technology, E-Health, Electionic Health Record, Health Informatics, telemedicine, telehealth and the differences between telemedicine and e-health. Particular importance shall be given to mobile and pervasive health-care.
We review applications of ICT in health-care, highlighting their benefits and drawbacks.
We finally describes current challenges affecting this area and the vision of Hospital 4.0.

2.1 Technological Influence in Medicine

Technology today pervades every single aspect of modern society. Telecommunication technologies have changed and influenced the entire structure and organization of the medical environment in unpredicted and irreversible way. These technologies allow to provide treatment to patients away from health facilities and simplify the exchange of information between all the parties involved (patients and physicians)[24].
Over time many terms are born for defining and describing every aspect of this

area and this fact does not make it easy to understand what does each of these terms mean. The following subsection is useful to clarify these concepts.

2.1.1 Disambiguation

According to [25], **Health Information Technology** (HIT) is defined as "*the application of information processing involving both computer hardware and software that deals with the storage, retrieval, sharing, and use of health-care information, data, and knowledge for communication and decision making*". In this case, technology includes machines that can be networked to allow secure health information exchange.

E-Health, acronym of Electronic Health, is a term born in 1999 and it refers to health-care delivery through Internet. Several authors give different definitions of the term, but it can be considered as an "umbrella term" needed to describe the use of information and communication technology in health-care area [24].

Among many definitions, the most significant one we think could be the following: "E-Health is a field rising halfway between medical informatics, public health and business. This field concerns health services and information provided through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve health-care locally, regionally, and worldwide by using information and communication technology" [26]. The goal of E-Health is increasing the efficiency of health-care, exploiting a mean (Internet) that allows to do what previously was impossible [24].

E-Health includes component of health information technology such as Electronic Health Record (EHR), Health Information System, Telemedicine, M-Health, and others.

Electronic Health Record, previously known as Electronic Medical Record (EMR), is the systematic collection of patient and population informations stored on electronic media. The correct definition of these term is controversial. While on one hand EHR is a transversal collection of electronic health informations about patient and population, on the other EMR is born to store health information

about patients within health-care facility and for specific use of medical staff. EHR draws on EMR information.
EHRs are networked to allow information exchange and captures the state of patients across time. The EHR system is basically a repository of health digital informations of patients [27].
Health Informatics, also known as Health Information System, understood as the systematic application of HIT to improve health-care, is defined by United States National Library of Medicine (NLM), the world's largest medical library, as "the interdisciplinary study of the design, development, adoption and application of IT-based innovations in health-care services delivery, management and planning" [28] and it includes several discipline such as computer science, social science, and management science, in order to reduce costs and increase availability, optimizing the management and use of informations.
Telemedicine is the use of telecommunication and information technology to provide health-care services, clinical information, and education over distance. In many cases, no physician is involved and interactivity is not necessary [24].
These technologies allow communications between patient and medical staff in a safe and convenient way.
The WHO defines **telehealth** as "the integration of telecommunication systems into the practice of protecting and promoting health, while telemedicine is the incorporation of these systems into curative medicine" [24]; this practice includes preventative and curative care delivery such as non-clinical applications like administration and provider education.
Telehealth and telemedicine are considered by The American Telemedicine Association synonyms [29], but generally it is commonly referred to telehealth as something used more broadly for remote health not involving active clinical cares.

2.1.2 Comparison between E-Health, Telemedicine and Telehealth

With the advent of Internet, the birth of E-Health should be not understood as a replacement of telemedicine and telehealth, but rather as a complement. Now health-

care is not just accessible, it can be radically changed [24]. The first and, maybe, most important difference between E-Health and telehealth and telemedicine is not being for professionals uses only [24]: e-health is driven by non-professionals, while telemedicine and telehealth remains connected to medical professionals [30]. There are many E-Health services that lead to a possible financial gain, whereas it is not the case for telemedicine and telehealth [24].
E-Health can be introduced as "the death of telemedicine" because in a context where medical systems have to communicate, telemedicine will no longer exist as a traditional medical informatics field. E-Health is a common name for all such technological fields [30].
According to professor Vincenzo Della Mea, the meaning of E-Health is properties, possibilities and consequences of integrated-health-care-systems that are (in a holistic approach) more than the sum of the single-component outcomes [30].

2.1.3 Mobile Health

In 2011, the mobile technology penetration rate was the 87% worldwide. In developing countries it surpassed infrastructures like paved roads, electricity and running water [31]. As reported in [32], by end 2015, there are more than 7 billion mobile phone subscriptions, corresponding to a penetration rate of 97% . Diffusion, convenience and practicality of use make mobile devices suitable platforms for accessing, managing and providing health-care services. *M-Health* (Mobile Health) is defined as the health-care supported by networked mobile devices and mobile communications [33].
This emerging concept can be considered as an aspect of E-Health and it marks the passage from telemedicine that worked through use of traditional platforms to health-care passing through mobile device such as mobile phone, tablet computers, PDAs (Personal Digital Assistant) and wearable devices for health services, information and data collection [33].
Aspect of fundamental importance in m-health is communication between devices that must be always reliable, interactive and available to improve the administration of health-care services [31].

Pervasive health-care is the environment in which M-Health is located, which includes a wide scale deployment of wireless networks; as a result, health-care services are delivered anytime and anywhere, with a reduction of medical errors and an improvement of information access.
Pervasive health-care systems contains everyday objects equipped with sensors and memory which make them capable of collecting data from environment, exchanging information each other and reacting on the basis of constraints previously defined [34].
Another fundamental aspect of pervasive health-care is the concept of "wearable computing". Computers that become part of everyday clothing always connected to devices that assist users in everyday situations [34].
Social networks are changing the everyday people life. More and more people exchange information through social networks so M-Health may exploit the network to promote healthy behaviors and encourage cooperation among patients in groups and communities [27].
We will discuss the m-health technologies more in detail in the following chapter, in particular applications concerning pregnancies.

2.2 Current Uses

The worldwide development of telecommunication technology in health-care field, expresses itself in an integrated system comprising synchronous and asynchronous technologies such as real-time and store-and-forward ones, created to providing optimal care to anyone, anytime and anywhere [24]. In the sequel we use E-Health, Telemedicine and Telehealth interchangeably for simplicity, using these terms to generally indicate the application of ICT in the health-care area.

2.2.1 Applications

Nowadays, several studies show that information and communication technology in medical field is an increasing practice for providing medical treatments and services [35]. In general, technology has deeply influenced many aspect of health-care.

The multiple applications can be classified based on particular health-care area:

1. *Clinical Applications*: this kind of applications includes all areas of *patient* care (diagnostic, treatment and monitoring services). This area covers real-time or store-and-forward technologies such as everyday electronic devices like telephones and fax machines, e-mails, chat rooms, audio- and video-conferencing [24].

2. *Administrative Applications*: administrative area includes billing summarize data, connections with pharmacies for drug prescriptions and control for conflicts between drugs, checking medical records for mistakes or contradictions between treatments, public health records management [24].

3. *Remote Medical Instrument*: these applications comprehend a whole range of medical devices such as pressure sensors, imaging technologies and specialized robotics in context of medical areas. Typical devices of this area are remote blood pressure cuffs, thermometers, and portable EKG units with plug-ins for computer transmission of reports [24], order entry systems that allow the access to medical records from a distance and smart alarms that bring services and expert assistance in unequipped locations [35].

4. *Educational Applications*: educational applications refer on one side to courses of study and updating for professionals, and on the other to patients with educational resources and self-monitoring devices needed to help them obtain behavioral changes agreed. Telementoring is an application that allows you to learn through consultation. This is the case of professionals who shall consult with specialist on how to diagnose and manage a specific clinical problem in order to avoid future consultations.
   Practitioners in developing countries also are able to keep informed of the latest medical information, but in these countries there are many limitations related to health data sharing and management. Thanks to E-Health, these physicians can now connect with each other and other professionals [24].

Particular important are applications that concern *nursing*, especially in dialysis unit. Nurses that use such kind of applications appreciate the increase of control

in treatment and communication with their patients in the absence of supervising doctor.
The role of telemedicine in management of chronically ill patients in their homes is particularly important. Through telemedicine devices, patient can communicate the doctor informations related to his/her status and immediately receive directions on what to do next. In the same way, patients can communicate with their doctor located in hospital through home nurse and the nurse can receive feedback useful to know how to proceed accordingly [35].
Other applications of telemedicine includes *military environments* and *prisons* too. In military arena telemedicine can connect people who treat victims on the battlefield with doctors in specialized areas, avoiding the physically presence of physician who can treat another patient in hospital. Patients in prison can be treated following the same procedure [35].

2.2.2 Benefits

Telemedicine, as seen, offers so many benefits to all patients, physicians and community as a whole [35] because it resulted in an impressive change.
Benefits arise from known problems like unequal distribution of health-care facilities and medical staff, limited access to health-care resources for a portion of population and continuous increase of public and private health-care costs [24].
Telemedicine and telehealth increased the *quality* and *specialization* of health-care for patients. Patients receive assistance faster and more conveniently if a local practitioner has the possibility to communicate immediately with a specialist.
Internet, in addition, allows to transmit many kind of medical images as well as audio- and video-streaming.
Patients are incentivized to communicate with nursing and medical staff through encrypted e-mails, consult web-based applications dedicated to disease management and personal health record and self-monitoring [24] without continuous need to travel. As such it also can eliminate the possible transmission of infectious diseases or parasites between patients and medical staff.
E-Health could also reduce test duplication because physicians can access to patient's most recent health information. Access to updated and complete infor-

mations about patients can improve the quality of decision making: information collection and storage leads to improve efficiently and safety by allowing physicians to make better and more informed decisions [36].
Educational applications keep medical professionals *up-to-date* without worrying about where they are. They receive information from on-line databases and remote expert systems about nearly every condition and diagnosis [24].
E-Health sites provide *medical informations* about drugs and treatments to people who should otherwise physically go to equipped facilities. This kind of services also provides better health information for Internet surfers [35].
For groups of people like senior citizens with neurological and mobility disorders, those who lives in high crime areas and other patients with psychiatric disorders that live in their houses, get adequate health-care could be difficult. Technology offers a range of practical tools that improves and makes access to health communication and services *easier* for these groups of people [24].
Telehealth makes a more effective allocation of health-care resources between different health-care facilities. Regardless of where the patient is, telehealth allows him/her to access to medical experts, rapid diagnosis and correct treatments [24].
Some professionals work in a rural or remote environment; rural communities create together a "*televillage*" to reduce isolation and improve health-care services in general by sharing telecommunication networks and related services [24].
Health communications are improved through telemedicine and telehealth. Communications, indeed, are no longer subject to time constraints thanks to *real-time interaction*. This leads to decrease patient anxiety caused by long waiting times for a health-care provider [35].
Health organizations have now the opportunity to exceed space and time constraints by working outside their catchment area through telehealth technologies [24].
Telemedicine can *minimize the costs* related to health-care services. It reduces travel time and time needed to organize appointments in order to facilitate communication [35]. It also offers training for family caregivers, group support through e-mail discussion groups and direct e-mail contact with medical staff [24].
From administrative viewpoint, telemedicine decreases costs and increases efficiency by simplifying patient scheduling, medical records acquisition and through

rapid transfer of information about patients [24].
With the widespread diffusion of the Internet, health information systems can be accessed by anyone who have a browser web and a proper identification, such as username and password. This information system contains every personal health information from the administrative to clinical ones and security while confidentiality are guaranteed by tunneling technologies [24].

2.2.3 Drawbacks

The first and most frequently criticism moved to telemedicine is that it *decreases physical interaction* between medical staff and patients. Communications are conveyed through technological devices in which human contact is absent. The way telemedicine works aims to dehumanize, dissocialize and depersonalize human interaction. Communication and data exchanges occur through health-care systems between digitized people without the need of face-to-face interaction [35].
The exchange of e-mails instead of talking to each other, deprive the speech of all non-verbal language (facial expression and gesture) leading to decrease interpersonal contact. Many Internet-based services actually reduce the need of contact.
From viewpoint of some nurses, the contact of touching patient coming undone. This fact becomes particularly evident in patients with chronic pain that stay at home that do not receive the visit of medical staff [35].
In general these technologies should not be intended as a substitute for the patient-doctor relationship, but they should be considered as an important support tool to it.
The adoption of telecommunication technology in health-care leads to *financial problems*. Implementation cost includes hardware and software costs. Hardware must be purchased, configured and periodically replaced. Software must be installed and periodically updated. Additional costs (in terms of time and money) are for staff technical training and support [37].
In addition to system implementation and maintenance costs, temporary loss of productivity may cause a decline in revenue. The adoption of telecommunication technologies radically change work-flow for medical staff and providers that may cause a temporary loss of productivity [37].

Another serious drawback of telemedicine includes issues related to patient *privacy*. Patients' concern of privacy violation increases with the increase in the amount of personal health-care data electronically stored and transmitted [37].
In M-Health standard architecture, sensitive data is exchanged through wireless networks and this, along with public health information management, is cause of important problems related to patient privacy [27].
Among negatively unintended consequences, there are an increase of medical errors and an over-dependency on technology. Many medical errors are due to systems interfaces that are often counterintuitive and the technical trainings that are not sufficiently detailed. Continuous and massive use of technology has become addictive to organizations, that should still guarantee basic medical care without technology, especially if a temporary disruption may be critical [37].
Cases of poor quality of many kind of medical images or patient progress reports can compromise the quality and continuity of patient care for the reporting doctor. Legal liabilities for some telemedical practices and difficult procedures for requesting refunds are disincentives to the use of telecommunication technologies. Scenarios in which assigning responsibilities is legally regulated differently from state to state still exists, but evolution of technology will result in discover feasible solutions to these problems [35].
The technological evolution of the last few years has forced the medical environment to adopt standards to avoid communications through all technologies. The greater the number of technologies involved, the greater the likelihood that they will be incompatible. These problems may have caused a considerable loss of time [37].

2.3 Challenges

The introduction of telehealth and E-Health in professional practice is an issue hotly debated. On one hand there is a group of professionals that embraces technological change and innovation, on the other those who want empirical validation before adopting these practices. Most professional groups proceed cautiously [24]. From a legal viewpoint, states are adopting laws that regulate this practice and they have potentially different legislations, so several groups, such as Federation of

State Medical Boards, are passing laws to allow professionals to practice telehealth across state boundaries [24].

The problem of practitioner-patient relationship through technological tools is controversial. It is necessary to have guidelines that clarify the rules for an appropriate use of such technology and assign right responsibilities so that physicians can understand their own by studying such guidelines [24].

Refund requests for telehealth has increased significantly in the last few years. The difficulty of receiving services reimbursement from insurance companies is a problem to be reckoned with [35]. In order to refund telehealth services, many states promulgated laws to support it [24].

Organizations such as World Health Organization, many branches of the U.S. government, American Health Information Management Association and the American Medical Informatics Association, consider the problem of patient privacy very seriously. They work to provide and preserve protection of patient informations [24].

A key aspects of telecommunications technology in health-care is training the staff. This training, that may be expensive, time consuming and frustrating, is necessary to be able to make the best use of such a technology. Telecompetence is a term coined to indicate a set of competence that a professional must have to approach the telemedicine. Achieving this level of competence requires considerable training and finances that not all medical realities can afford. For this reason, in some medical settings with limited resources, telemedicine may not be a feasible or affordable option [35].

Cooperation among M-Health applications is needed. Physicians and patients should be able to use different services and cooperate with each other to achieve a common result and improve performance and efficiency of devices [27].

M-Health systems play a key role in renewal process of old health-care services that are still based on physical relationship between patient and medical staff [27].

2.3.1 Hospital 4.0 and Internet of Things

We hear a lot about **Hospital 4.0** lately. The label "4.0" identify something important: the 4^{th} Industrial Revolution.
The whole world is experiencing a profound change in society that conditions it in several levels, from technological to research one. This change concerns the way we live and the comprehension we have about different aspects of society.
In industry, the integration of different technologies such as big data, robotics and cloud computing, leads to a complete revisitation of concept of the industry itself. At the heart of revolution there is **IoT** (Internet of Things), the network which enables these everyday objects to connect and exchange data. Internet becomes the means that connects these objects that were previously "dead", without computational ability. These "things" now perceive reality and can interact with the rest of the system that has been created. Computers will disappear because everything around us will have computational ability.
In health-care area, many electro-medical devices are now able to send parameters that can feed in real time the wealth of clinical information of each patient. From a strictly technological viewpoint, health-care facilities are the place where thousands of byte are generated and transported by thousands of devices every day. These data, correctly analyzed, potentially allow reactions that anticipate a possible problem.
These systems, composed of devices equipped with sensors, continuously collect a large amount of data related to any event that occurred. They learn and reason from the data they sense without the need to be pre-programmed, allowing themselves to make decisions that lead to benefits that were previously unthinkable.
According to experts of the field, collecting as much information as possible about the patient on the way is especially important in emergency situations where is essential to make the right decisions. Networked devices that continuously collect and exchange data support professionals in making more informed decisions.
Many countries still adopt old health-care model which dates back to the 20th century, but hospitals investing in ICT has doubled in the last few years. Since the 1980s, countries have invested in health-care technologies, but now these investments are decreasing and M-Health is becoming the way to reduce health-care

costs [27].
M-Health brings with it a new paradigm where patients and physicians exploit the benefits of technology which have revolutionized the world of health-care delivery [27]. The Hospital 4.0 is the place where clinic engineering and information technology converge because are the technologies themselves that converge.
The need to have a collective network that allows the wireless exchange of information is urgent. There are too many wires that connect devices to patients. These wires make medical staff movement very difficult and a possible disconnection can be a source of errors and loss of information.

Chapter 3

ICT for Pregnancy

This chapter provides an exploration of ICT applications in the specific field of pregnancy monitoring. We describe which systems are used to support pregnant women achieving a healthy pregnancy, in particular in nutrition, self-management and fetal signs monitoring fields.
We show Mobile Health systems architecture with particular attention given to data processing techniques such as Machine Learning and Simulation Techniques. Finally we describe Agent-Based Modeling and Simulation approach showing main characteristics of such systems.

3.1 M-Health Technologies for Pregnancy

One of the most important area in health-care is *pregnancy* and *maternal health*. Negative pregnancy outcomes have consequences, of course on families, but also on health-care system. Pregnancy complications leads to an increase of costs; for example, a C-sections is more expensive than a natural childbirth as well as hospital costs for pre-term births and low-birth weight are almost 50% of hospitalization costs related to neonatal department [38].
According to [38], some studies show that an hospitalization for uncomplicated delivery is more than 2.5 times much cheaper than hospitalization for complications such as pre-term birth and low-birth weight infants. Negative outcomes produce also long-term consequences such as disability and childhood neurodevelopmental

disorders that lead to further societal costs related to special education services and decrease of productivity by members of family caused by reduction of working hours or job loss.
Access to prenatal care is essential to improving maternal and fetal health, and technology gives this possibility delivering prenatal support to high-risk women wherever they are.

3.1.1 Nutrition

Nutrition and lifestyle are particularly important during pregnancy for both mother and baby. In this period, intervention about lifestyle are real investments for health of current and future generations. It is important to make the future parents aware of this.
These interventions mainly concern *body weight regulation*, *correct nutrition*, *supplement of folic acid* and *reduction in the use of tobacco* [39].
Mobile Health have the potential of improving inadequate nutrition and lifestyle providing necessary information to users. Several studies shows how this objective is possible by using mobile phones and smartphones in order to monitoring patient behavior during pregnancy. Mobile phones are used to collect data, keep medical records up-to-date, promote communication between physicians and patients and give them advices on healthy behaviors [40].

3.1.2 Self-Management

M-Health systems allow users to self-manage their own health situation. This includes regular monitor, reporting changes in health status and changes in treatments as a result of received informations from patient [40].
Self-Management relies on data acquisition and processing from which feedback is obtained. The way data are processed and information presented depends on specific situation in which patient is [40].
Some studies show that text and vocal messages are used like reminder to change patient behavior and to communicate with medical staff mostly in low and middle incoming countries [41].

An online Web-based platform can be exploited to provide such kind of informations. Technologies like this one have to focus on prevention of Non-Communicable Disease through providing suitable educational programs and allow an easy access to on-line resources [39].

3.1.3 Fetal Kicking and Heart Rate Monitoring

Systems that collect data from fetal kicking and heart rate monitoring use *sensors* placed on mother abdominal region through an elastic belt. Sensors are connected to an computational unit that receives and processes data. Processed data are typically sent to a mobile device, which is accessible to both patients and medical staff, that displays them [41].
Collecting data about fetal movements and heartbeat provides important informations about the health status of the baby. Decrease or absence of recorded signals could be symptomatic of a fetal loss.
Among non-invasive method that can diagnose a possible pregnancy complications there are Doppler[1] and Ultrasound echography. They are normally employed in hospitals. This kind of examination adds important informations on health status of mother and child when remote consultation is needed [33].
M-Health systems such as MobiHealth BAN allow women with high-risk pregnancy to stay at home and postpone hospitalization, through continuous monitoring. This reduces costs because fetal signs, like heartbeat and blood flow in the umbilical cord and in placenta, and physiological parameters are transmitted to hospital [33].

3.2 Architecture of M-Health System

Concept of IoT (Internet of Things) based on mobile or stationary devices that receive data from sensors capable of capturing aspects of the real world [42]. The

[1]Doppler is a clinical examination that exploits the doppler effect on ultrasound to check the functionality of large blood vessels

big load of captured data can be processed internally or more likely be sent to some sort of cloud infrastructure where the computational ability is greater. This allows a faster elaboration and thus a better quality of health-care services provided [27].

3.2.1 Sensors

Sensors can collect data in real time from environment and patients body (physiological parameters). In case of emergency, remote patient monitoring allows medical staff to to handle situation and intervene promptly. Processed data is used to support physicians during decision making. Smart intelligent sensors, some of them implanted, are developed to allow communication with personal server in complete mobility [33].
Wearable health monitoring devices exploit PAN (Personal Area Network) or BAN (Body Area Network) to communicate with each other.
PAN is a network for interconnecting devices centered on an individual workspace, and BAN, on other hand, is a wireless network of wearable computing devices.
A set of wired sensors is usually connected with processing unit integrated to user's clothes. This system can continuously monitor the patient's health status even during activities even if it is unsuitable for long monitors [33].
Better results are obtained with new generation of medical monitors that integrate intelligent sensors into wireless BAN through Bluetooth and Infrared Data Association.
Elaboration results should be accessed in a distributed, heterogeneous environment [42].

3.2.2 Data Processing

Data sent to computational devices have to be processed to produce significant result. This process is usually achieved in two ways: by *machine learning* or *simulation* techniques.

Machine Learning Techniques

Machine Learning is a fundamental area of *Artificial Intelligence*. It includes techniques and algorithms capable of automatic learning.
Machine learning techniques like neuronal networks, decision tree, SVM (Support Vector Machine), Bayesian network, genetic algorithms, are widely use to support decision making process. These techniques achieve usually better results than statistical traditional methods [43].
Machine learning, in turn, includes *data mining* analysis that discover previously unknown, interesting patterns from a large amount of data in order to extract useful informations. Pattern identifies a *subset of data* or a *model* applicable to the subset [44].
Data mining analysis aims to *predict* unknowns values of variable based on values of other variables or *describe* patterns in data previously not human-interpretable. These kind of techniques aims to semi-automatic or automatic analysis of data through [44, 45]:

- *Classification*: Predictive activity that aims to find a model to predict value for classification attribute based on values of other attributes.

- *Clustering*: Predictive activity that aims to find in a set of points, those ones that are more similar to each other than among other subsets.

- *Association rule learning*: Descriptive activity that aims to search for relationships between variables.

- *Regression*: Predictive activity that aims to predict continuous values variable based on the other assuming linear/non-linear description model between attributes.

- *Anomaly detection*: Predictive activity that aims to identify an abnormal behavior that could be a data error or an interesting deviation that requires more investigations.

Simulation Techniques

Computer simulation is a comprehensive method for studying the evolution process of *complex systems*. It attempts to reproduce the behavior of a system using a mathematical model that predict analytical solution to a given problem. Usually simulation concerns real world situations [46].
Many natural systems like physical and biological ones, and human systems like economic ones, can be mathematical modeled through simulation.
This definition brings out concept of *complex system* that is one in which components interact with each other: in holistic view, the whole is more than the sum of system parts because of the interactions between the parts [47, 48].
These systems are difficult to study for severe reasons like ethical or practical ones, evolution too slow or too fast, systems that do not exist (or do not exist yet), small perturbation that can lead the system to extremely complex overall behavior, unpredictable evolution [47]. Simulation helps us understand real phenomena, by nature difficult or impossible to reproduce under controlled condition.
Simulation process begins with choice or creation of the model, and then it has to be implemented on a computational device [46]. A *model* can be used as representation or abstraction of a system [47].
The implemented model receives input as a specification of the system's state in the form of parameters and initial conditions. Data are processed reflecting system's state evolution and elaboration results, which are based on modeled behavior, and are displayed accordingly.
Algorithms and rules used to describe system behavior represent the model. Computer simulation is the process of running a model through computational tools.
Simulation is particularly suitable to understanding complex systems behavior.
Several types of simulation can be defined by the granularity of their elements [49]:

- *Micro-simulation*: system is described as *a set of smaller entities*. Each entity is described by the only rules that determine their behavior. Individuals interact with each other.

- *Macro-simulation*: system is described as *one entity*. System's components that are described by variables and rules that define their behavior are attributed to this entity. Macro level is an aggregation of micro level activities results and it used to observe emergent phenomena.

- *Multi-level simulation*: intermediate form in which system is described at *different time scales*. Interactions occur intra- and inter-levels. This kind of simulation is considered the better way to describing complex systems because it allows to describe the influence that the parts have on the whole system (upward causation) and the constraints impose to parts by the whole (downward causation) [47].

In order to highlight progress made by simulation, *Roberto Visentin at al.* have presented their Type-1 Diabetes Metabolic Simulator (T1DMS) that recently received the Food and Drugs Administration (FDA) acceptance as a substitute for pre-clinical animal testing of new treatment strategies [1]. Such model, implemented in Simulink/MATLAB, is able to describe physical glucose-insulin dynamics through the simulation. In the following will be investigate in details the Agent-Based Modeling and Simulation approach. Recent simulation systems like [1] show the great progress in this area. The modified and updated simulator proposed by *Roberto Visentin at al.*, is able to describe the glucose concentration changes in blood by simulating physical glucose-insulin dynamics through differential equations. This simulator is accepted by the Food and Drugs Administration (FDA) as a substitute to pre-clinical trials involving animals for several insulin treatments.

3.3 Agent-Based Models

Agent-Based Modeling (ABM) is a relatively new approach that allows to describe a complex system as a collection of autonomous entities called "agents" which interact with each other. The interactions among agents influence their behavior [48, 50].
An example of Agent-Based Model is shown in 3.1 Each agent has a behavior defined by a set of rules, but they also can evolve, allowing unanticipated behaviors to emerge. Evolution and adaptation is achieved through providing learning

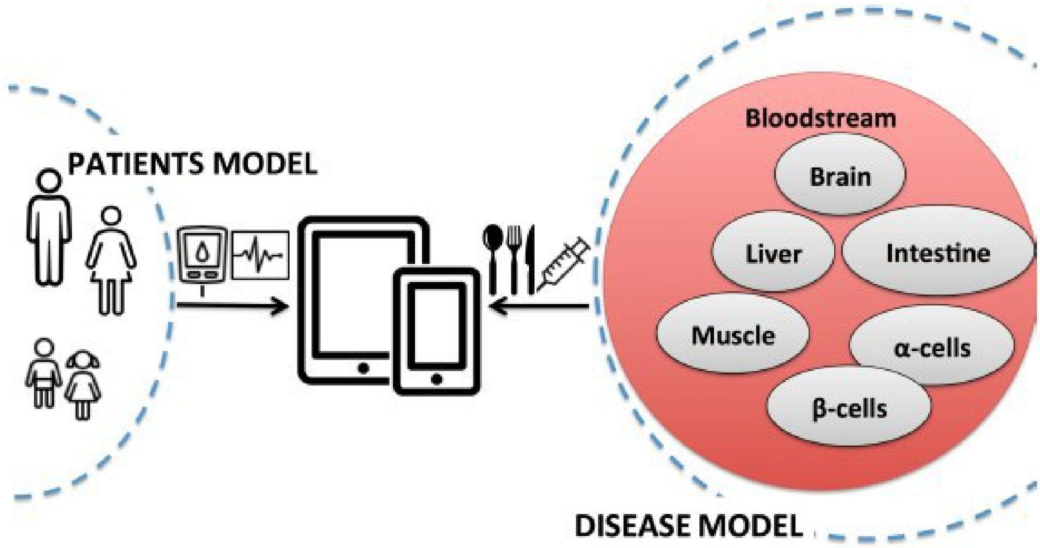


Figure 3.1: Example of a self-management Aget-Based model [2]

techniques such as neural networks [48].
A multi agents model contains [47]:

1. *Agents* with their attribute and behaviors

2. *Society* defined by interactions among agents

3. *Environment* defined by topology and internal relationship

3.3.1 Characteristics of an Agent

The fundamental characteristic defining an entity as an agent is the capability of being *autonomous*. Agents are active entities: their behavior is not controlled by external directions but is autonomous. In addition, they can evolve over time and learn by environment and other agents (pro-active behavior). Some authors assert that capabilities like learning and changing are necessary to call such entities "agents" [50].
As shown in [50], other characteristics of agents are explained in the follow.
Agents are *uniquely identifiable individual*. Agents are all different from each other

and identifiable by their own attributes.
Their capability of acting independently in their environment makes them *self-directed*. According to the model, agents can interact within a subset of a system and over a limited situations of interest to model. An agent acts and makes decision on the basis of other agents behavior. Information exchange takes place through interaction among agents and environment.
Adaptive mechanisms are achieved by advanced machine learning techniques or set of simple rules.
Agents may have goals to achieve related to their behavior. Being goals-directed allow agents to compare their own outcomes and evaluate which behavior is the best one to pursue in the next iterations.
An agent have a set of attribute values that defines its *state* at a given time. The state can change over time. Agent's state influences its behavior. The model's state is the collection of all agent's states along with environmental one.
Static attributes (e.g. a name) do not change during simulation, the dynamic ones do (e.g. a list of actors neighbor).

Benefits of Agent-Based Modeling

One of the main benefits provides by Agent-Based Modeling is, as already mentioned, the description of *emergent phenomena* resulting by interaction among agents.
The relationship between agents provides a *natural description* of the system rather than describing it in terms of processes. The use of differential equations is possible, but complexity of equations quickly increases as complexity of interactions increases, until it becomes an intractable problem [48].
Agent-based model is *flexible* by several dimensions. Adding more agents to the model it's simple as well as changing level of the system's aggregation [48].

Issues of Agent-Based Modeling

The main issues concerned agent-based modeling are two [50]: *which agents can interact with whom* and *what is the dynamic behind these interactions.*

Interactions between agents are usually managed by protocols which define behavioral constraints.
Topology of these systems is *decentralized*: there is no central unit that provides global informations to all agents or that controls agents behavior. Agents are only aware of local informations provided by their *neighbors*. In this way, no agents can interact with all other ones at any time as, instead, it happens in real systems.
This topology doesn't allow a centralized authority to control the whole system in order to optimize performances.
Concept of "neighborhood" is introduced by the notion of *networks* where nodes (agents) are linked (relationships) to the subset of their neighbor. Networks may be *static* if the links are pre-determined and they do not change over simulation progress, or *dynamic* if their link are modified according to programmed rules in the model.
General speaking, Eric Bonabeau in [48] has defined an issue that expresses all the other ones; he wrote "*One issue is common to all modeling techniques: a model has to serve a purpose; a general-purpose model cannot work. The model has to be built at the right level of description, with just the right amount of detail to serve its purpose; this remains an art more than a science.*"

Chapter 4

Self-Management of Gestational Diabetes Mellitus

This chapter provides a physiological description to Gestational Diabetes Mellitus model. In particular we describe glucose metabolism and the physiology of main organs involved in it.
We describe metabolic changes arising from pregnancy and its physiological influence on metabolism. We show what are consequences of adding placenta organ to organism and how the changed metabolic system may leads to Gestational Diabetes Mellitus.
At the end of chapter we introduce the Self-Management system model used to simulate a healthy and Type-1 diabetic patient glucose metabolism.

4.1 Metabolic System

Glucose is the main energy source for human body. Every cells of human body needs glucose to perform its function.
Importance of glucose is related to its regulation in overall organism. Organs and hormones work together in order to keep the delicate balance between parts of this system. A description about metabolic system behavior is depicted in [?]

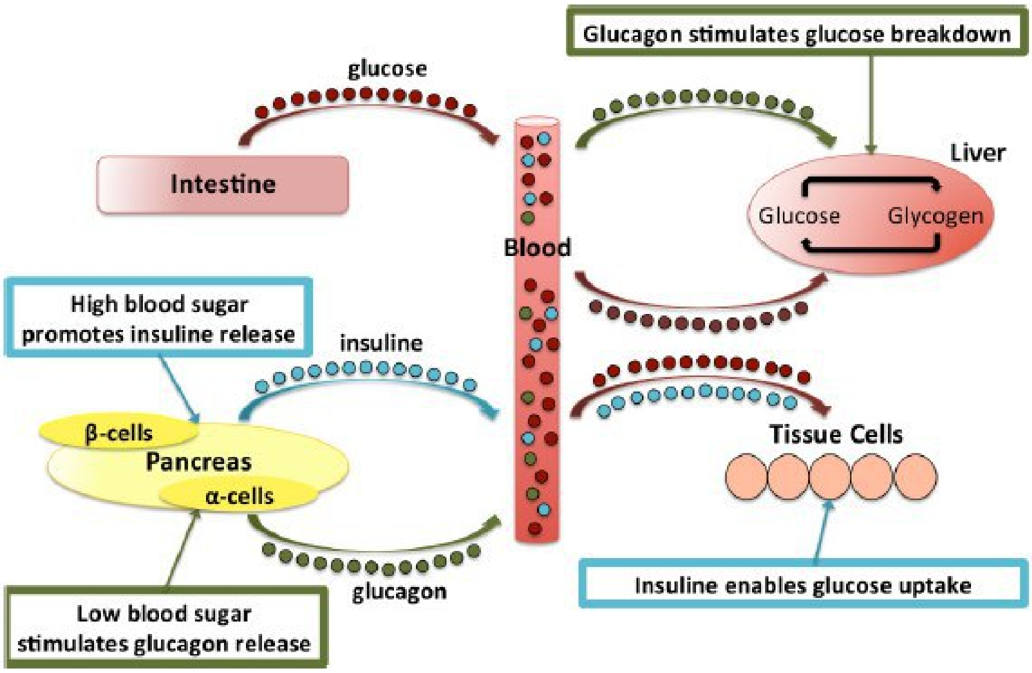


Figure 4.1: Metabolic System [2]

4.1.1 Glucose

From the chemical viewpoint, glucose is a simple sugar with the molecular formula $C_6H_{12}O_6$.
Glucose is introduced with the diet and a part of it is immediately used by organism while the remainder one is stored as *hepatic* and *muscle glycogen* (molecular formula: $C_6H_{10}O_5$) which consists of several glucose molecules. A smaller quantity of glycogen is stored in heart, kidney and adipose tissue [43].
Glycogenolysis is the process whereby glycogen is split into glucose. *Glycogenesis* is the process in which glucose molecules are added to chains of glycogen for storage.
Glycemia is typically measured in milligrams of glucose in deciliters of blood. It tends to be stable in fasting situation and rapidly grows after eating. Two to three hours after the meal, the blood sugar level has to return to basal values. The organism regulate glycemia in order to not exceeded healthy range (both above or

below).
Dott. *Cecilia Ragazzini*, endocrinology and diabetology expert working at Ospedale Bufalini in Cesena, gave us an interview about normal regulation of sugar blood and diabetes. She told us that standard fasting sugar blood level is *between 60 and 110 mg/dL* and postprandial peaks should *not exceed 140 mg/dL*.
Glycemia in pregnancy women is lower in fasting condition and a little bit greater in postprandial condition.
Gestational Diabetes Mellitus is diagnosed due to *75g OGTT* (Oral Glucose Tolerance Test) [51]. This test involves oral ingestion of 75g of glucose solution. Glycemia is registered tree times: before glucose ingestion, after one and after two hour from ingestion. Values of blood sugar have to be respectively lower than 92, 180, 153 mg/dL to avoiding possibility of GDM diagnosis.

4.1.2 Insulin and Glucagon

Glycemia is regulated mainly by two hormones: insulin and glucagon.

- **Insulin**: hormone responsible for *glucose uptake*. Insulin allows fat and muscle cells to absorb glucose. It is secreted by pancreatic β-cells reacting to glycemical increase. It usually measured in microUI (International Unit) of insulin in milliliters of blood.

- **Glucagon**: hormone responsible for *glucose release* in blood flow. It allows the liver to start glycogenolysis from which glucose is derived. It is secreted by pancreatic α-cells reacting to glycemical decrease. It is usually expressed in picograms in milliliters of blood.

4.1.3 Organs Physiology

Tissues involved in glucose metabolism are mainly three: **intestine**, which is responsible for glucose intake from meals, **liver**, which is responsible for glucose storage and release in bloodstream, and **muscles** which are responsible for glucose storage and utilization for physical activity.

Intestine Intestinal absorption is the way in which glucose become usable by organism. The food ingested is reduced to glucose.
The amount of glucose associated to each meal is defined as *Glycemic Load* (GL). One unit of Glycemic Load approximates the effect of one gram of glucose in bloodstream [52].
Glycemic Load definition is related to the *Glycemic Index* (GI) one, that describes the metabolic response to food intake. Low-GI food is metabolized much more slowly than the high-GI food. This one, in fact, releases glucose quickly creating high and narrow peaks in sugar blood [52].

Liver Liver is an insulin-independent organ that stores glucose from bloodstream in the form of hepatic glycogen and releases glucose when the blood sugar level is too low. Glucose uptake occurs regardless of presence of insulin in blood. Process of releasing glucose begins if there's glucagon.
Liver releases glucose from its stored glycogen.

Muscles Muscles are insulin-dependent tissues that absorb glucose from bloodstream. They can absorb glucose only if pancreas (β-cells) released insulin.
Muscles can also storage glucose as glycogen, but resulted glucose from glycogenolysis is usable only by the muscles themselves during physical activity.

4.2 Physiology of Pregnancy

With the onset of pregnancy, many changes occur in women body. Metabolic balance is altered by organs requests concerning maternal and fetal needs.

4.2.1 Metabolic Changes in Pregnancy

From metabolic viewpoint, pregnancy can be divide in two phases [53]:

1. *Anabolic phase*, which lasts until about the 20th week. During this phase occurs an increased production of steroid hormones such as *estrogen* and

progesterone that brings to small increase of level of insulin sensitivity and consequently light hyperglycemia, to ensure right glucose provision to fetus [54, 55].

2. *Catabolic phase*, which lasts from about 20th to 40th week. In this period, hormones that counteract insulin activity such as prolactin, cortisol and hPL (human Placental Lactogen) cause insulin resistance in the liver, muscles and neurons and consequently stronger hyperglycemia [54, 55].

During pregnancy the fasting sugar blood level diminishes with a complex and not completely understood mechanism [55]. This decrease may be influenced by the increase of blood volume during early gestation, increase of glucose utilization (by both mother and fetus mostly in late pregnancy) and/or insufficient hepatic glucose production [55]. This effect is emphasized with prolonged fasting which means a probably decrease in level of glucose released by liver.
Experiments on fetal blood sampling seems to observe that both fetal size and gestational age influence fetal glycemia.

Placenta During pregnancy, fetus has to feed and breathe. *Placenta* is a temporary organ located in utero necessary to feed, protect and support fetal growth. The umbilical cord is a conduit between the fetus and the placenta.
Process of placental-fetal glucose exchange is insulin-independent [53] and it is achieved by concentration gradient difference through an active mechanism (energy consuming mechanism) [54].
Glucose crosses the placenta and feeds the fetus by means of the umbilical cord. Keeping a tight grip on recommended sugar blood level is fundamental to ensure a healthy pregnancy. Fetus exposed for a long time to an hyperglycemical environment is much more inclined to develop macrosomia.

Nutritional Changes In pregnancy, women have to increment the amount of calories from meals to deal with fetus needs.
According to guideline provided by Italian Ministry of Health [51], maternal body weight should be increment by 11.5 - 16 kg (from 0.35 to 0.50 kg weekly in second

and third trimester).
To achieve this objective is necessary to increment the diet of about 300 Kcal per day, considering a healthy lifestyle. In case of sedentary women, the assumption is about 150 Kcal per day [56].

Beta-cells Modification During pregnancy, insulin secretion is increased to satisfies both maternal and fetal needs [55].
In order to minimize the impact of tissue insulin resistance, pancreatic beta-cells produce an increased amount of insulin. The alteration of the body balance occurring with pregnancy, anyway, modifies insulin secretion even before insulin resistance becomes manifest [55].
The increase of beta-cells mass may contribute to producing more insulin in case of specific pharmaceutical drugs assumption like secretogogues during pregnancy [55].
Generally speaking, insulin resistance prepares organs to tolerate progressive beta-cells loss of functions. In susceptible women, however, may lead to gradual loss of glucose tolerance which may become Gestational Diabetes Mellitus or Type 2 Diabetes.

Muscle Modification The mechanism at the base of insulin resistance is not completely known yet. Increased hormones (such as human Placental Lactogen (hPL), progesterone, prolactin and cortisol) concentration in bloodstream , secreted by placenta, seems to impact on insulin resistance with the progressive growth of fetal-placental unit [55].
In late gestation, overall insulin sensitivity decreases from 33% to 78%. In early gestation, insulin sensitivity depends on pre-gravidic state of the mother [55].
According to [57], low estrogen levels increase insulin sensitivity while high estrogen levels increase insulin resistance.

Gestational Diabetes Mellitus

The balance established between mother and fetus is very delicate. In order to maintain an healthy level of blood sugar, maternal pancreas secrets *more insulin.* To prevent hyperglycemia it is important to continuously increase level of insulin,

but when the insulin resistance rises too, the level of the sugar blood also increases [58].
Hyperglycemia can be therefore transformed into Gestational Diabetes Mellitus (GDM). The stress of pancreas during pregnancy is immense, so those who previously had a form of insulin resistance or lowered ability to secrete insulin are more inclined to develop GDM [58].
Gestational Diabetes Mellitus is responsible for high fasting glycemia levels despite hepatic glucose releasing is similar to non-diabetic women [55].
Severe Gestational-Diabetic women in late pregnancy undergo a decrease in insulin sensibility up to 40% then the non-diabetic ones [55].

4.3 Self-Management System Model

The model presented in [2] aims to describe physiology of healthy and Type 1 diabetic patient. This model shows how healthy advices such as an increasing level of physical activity and healthy nutrition can improve overall health state of patient. System is structured in two levels: an *high-level model* that represent patient and his/her interaction with the system through a tool support, and a *disease model* that describes the physiological state of the patient.
A tool support like PDA (Personal Digital Assistant) makes possible the communication between models receiving data from patient such as composition of meals, physical activity levels and vital signs from wearable devices, and sending them to disease model for elaboration.
Simulation outlines the patient daily blood sugar flow and allows to predict him/her health state in short and long-term period. Where the values of parameters like levels of glycemia, hepatic and muscle glycogen, insulin and glucagon, are out of healthy ranges, advice related to nutrition and physical activity are provided.
Starting from this model, the thesis work includes an improvement of existing model and development of extensions related to *pregnancy* and *Gestational Diabetes Mellitus*.

Chapter 5

Case Study

In this chapter we introduce case study of current Type-1 diabetes self-management system model.
Before that, we explain the experience about the initial decision to using machine learning techniques in order to predict future outcome of high-risk pregnancy. We explain the changes made on the aforementioned system in order to simulate healthy pregnancy and Gestational Diabetes Mellitus complicated one. In particular, which improvements have been made on existing model and the addition of the placenta one to the system.
We show the changes introduced by the new organ on metabolism of the other ones.
Results of simulation are shown at the end of chapter.

5.1 Applications of Machine Learning Techniques

Initially, the work started with the purpose of applying machine learning techniques in order to *analyze data* related to pregnancies. Our intent was to exploit Machine Learning techniques, such as decisional tree and Support Vector Machine (SVM), to identify attributes that most affect pregnancy outcomes. Such attributes should have been the input for the following simulation process. Another idea has been to compare results of both elaborations for an evaluation purposes. The main requirement to use such techniques is related to have *meaningful data*

to be processed. Despite being in contact with *Ospedale Bufalini*, which has provided us the needed authorization to consult patient data, problems arose due to the necessary time to collect data.
Analysis for exploration purposes on the datasets [62] did not provide any appreciable result, so we decided to abandon this idea.

5.2 Improvement of Existing Model

Metabolic system presented in [2] is modeled as a Multi-Agent System in which bloodstream represents the environment. The patient is modeled as an agent described by age, weight and what kind of physical activity he/she performs.
Changes made to this model include: right *glucose intake* by meals, adjustment to *caloric consumption* related to basal metabolism and regulation of *liver behavior*.

Nutrition The digestive system is modeled making the assumption that patient can only ingests glucose. Thus, taking in account other nutrients (such as proteins and lipids) effect on the body is incorrect in current model. Modeled diet has to be only related to *glucose amount*.
Calories introduced with the diet have to be only those deriving from glycemic load of the meals.
Another assumption is meant to daily *calories consumption*: in the modeled basal metabolism of balanced system, calories intake must be the same amount of calories expended [59].

Digestion Another assumption is made about food time digestion: it is reasonable to think that main meals digestion requires more time than the necessary to snacks.
Period of digestion has been modified according to type of meal:

- if meals is one of three main daily meals such as breakfast, lunch or dinner, total time digestion is about *two and a half hours*;

- if meals is morning or afternoon snack, total time digestion is about *one hour*.

In the first third of time digestion (about 45 and 20 minutes respectively from eating), glucose released is the 40% of total glycemic load of the meal.
The remaining glucose amount is released in following minutes (95 and 40 minutes respectively).

Muscle-cell The amount of glucose is provided to the organism in order to fulfil its vital functions. This quantity is only related to caloric consumption of basal metabolism.
Caloric consumption must be relative only to carbohydrate.

Liver-cell Glucose is stored in liver as hepatic glycogen. Glycogen is obtained from glucose losing a water molecule:

$$C_6H_{12}O_6 - H_2O \longrightarrow C_6H_{10}O_5$$

In order to know how much glycogen is produced by glucose, it is necessary to know the molar mass of glucose (180.16 g/mol) and the water one(18.01528 g/mol) too. From X grams of glucose, therefore, is obtained

$$\frac{180.16 - 18.01528}{180.18} * X$$

grams of glycogen (about 90% of glucose is actually transform in glycogen).

5.3 The Placenta Model

The main change to the existing model is the addition of *placenta*. Among its functions, the one modeled during this work is its *metabolic role in insulin regulation*.
Model has been extended to simulate pregnancy aspects. Aspects that have been

modeled are the presence of *placenta*, increased *insulin production* and increased *insulin resistance*.

5.3.1 Placenta-cell

Placenta secrets hormones like prolactin, cortisol and hPL (human Placental Lactogen) that are placed in bloodstream.
These hormones are secreted incrementally with the progression of gestation.
Placenta is also responsible for a glucose absorption from bloodstream. Thanks to gradient concentration difference, glucose is consumed by placenta.
The following rules define *placenta-cell agent* behavior: Let G_{int} be concentration of free internal placental glucose

1. check glycemia value in bloodstream (G)

2. if internal free glucose concentration is lower than G, glucose intake is

$$G_a = k_a * (G - G_{int})$$

   where k_a is a coefficient indicating absorption speed.

5.3.2 Insulin Resistance

Muscle absorbs glucose if insulin level in bloodstream is greater than insulin basal values [2].
Muscles detect high levels of these hormones that are responsible for a lower glucose uptake. In order to achieved a standard glucose absorption, more insulin is needed.
The following rules define muscle-cell agent behavior: Let k_s be sensitivity insulin coefficient of muscle-cell;

1. checks hormones value in bloodstream (H)

2. checks insulin value in bloodstream (I)

3. if hormones exceed in quantity a certain threshold, $k_s = f(H)$ where $f(H)$ is a function that decreases as H increases.

4. insulin perceived by muscles is

$$I_d = k_s * (I - T_{ins})$$

where T_{ins} is a insulin threshold of 7 microUI/mL (basal insulin)

5.3.3 Insulin Increment

Pancreatic β-cells produce insulin if glucose level in bloodstream is greater than a specific threshold [2].
Pancreas reacts to insulin resistance by producing more insulin. Insulin resistance is the result of an increased hormone concentration, so transitively pancreas behavior reacts to the presence of such hormones.
The following rules define pancreatic β-cell agent behavior: Let k_p be coefficient that regulates insulin production

1. checks hormones value in bloodstream (H)

2. checks glycemia value in bloodstream (G)

3. if hormones exceed in quantity a certain threshold, $k_p = g(H)$ where $g(H)$ is a function that increases as H increases.

4. insulin to release in bloodstream is

$$I_r = k_p * [k_r * (G - T_{gly})]$$

where k_r is a coefficient indicating release speed and T_{ins} is a glycemia threshold of 75 mg/dL.

5.4 Data Simulation

Model was implemented thanks to a Java Multi-Agent Simulation Library named *MASON* (Multi-Agent Simulator Of Neighborhoods) [60].

MASON is a simple, fast in execution and portable Multi-Agent simulation platform designed to perform processes involving a large number of simulations.

5.4.1 Patient Settings

The considered patient is a sedentary woman weighing 60 kg.
She eat five times a day: she has breakfast at 7:10 a.m., morning snack at 10:00 a.m., lunch at 12:30 p.m., afternoon snack at 4:00 p.m. and dinner at 8:00 p.m. .
A sedentary patient doesn't take any particular physical activity.
Her activities are scheduled as described in the follow:

- she wakes up at 7:00 a.m.;
- from 7:10 a.m. to 11:00 p.m. she performs a desk job;
- from 11:00 p.m. to 7:00 a.m. she sleep.

5.4.2 Simulation Settings

Simulation starts with following values:

- *Glycemia* $\longleftarrow$ 75 (mg/dL): average blood sugar level.
- *Hepatic Glycogen* $\longleftarrow$ 20 (g): after nocturnal fast, glycogen stored is decreased to allow glycogenolysis.
- *Muscle Glycogen* $\longleftarrow$ 250 (g): generally after dinner, glucose is stored and not released during night. In the morning muscles have abundant reserves.
- *Insulin* $\longleftarrow$ 7 (microUI/mL): basal insulin in bloodstream.
- *Glucagon* $\longleftarrow$ 50 (pg/mL): standard glucagon level in blood is between 50 and 150 pg/mL.

Caloric Consumption The patient's sedentary lifestyle allows to burn about 0.91 Kcal/min during day and 0.64 Kcal/min during night. This consuming are related only to carbohydrates taken.

Meals Calories requirement has been calculated as about 2000 Kcal/day [61]. Considering the recommended amount of carbohydrates per day as about 55% of meals, and to burn 1 gram of glucose 4 Kcal are necessary, total caloric amount required per day is about *270* g of glucose, so daily glycemic load resulted in 270. Calories breakdown between meals, as recommended by Endrocrinology and Diabelotogy division of Ospedale Bufalini in Cesena, is the one suggested from the Gestational Diabetes Mellitus diet, as shown in 5.1.

Calorie Breakdown between Meals		
Meal	**Caloric Subdivision (%)**	**grams of Glucose**
Breakfast	15.19	41
Morning Snack	9.26	25
Lunch	40.74	110
Afternoon Snack	4.82	13
Dinner	30	81

Table 5.1: Glycemic Load associated to each meal

5.5 Simulation Result

In the following we introduce the simulation results we obtained at the end of thesis work. The following charts describe the two-days glucose metabolism simulation. The time is modeled as a "step", each step coincide to one minute, so simulations results are related to about 1444 minutes (24 hours) or 2888 minutes (48 hours). Every simulation starts at step 0, corresponding to 7:00 a.m., when patient wakes up in the morning. Every meal is administrated at the same time every day. Time and respective steps are shown in Table 5.2.

Meal Times		
Meal	**Time**	**Step**
Breakfast	7:10	10
Morning Snack	10:00	180
Lunch	12:30	330
Afternoon Snack	16:00	540
Dinner	20:00	780

Table 5.2: Meal time scheduling

5.5.1 Improved Model Results

The following charts show the improvements obtained after the adjustment made on simulator. These improvements are mainly about glycemic daily trend and the liver behavior concerning glucose. metabolism.
Glucose metabolism shown in simulation results is about a healty non-pregnant woman.

Glycemia

The Figure 5.1 shows glucose concentration in bloodstream before 5.1(a) and after 5.1(b) the thesis work.
The comparison depicts how, even if the two glicemic trends charts may look

similar, the values they represent are profoundly different. The peaks, known as glycemic peaks, highlight glucose intake from meals and in 5.1(a) are too low and thin to be considered plausible, as confirmed by literature and interviews with medical staff. On the contrary those in 5.1(b) are more plausible because they do not exceed the 140 mg/dL threshold and their width are appropriate to a digestion time spanning from 2 to 3 hours.
Should be noticed that afternoon snack peak in 5.1(a) is absent.
Both graphs show a slight raise in glycemia during night because of *glycogenolysis*. *Dott. Cecilia Ragazzini* explained us that organism needs glucose to prepare itself to daily activities. Liver releases glucose from hepatic glycogen in this span of time.
The shown results cover 25 hours in order to highlight how the glucose metabolism level is equal to the one depicted at the starting point, so all glucose ingested is actually consumed during the day. Thus the metabolic system modeled is able to keep the balance.

Hepatic Glycogen

In Figure 5.2 hepatic glycogen levels are shown. In the 5.2(a) the liver had a constant glycogen income and an almost null absorption. The liver is the main organ responsible of the glycemic regulation. After a meal intake, liver absorbs glucose from bloodstream (until its glycogen reserve is full) in order to lower glocose level in bloodstream, which is higher after a meal.
When the bloodstream glycemic level is too low, it releases glucose after transforming its own stored glycogen. In this way, balance is guaranteed. This behavior is clearly noticeable in 5.2(b). It is also shown how after a prolonged fasting (like the nocturnal one) the stored glycogen level goes down to a physiological level of 20 g. The maximum amount of storable glycogen is 120 g.

5.5.2 Pregnancy Model Results

In the follow of this section are shown the results about the addition of the placenta organ to the simulation, as well as the changes in glycemic level after the onset of a pregnancy.

The time interval simulated span about two days in order to show the recurring behavior.

Glycemia

In Figure 5.3(a) is shown the glycemia of a non-pregnant woman, already described in the precedent section.
Figure 5.3(b) depicts the glucose concentration in the bloodstream of a woman who is carrying on a physiological pregnancy. The overall trend is very similar to the non-pregnant woman, but fasting glucose level is on average lower than non-pregnant one, and peaks are higher. In order to fulfill the fetus needs, the mother endures a slight hyperglycemia. Still, glycemic level is in a safe range (60-140 mg/dL).
In Figure 5.3(c) is shown a pregnancy complicated by Gestational Diabetes Mellitus. In this case, the increasing of glycemia level is more prominent.

Hepatic Glycogen

In Figure 5.4(a) is shown the hepatic glycogen of a non-pregnant woman, already described in the precedent section.
Figure 5.4(b) depicts the hepatic glycogen of a woman who is carrying on a physiological pregnancy. Even though the trend is similar to the precedent chart, there is a subtle difference in the releasing phase of glucose: despite the production of glycogen substantially does not change from a non-pregnant woman, its release is slower, as the literature confirms. This leads to an overall increase glycogen level. The liver in a GDM-complicated pregnancy, as shown in Figure 5.4(c), behaves as a physiological pregnancy one.

Muscle Glycogen

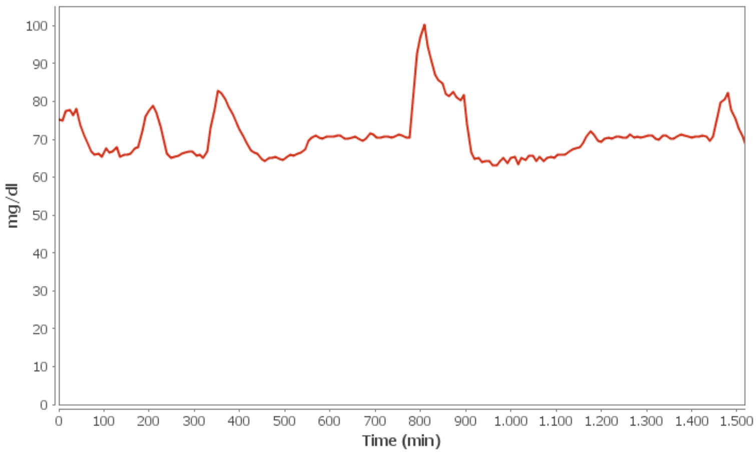
In Figure 5.5(a) is shown the muscle glycogen of a non-pregnant woman. As described in precedent chapters, the activity level of simulated patient is always sedentary. This leads to a minimum consumption of muscle-glycogen. The use of muscle glycogen is a consequence of physical activity. Glucose from muscles

cannot be reinserted in bloodstream, but only be used by the muscles themselves. Figure 5.5(b) depicts the muscle glycogen of a woman who is carrying on a physiological pregnancy. In this case, increasing levels of hormones in bloodstream causes a muscular resistance toward insulin activity, so in order to keep the same level of stored glycogen, is needed more insulin.
In Figure 5.5(c) is shown a pregnancy complicated by Gestational Diabetes Mellitus. In this case, the increased insulin resistance does not allow glucose to penetrate, despite the high amount of insulin secreted by pancreas. In this way less amount of glycogen is produced.

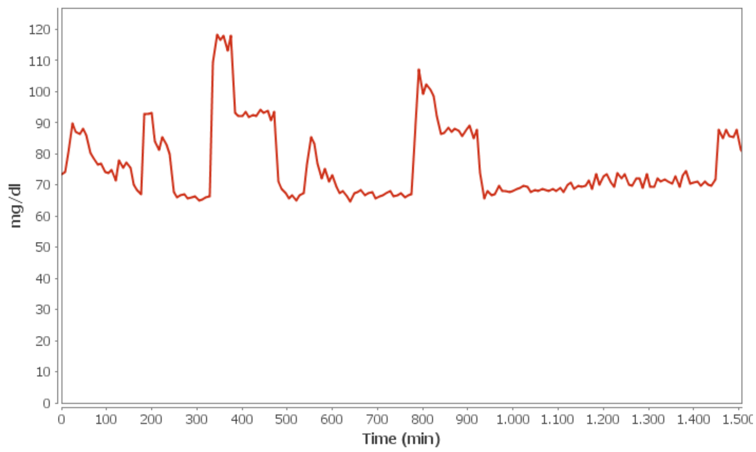
Insulin

In Figure 5.6(a) is shown the insulin trend of a non-pregnant woman. Insulin is an hormone physiologically produced by pancreatic β-cells when a glycemic load occurs, and is receipted by muscles to achieve the ability to absorb glucose from bloodstream. As glycemia, the overall trend is substantially the same, but peaks in pregnant woman, as shown in 5.6(b), are higher than non-pregnant ones. Muscle insulin resistance causes an increment in insulin production. This simulation seems to confirm the physiological trend of insulin release in bloodstream.
In GDM-complicated pregnancy, as shown in 5.6(c), the huge secreted insulin amount is not enough to overcome the muscles request to be able to absorb glucose. This behavior is noticeable by comparing charts in Figure 5.6 to Figure 5.5 respectively.

5.5.3 Charts Simulation Results

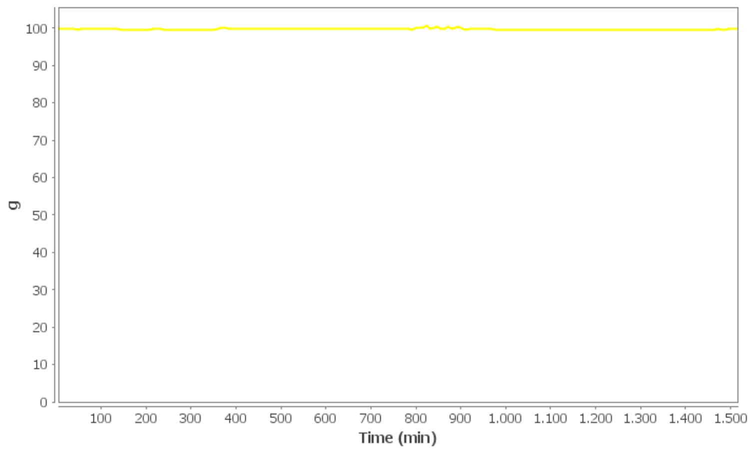


(a)

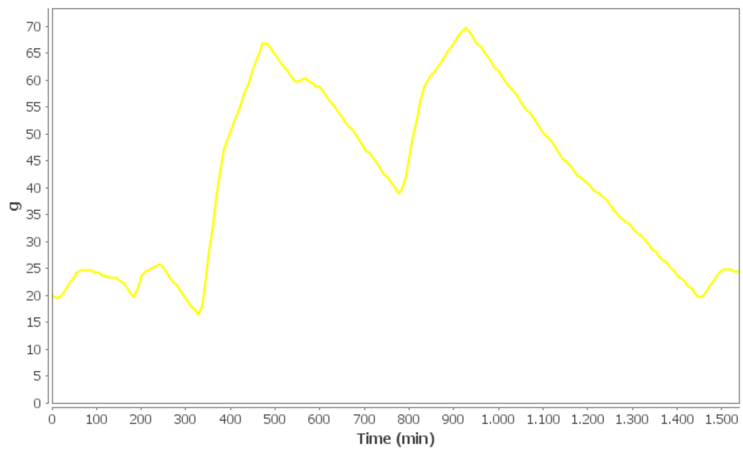


(b)

Figure 5.1: Previous and actual glycemia trends

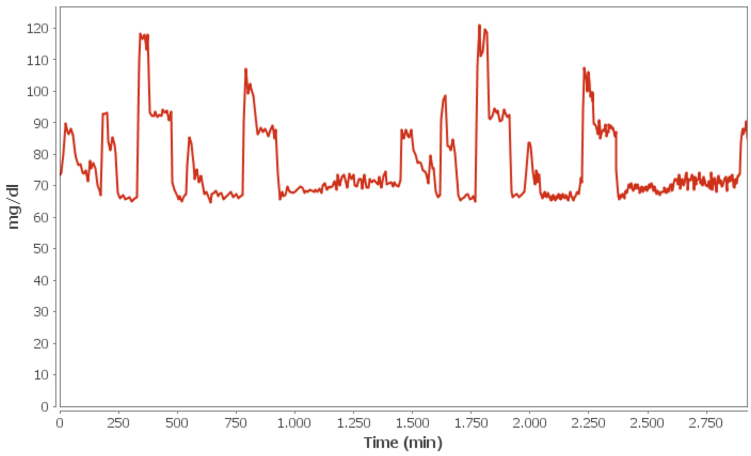


(a)

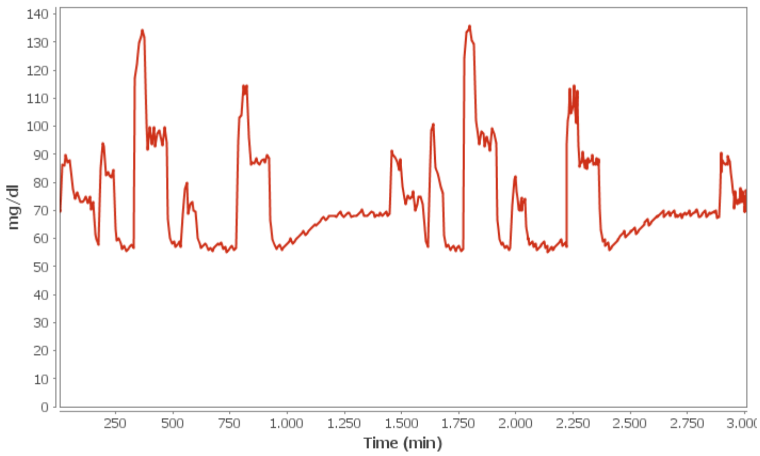


(b)

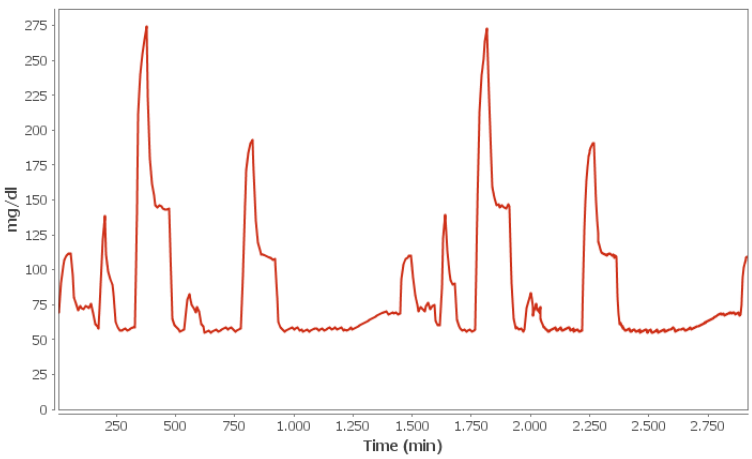
Figure 5.2: Previous and actual hepatic glycogen trends



(a)

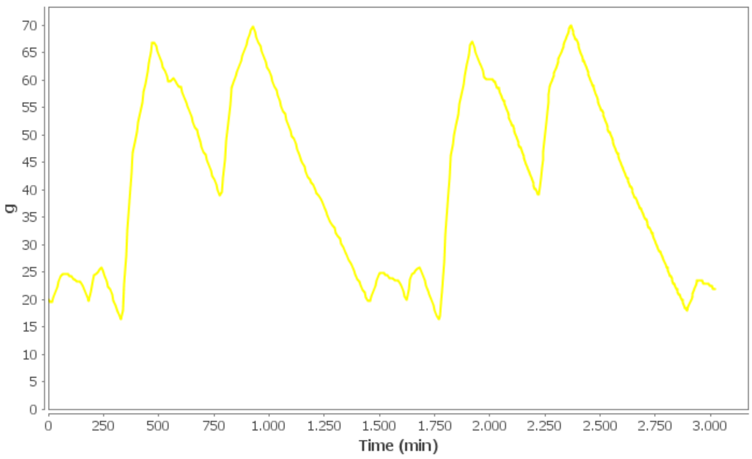


(b)

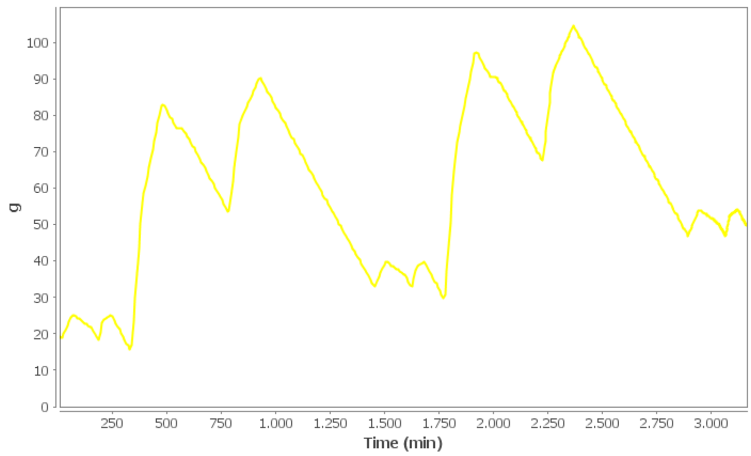


(c)

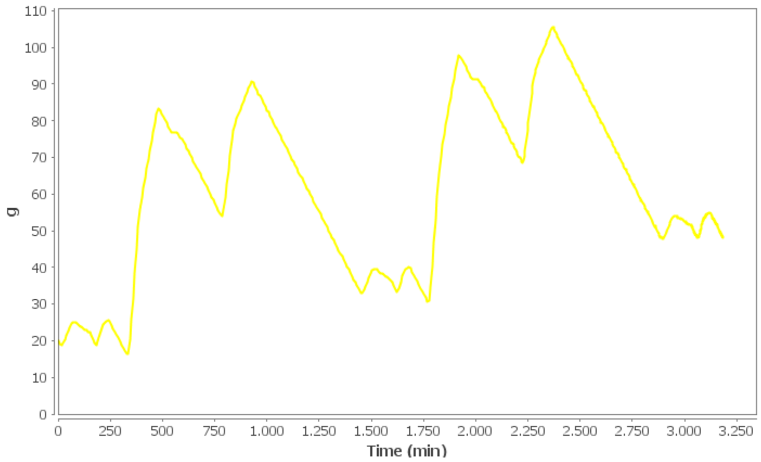
Figure 5.3: Non-pregnant, pregnant, GDM-suffering woman glycemia



(a)

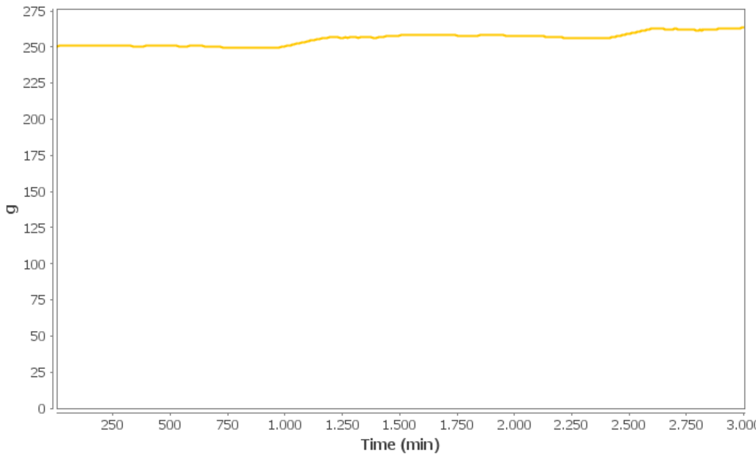


(b)

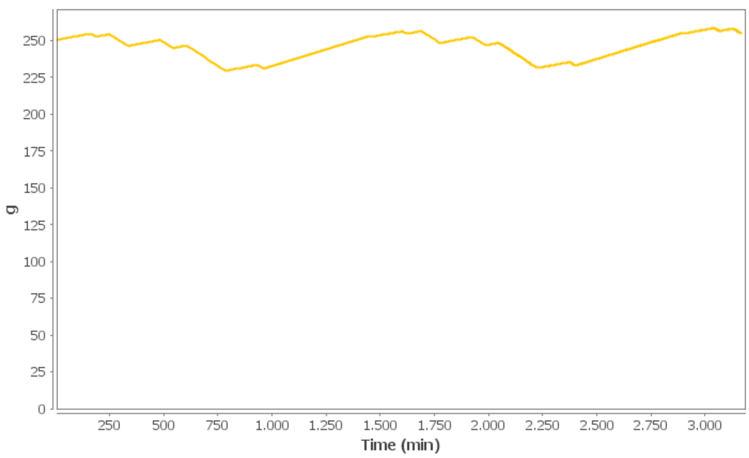


(c)

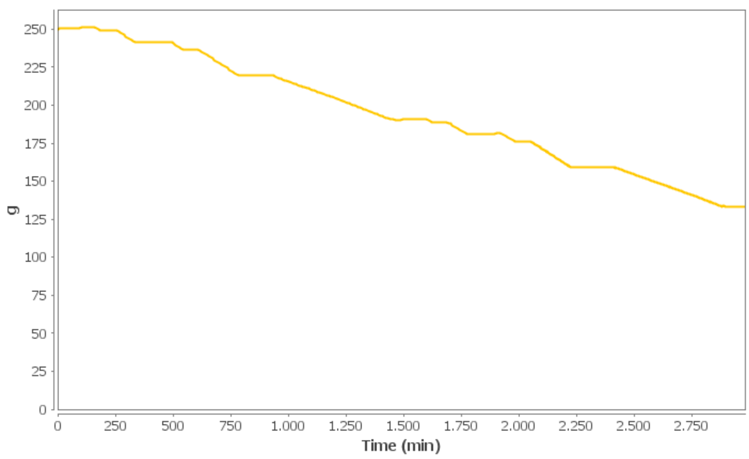
Figure 5.4: Non-pregnant, pregnant, GDM-suffering woman hepatic glycogen



(a)

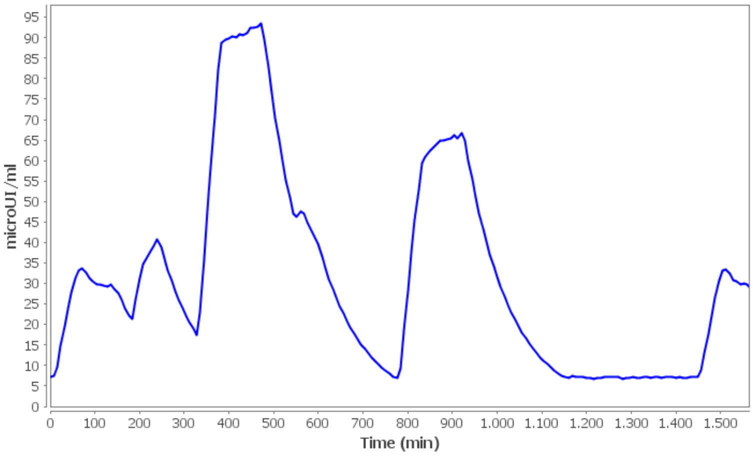


(b)

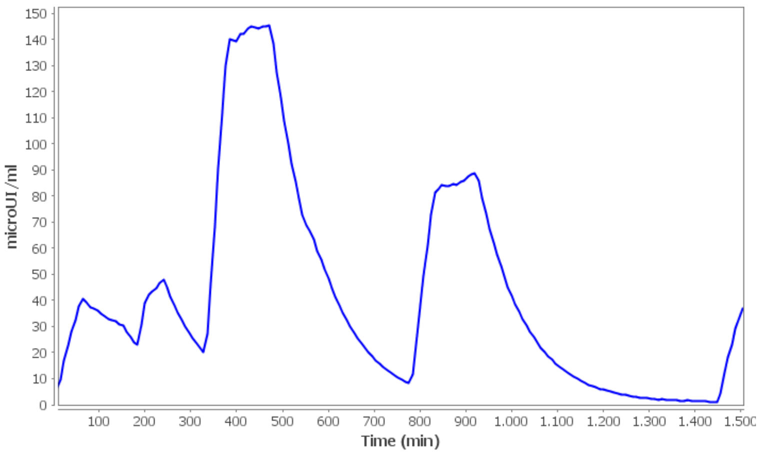


(c)

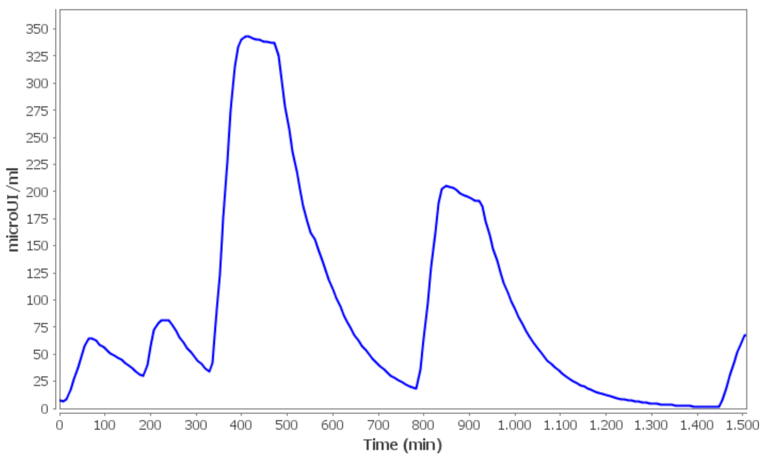
Figure 5.5: Non-pregnant, pregnant, GDM-suffering woman muscle glycogen



(a)



(b)



(c)

Figure 5.6: Non-pregnant, pregnant, GDM-suffering woman insulin level

Conclusions

This thesis work may be divided in two different phases: a first exploratory phase and a second one taking care of modeling and implementation.
During the first phase we performed an exploratory analysis on the problem of maternal and fetal mortality in particular on high-risk pregnancies and how these may be supported by technology.
Afterwards we analyzed in detail the physiology of glucose metabolism and how it evolves during pregnancy. At the end of this phase we performed a feasibility analysis concerning the use of machine learning techniques providing descriptive capability. We have tried to apply these algorithms on free datasets found on the Internet, but sadly this approach did not provide any appreciable result on such data because of absence of meaningful data to be processed or their incompleteness [62].
During the modeling and implementation phase we paid attention on describing the role of placenta in glucose metabolism. In particular, we focused on the physiological reactions that it induces on the body.
Before even starting the implementation phase, the existing agent-based model of the simulator has been analyzed to understand its internal structure and behavior. Such behavior actually simulated a correct physiological one, but from a numerical point of view did not return probable values. A significant contribution this work has given, it's the improvement of the hepatic function in glucose metabolism and the adjustment of energy intake and consumption. At the end of this particularly time-consuming phase, a good similarity level between real-world process and simulated process is obtained.
After the improvement of existing model, we modeled metabolic changes in pregnancy. Such modeling was another fundamental point of this work because it

allowed to describe the physiological phenomenon from a mathematical point of view through a set of well-defined rules defining the involved organs behavior.
We have then implemented an improvement of the existing self-management type-1 diabetes model and a prototype of the placenta organ that simulates the state of pregnancy. Such analysis was based on informations about the physiological phenomena obtained by inspecting the literature and by interviewing expert physicians. Every implementation choice about the modeled phenomena has been justified by reliable sources such as the guideline of Italian Ministry of the Health or World Health Organization.
We can state that the simulated glucose metabolism correctly models the real physiological phenomena related to the glucose absorption and its release in the bloodstream, even during physiological or GDM-complicated pregnancy. The introduction of the placenta organ alters the system's dynamics and it allows to correctly describe the metabolic behavior of entities involved in the process. From the implementation point of view, the improvement of the existing approach leads to a much more robust and suitable model opening to novel and interesting research directions, which are presented in the following paragraph.

Future Works

Among future works related to this thesis the main one is the use of such system to elaborate a real patient data in order to predict the future outcome of his/her conditions in a given time interval. The results may be compared to ones obtained through traditional machine learning techniques, or even the former may be used as input for the latter.
Before that, further improvements are required to refine the system. Among these refinements there is, for example, one related to basal metabolism, which should be borne by all the organs involved.
The introduction of placenta organ to the considered system lays the foundation for a possible, better, future implementation of the simulator. At current the state-of-the-art simulator, indeed, the implementation is almost inaccurate.
Other pathological conditions may be modeled by adding new organs and functionalities.

Changing the execution of simulation from (current) sequential to a parallel one could provide appreciable and unexpected results that best model the physiology of human body and could be provide a further new line of development of such system.

Bibliography

[1] Roberto Visentin, Chiara Dalla Man, Boris Kovatchev, and Claudio Cobelli. The university of virginia/padova type 1 diabetes simulator matches the glucose traces of a clinical trial. *Diabetes technology & therapeutics*, 16(7):428–434, 2014.

[2] Sara Montagna and Andrea Omicini. Agent-based modeling for the self-management of chronic diseases: An exploratory study. *SIMULATION*, 93(9):781–793, 2017.

[3] Katja Iversen. Diabetes in pregnancy: A neglected cause of maternal mortality. https://www.mhtf.org/2017/05/10/diabetes-in-pregnancy-a-neglected-cause-of-maternal-mortality/, May 2017.

[4] Petra C Arck, Mirjam Rcke, Matthias Rose, Julia Szekeres-Bartho, Alison J Douglas, Maria Pritsch, Sandra M Blois, Maike K Pincus, Nina Brenstrauch, Joachim W Dudenhausen, Katrina Nakamura, Sam Sheps, and Burghard F Klapp. Early risk factors for miscarriage: a prospective cohort study in pregnant women. *Reproductive BioMedicine Online*, 17(1):101 – 113, 2008.

[5] European Commission. Implementation research for maternal and child health. available at: https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/sc1-bhc-19-2019.html, October 2017.

[6] WHO World Health Organization. Maternal mortality. available at: http://www.who.int/mediacentre/factsheets/fs348/en/, November 2016.

[7] United Nations. The sustainable development goals report 2017. Available at: https://unstats.un.org/sdgs/report/2017/.

[8] JP Souza, Ö Tunçalp, JP Vogel, M Bohren, M Widmer, OT Oladapo, L Say, AM Gülmezoglu, and Marleen Temmerman. Obstetric transition: the pathway towards ending preventable maternal deaths. *BJOG: An International Journal of Obstetrics & Gynaecology*, 121(s1):1–4, 2014.

[9] Anil Kapur. Links between maternal health and ncds. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 29(1):32–42, 2015.

[10] WHO-World Health Organization Unicef. Integration of the prevention and control of non-communicable diseases and maternal and newborn health programmes and services - a case for action, March 2016.

[11] World Diabetes Foundation et al. Diabetes, women, and development: meeting summary, expert recommendations for policy action, conclusions, and follow-up actions. *International Journal of Gynecology & Obstetrics*, 104:S46–S50, 2009.

[12] Ronald CW Ma, Juliana CN Chan, Wing Hung Tam, Mark A Hanson, and Peter D Gluckman. Gestational diabetes, maternal obesity, and the ncd burden. *Clinical obstetrics and gynecology*, 56(3):633–641, 2013.

[13] Zheng Wang, Lovney Kanguru, Julia Hussein, Ann Fitzmaurice, and Katherine Ritchie. Incidence of adverse outcomes associated with gestational diabetes mellitus in low-and middle-income countries. *International Journal of Gynecology & Obstetrics*, 121(1):14–19, 2013.

[14] Caroline A Crowther, Janet E Hiller, John R Moss, Andrew J McPhee, William S Jeffries, and Jeffrey S Robinson. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine*, 352(24):2477–2486, 2005.

[15] MT Castiglioni, L Valsecchi, P Cavoretto, S Pirola, L Di Piazza, L Maggio, A Caretto, TS Garito, S Rosa, and M Scavini. The risk of preeclampsia beyond the first pregnancy among women with type 1 diabetes parity and

preeclampsia in type 1 diabetes. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, 4(1):34–40, 2014.

[16] Lale Say, Doris Chou, Alison Gemmill, Özge Tunçalp, Ann-Beth Moller, Jane Daniels, A Metin Gülmezoglu, Marleen Temmerman, and Leontine Alkema. Global causes of maternal death: a who systematic analysis. *The Lancet Global Health*, 2(6):e323–e333, 2014.

[17] CM Tucker, K Berrien, MK Menard, AH Herring, J Daniels, DL Rowley, and CT Halpern. Predicting preterm birth among participants of north carolinas pregnancy medical home program. *Maternal and Child Health Journal*, 2015.

[18] Anil Kapur. Pregnancy: a window of opportunity for improving current and future health. *International Journal of Gynecology & Obstetrics*, 115:S50–S51, 2011.

[19] Lindsey M Russo, Carrie Nobles, Karen A Ertel, Lisa Chasan-Taber, and Brian W Whitcomb. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Obstetrics & Gynecology*, 125(3):576–582, 2015.

[20] Mikel Donazar-Ezcurra, Cristina López-del Burgo, and Maira Bes-Rastrollo. Primary prevention of gestational diabetes mellitus through nutritional factors: a systematic review. *BMC pregnancy and childbirth*, 17(1):30, 2017.

[21] Every Woman Every Child. *Global Strategy for Womens, Childrens and Adolescents Health (2016 - 2030).* 2017.

[22] United Nation. Sustainable development goals explained: Good health and well-being. Available at: http://www.un.org/sustainabledevelopment/health/, Accessed: November 2017.

[23] C Lupi, E Perrone, V Basevi, et al. La nascita in emilia-romagna. 14 rapporto sui dati del certificato di assistenza al parto (cedap)-anno 2016. *Bologna: Regione Emilia-Romagna*, 2017.

[24] Marlene Maheu, Pamela Whitten, and Ace Allen. *E-Health, Telehealth, and Telemedicine: a guide to startup and success*. John Wiley & Sons, 2002.

[25] Tommy G Thompson and David J Brailer. The decade of health information technology: delivering consumer-centric and information-rich health care. *Washington, DC: US Department of Health and Human Services*, 2004.

[26] Gunther Eysenbach. What is e-health? *Journal of medical Internet research*, 3(2), 2001.

[27] Bruno MC Silva, Joel JPC Rodrigues, Isabel de la Torre Díez, Miguel López-Coronado, and Kashif Saleem. Mobile-health: A review of current state in 2015. *Journal of biomedical informatics*, 56:265–272, 2015.

[28] NLM. Health informatics definition. Available at: https://www.nlm.nih.gov/hsrinfo/informatics.html.

[29] American Telemedicine Association. available at: http://www.americantelemed.org/about/about-telemedicine.

[30] Vincenzo Della Mea. What is e-health (2): The death of telemedicine? *Journal of medical Internet research*, 3(2), 2001.

[31] Simon Liu and Thomas Jepsen. Mobile health. *IT Professional*, 14(3):11–12, 2012.

[32] ICT Facts. Figures-the world in 2015. *Geneva: The International Telecommunication Union (ITU)*, 2015.

[33] Robert Istepanian, Swamy Laxminarayan, and Constantinos S Pattichis. *M-health*. Springer, 2014.

[34] Martina Ziefle and Carsten Röcker. Acceptance of pervasive healthcare systems: A comparison of different implementation concepts. In *Pervasive Computing Technologies for Healthcare (PervasiveHealth), 2010 4th International Conference on-NO PERMISSIONS*, pages 1–6. IEEE, 2010.

[35] Jonathan Matusitz and Gerald-Mark Breen. Telemedicine: Its effects on health communication. *Health Communication*, 21(1):73–83, 2007.

[36] Upkar Varshney. Mobile health: Four emerging themes of research. *Decision Support Systems*, 66:20–35, 2014.

[37] Nir Menachemi and Taleah H Collum. Benefits and drawbacks of electronic health record systems. *Risk management and healthcare policy*, 4:47, 2011.

[38] James Bush, Dilek E Barlow, Jennie Echols, Jasmine Wilkerson, and Katherine Bellevin. Impact of a mobile health application on user engagement and pregnancy outcomes among wyoming medicaid members. *Telemedicine and e-Health*, 23(11):891–898, 2017.

[39] Matthijs R Van Dijk, Nicole A Huijgen, Sten P Willemsen, Joop SE Laven, Eric AP Steegers, and Régine PM Steegers-Theunissen. Impact of an mhealth platform for pregnancy on nutrition and lifestyle of the reproductive population: a survey. *JMIR mHealth and uHealth*, 4(2), 2016.

[40] Emmanuele Ghigi. *Sistemi di Mobile-Health per il monitoraggio e l'assistenza alla gravidanza*. PhD thesis.

[41] Jessica L Watterson, Julia Walsh, and Isheeta Madeka. Using mhealth to improve usage of antenatal care, postnatal care, and immunization: A systematic review of the literature. *BioMed research international*, 2015, 2015.

[42] Mário WL Moreira, Joel JPC Rodrigues, Antonio MB Oliveira, and Kashif Saleem. Smart mobile system for pregnancy care using body sensors. In *Selected Topics in Mobile & Wireless Networking (MoWNeT), 2016 International Conference on*, pages 1–4. IEEE, 2016.

[43] Francesco Degli Angeli. *Self-management di malattie croniche in sistemi di mobile Health: sviluppo di un modello agent-based per casi di diabete*. PhD thesis.

[44] Usama Fayyad, Gregory Piatetsky-Shapiro, and Padhraic Smyth. From data mining to knowledge discovery in databases. *AI magazine*, 17(3):37, 1996.

[45] Matteo Golfarelli. Data mining lecture note.

[46] Stanford Encyclopedia of Philosophy. Computer simulations in science, https://plato.stanford.edu/entries/simulations-science/.

[47] Andrea Omicini Sara Montagna. Simulation & multi-agent systems: An introduction.

[48] Eric Bonabeau. Agent-based modeling: Methods and techniques for simulating human systems. *Proceedings of the National Academy of Sciences*, 99(suppl 3):7280–7287, 2002.

[49] Adelinde M Uhrmacher, Daniela Degenring, and Bernard Zeigler. Discrete event multi-level models for systems biology. In *Transactions on computational systems biology I*, pages 66–89. Springer, 2005.

[50] Charles M Macal and Michael J North. Tutorial on agent-based modelling and simulation. *Journal of simulation*, 4(3):151–162, 2010.

[51] Ministero della Salute. Gravidanza fisiologica linea guida. aggiornamento 2011.

[52] Glycemic Research Institute. Glycemic index defined, glycemic load defined url: http://www.glycemic.com/glycemicindex-loaddefined.htm.

[53] Augusto G Ferrari and Luigi G Frigerio. Ginecologia e ostetricia. *AGE*, 2017:2016, 2015.

[54] Chiara Agostinis. L'immunità innata nello sviluppo placentare in condizioni fisiologiche e patologiche della gravidanza. 2009.

[55] Kristine Y Lain and Patrick M Catalano. Metabolic changes in pregnancy. *Clinical obstetrics and gynecology*, 50(4):938–948, 2007.

[56] Dott.ssa Giovanna Codella. Alimentazione in gravidanza, available at: http://www.dietabit.it/alimentazione/gravidanza/.

[57] A Cagnacci, M Generali, R Zanin, and A Volpe. Interferenza degli estro-progestinici sul metabolismo lipidico, glucidico e sui fattori dell'emocoagulazione. *REPRO NEWS*, 8:25–26, 2006.

[58] Moshe Hod, Anil Kapur, David A Sacks, Eran Hadar, Mukesh Agarwal, Gian Carlo Di Renzo, Luis Cabero Roura, Harold David McIntyre, Jessica L Morris, and Hema Divakar. The international federation of gynecology and obstetrics (figo) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. *International Journal of Gynecology & Obstetrics*, 131(S3), 2015.

[59] FAO Joint and WHO Expert Consultation. Carbohydrates in human nutrition (fao food and nutrition paper 66). *Rome, Italy: FAO*, 1998.

[60] Mason, available at: https://cs.gmu.edu/ eclab/projects/mason/.

[61] available at: http://healthyeating.sfgate.com/recommended-amount-percent-carbohydrates-per-day-7287.html.

[62] Open Government Data (OGD) Platform India. Dataset available at: https://data.gov.in/catalog/annual-health-survey-woman-schedule.