Faculdade de Engenharia da Universidade do Porto

A model for educational simulation of drug dependent intrauterine pressure signals during labor and delivery

(Um modelo para simulação educacional de sinais da pressão intra-uterina fármaco-dependente durante o parto)

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Abstract

During labor and delivery maternal or fetal complications may arise very quickly and unexpectedly. It is mandatory for optimal pregnancy outcome that a well-defined program be established providing careful surveillance of the well-being of both mother and fetus during labor. The frequency, intensity and duration of uterine contractions, and the response of the fetal heart rate to the contractions, are of considerable concern during this period. Training interpretation of monitored signals and implementation of therapeutic measures is essential in the often time-critical diagnosis and management of clinical incidents. Mathematical models of human physiology and pharmacology are a critical component of high fidelity simulators for medical education.

The general goal of this project was to develop a uterine activity simulation engine for educational simulation of intrauterine pressure signals. Spontaneous intra-partum evolution of uterine activity in normal or selected abnormal situations, as well as realistic responses to administration of selected drugs that affect uterine activity, are the general requirements for this simulation engine.

Established detailed model requirements and a critical review of previous work and published models for the simulation of uterine contractions allowed for the definition of specific needs for further model development. Based on this analysis, an original simulation engine was designed consisting of: A spontaneous uterine activity engine, an oxytocin pharmacokinetics model, an oxytocin pharmacodynamics model, and a uterine pressure signal generator. The uterine contractions signal is described in its waveform features, allowing for intuitive manipulation of selected model parameters by clinical instructors. The proposed simulation engine structure will allow for easy incorporation of additional pharmacologic models.

Simulation results demonstrate that this engine allows for simulation of spontaneous as well as drug dependent evolution of intrauterine pressure signals. A variety of clinical situations and individual patients are simulated. A pilot evaluation by clinical experts complements this verification of the developed uterine activity simulation engine.

Sumário

Durante o trabalho de parto complicações maternas ou fetais podem surgir súbita e inesperadamente. Para um desfecho ideal é essencial estabelecer um programa bem definido que permita uma observação cuidada do bem-estar da mãe e do feto durante o trabalho de parto. A frequência, intensidade e duração das contracções uterinas, e a resposta da frequência cardíaca fetal às contracções, são aspectos de considerável relevância durante este período. O treino da interpretação de sinais monitorizados e da implementação de medidas terapêuticas é essencial nos incidentes clínicos que têm muitas vezes um tempo crítico de diagnostico e resolução. Modelos matemáticos da fisiologia e farmacologia humana são elementos fundamentais em simuladores de alta-fidelidade para educação médica.

O objectivo geral deste projecto foi desenvolver um motor de simulação (*simulation engine*) da actividade uterina para simulação educacional de sinais da pressão intra-uterina. A evolução espontânea da actividade uterina durante o parto, em situações seleccionadas, normal e irregulares, bem como respostas realistas à administração de determinados fármacos que afectam a actividade uterina, são os requisitos genéricos deste motor de simulação.

A definição detalhada dos requisitos do modelo, juntamente com uma análise crítica do trabalho previamente desenvolvido e de modelos publicados para a simulação de contracções uterinas, permitiram determinar necessidades específicas para desenvolvimentos adicionais do modelo. Com base nesta análise, foi desenhado um motor de simulação original constituído por: um gerador da actividade uterina espontânea, um modelo farmacocinético da ocitocina, um modelo farmacodinâmico da ocitocina, e um gerador da pressão uterina. O sinal das contracções uterinas é descrito por características que definem a sua forma, permitindo aos instrutores clínicos uma manipulação intuitiva de determinados parâmetros do modelo. A estrutura proposta do motor de simulação permitirá uma fácil incorporação de modelos famacológicos adicionais.

Os resultados de simulação demonstram que este motor (*engine*) permite a simulação de uma evolução espontânea ou fármaco-dependente de sinais da pressão intra-uterina. Foi simulada uma variedade de situações clínicas e de pacientes. Uma

avaliação piloto feita por especialistas clínicos complementa esta verificação do motor de simulação da actividade uterina desenvolvido.

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$I_{up}(t)$ – Intrauterine pressure (mmHg)

OT(t) – Oxytocin infusion rate (mU/min)

$C_{pl}(t)$ – Plasma concentration of exogenous oxytocin (μg/ml)

$Amp_{Spon}(n)$ – Spontaneous uterine contraction amplitude (mmHg)

$Freq_{Spon}$ (n) – Spontaneous uterine contraction frequency (contractions per 10 min)

Dur_{Spon} (n) – Spontaneous uterine contraction duration (min)

RT_{Spon} (n) – Spontaneous uterine contraction resting tone (mmHg)

Amp(n) – Uterine contraction amplitude (mmHg)

Freq(n) – Uterine contraction frequency (contractions per 10 min)

Dur(n) – Uterine contraction duration (min)

RT(n) – Uterine contraction resting tone (mmHg)

γ - Oxytocin pharmacodynamic model Hill coefficient

A_{max} – Amplitude of uterine contractions at maximum drug effect maximal (mmHg)

F_{max} – Frequency of uterine contractions at maximum drug effect maximal (contractions per 10 min)

D_{max} – Duration of uterine contractions at maximum drug effect maximal (min)

AC_{50} – Concentration associated with 50% of maximum effect in contraction amplitude (at a given spontaneous activity) (μg/ml)

FC_{50} – Concentration associated with 50% of maximum effect in contraction frequency (at a given spontaneous activity) (μg/ml)

DC_{50} – Concentration associated with 50% of maximum effect in contraction duration (at a given spontaneous activity) (μg/ml)

AU - Alexandria Units (mmHg)

MU - Montevideo units (mmHg)

UAI – Uterine activity integral (kPas/15min)

CTG - Cardiotocogram

AU_{cra} – Uterine activity in Alexandria Units from (Cra91)

AU_{sim} – Uterine activity in Alexandria Units from simulated uterine contractions

1. Introduction

Simulation has been used by the aviation industry and the military for several decades, but only during the past decade has become a teaching method in medicine. Recently, three fundamental changes have been introduced in medical education, all of particular importance to critical care medicine: (1) clinical teaching and medical practice now emphasize evidence-based medicine; (2) patient safety aspects are increasingly stressed; and (3) use of simulation in medical training is spreading rapidly (Gren04). Advantages of simulation-based training over traditional medical education methods include practice and learning of diagnosis and management of clinical problems in a controlled environment with no risk to real patients. This will better prepare the students, or other trainees, for safe administration of health care to patients (Mac03). Within the next decade, use of computerized simulators for evidence-based education and training in medicine is expected to develop considerably and spread rapidly over medical schools throughout the entire world (Gren04).

Simulators in medicine are used not only to train medical students, but also experienced personnel (e.g. nurses, anesthetists, and obstetricians). Depending on the target audience of a simulation-based exercise, the training program needs to be adapted. For example, experienced personnel are more likely to train rare life-threatening incidents and novices are more likely to train basic skills. The training program has to fit the curriculum, but also provide indications of the necessary equipment for the simulation environment.

Technological advances in recent years have seen the development of a variety of models and manikins ranging from simple replications of body parts for task-based learning of some examination skills, to high-fidelity patient simulators driven by complex pathophysiological models (Bra04, Van98b). The mathematical models of human physiology and pharmacology are used in an integrated software implementation to provide real-time, life-like reactivity to the simulated patients.

Even though human error has been documented to play a significant role in adverse outcomes in obstetrics and gynecology (CES01), simulation-based training in this area has not known the evolution of this technique, as in other areas of acute care medicine. However, simulation in obstetrics and gynecology has also the potential to

improve education, training, and evaluation and ensure competency (Mac03, Dra06). Critical situations in obstetrics can result in the need for neonatal intensive care. Early and accurate recognition of critical incidents and timely application of appropriate therapeutic interventions are important for survival and quality of life.

A major part of perinatal safety depends on the fetal monitoring system. During labor and delivery, the two key monitored signals are: fetal heart rate and uterine contractions. Appropriate fetal heart rate monitoring and its accurate interpretation are essential for the assessment of fetal well-being. Correct uterine activity appraisal is a fundamental aspect of this monitoring system, since the proper interpretation of the uterine contractions signal enables the obstetrician or midwife to assess the quality of labor in progress. Together with fetal heart rate, the uterine contractions signal forms the basis for an early diagnosis of abnormal or ineffective labor patterns (Kla77).

Our general goal is to improve perinatal safety through simulation-based training of diagnostic and therapeutic skills in labor and delivery. In this context, the main objective of this master thesis was to develop a uterine activity simulation engine for educational simulation of labor augmentation. This engine should be able to reproduce realistic and relevant intra-partum uterine contractions patterns, and should react appropriately to administration of drugs that affect uterine motility.

The following chapter gives background information needed for the understanding of this project. The chapters that follow establish requirements for a uterine activity simulation engine in intra-partum acute care simulation (Chapter 3) and provide a critical evaluation of previous work on uterine activity and its modeling (Chapter 4). Elaborating on previous work, Chapter 5 presents an original uterine activity simulation engine. The last two chapters present simulation results and a preliminary evaluation by clinical experts (Chapter 6) and discuss results, and present conclusions and suggestions for further model development (Chapter 7).

2. Background

This chapter includes an overview of the following:

- educational simulation as a complement to traditional education and as a context to this project (section 2.1);
- a description of the major phenomena that occur during labor, emphasizing the importance of uterine activity monitoring in normal and abnormal clinical scenarios (sections 2.2 and 2.3);
- pharmacokinetics and pharmacodynamics with special reference to drugs that affect uterine motility (sections 2.4 and 2.5);
- modeling considerations (section 2.6).

Depending on his or her background, the reader may be able to skip selected sections of this chapter.

2.1 Educational Simulation in Intra-partum Acute Care

Being able to make accurate diagnoses in short periods of time for a vast number of clinical situations requires medical knowledge and clinical skills. For training the latter, simulation is a powerful tool because it allows for repetitive and comprehensive practice of different relevant clinical situations.

Advantages of simulation-based training over traditional medical education methods include provision of a safe environment for both patient and student during training in risky procedures, unlimited exposure to rare but complicated and important clinical events, the ability to plan and shape training opportunities rather than waiting for a suitable situation to arise clinically, the ability to provide immediate feedback, the opportunity to repeat performance, and the opportunity for team training (Gren04).

In obstetrics and gynecology, simulation can be used as an educational tool to assist in (1) transfer of knowledge, (2) practicing diagnostic and simple practical skills, (3) surgical skills training, (4) emergency drill training, and (5) human factors and team training. Simulators in this area of medicine take on a variety of types and shapes, like anatomical 3D cervical effacement and dilation models (Cro05), screen-based electronic fetal monitoring simulators (Van03), and full-body delivery simulators (Egg03). Thanks to them, it is possible nowadays to enhance training in obstetrics. However, the currently available simulator technology and simulation-based

curricula in obstetric acute care have limited capabilities and fidelity. For this reason, the modeling and simulation research program of the Institute of Biomedical Engineering set out to improve simulation technology in intra-partum acute care by designing a simulation engine composed of several mathematical models that interact properly in order to reproduce relevant aspects of human physiology and pharmacology for different critical incidents and pathologies. One of the main advantages of the use of mathematical models in simulation-based training, as opposed to script driven scenarios, is that these models will react automatically to a set of possible therapeutic interventions. This automaticity reduces the need for instructor input, proving a more realistic and real-time reaction of the simulator and freeing up time for instruction.

The set of mathematical models of human physiology and pharmacology should be able to simulate (at least) a selected number of clinical scenarios established based on an analysis and common understanding of the obstetrician and midwife task environment. We will come back to clinical scenarios with relevance for this thesis in Chapter 3.

2.2 The electronic fetal monitoring system

The main tool used for fetal assessment is the electronic fetal monitoring system. As mentioned before, this system monitors two signals: fetal heart rate and uterine contractions. For recognition of the fetal heart rate, the device can use the R-wave of the fetal electrocardiogram (measured through an electrode that is attached to the fetal scalp), or a signal generated by the movement of a cardiovascular structure (using ultrasound and the Doppler principle). Uterine contractions are detected either by a catheter inserted transcervically into the amniotic cavity and attached to a strain-gauge transducer (measuring intrauterine pressure), or by an external device, termed *tocodynamometer*, witch is placed on the maternal abdomen and which recognizes the tightening of the maternal abdomen during a contraction (measuring external uterine pressure) (Par97, Har92). Monitoring with devices that are attached directly to the fetus or placed within the uterine cavity is called direct, internal, or invasive monitoring. Devices that do not require direct connection with the fetus or the uterine cavity are called indirect, external, or noninvasive. In the internal, invasive technique, the pressure changes are translated to an electrical signal, which is displayed and calibrated directly in millimeters of mercury of pressure (mmHg).

The tocodynamometer is an external device that detects uterine activity by the pressure exerted on a small button in the center of the transducer by the maternal abdominal wall tightening (generally on the uterine fundus). In a sense, the apparatus acts just like the hand on the abdomen, detecting uterine activity. The tocodynamometer detects frequency and often duration of uterine contractions, but ordinarily cannot be calibrated for intensity as in direct pressure measurements (Par97).

For a better understanding of uterine activity during labor and delivery, the next section explains the relevant aspects of uterine contractility.

2.3 Labor and delivery and intra-partum uterine activity

The uterus may be thought of as a hollow organ consisting of three muscular coats: endometrium, myometrium and peritoneum. It can further be subdivided into an upper contractile segment and a lower passive segment. It is inside this organ that an embryo develops into a fetus and after approximately nine months is expelled by a series of strong, rhythmic contractions of the uterus, commonly called labor (Kla77).

One of the most critical diagnoses in obstetrics is accurate diagnosis of labor. If labor is falsely diagnosed, inappropriate interventions to augment labor may be made. Conversely if labor is not diagnosed, the fetus may be compromised by unexpected complications occurring in sites remote from medical personnel and adequate medical facilities (Lev03). Although the differential diagnosis between false and true labor is difficult at times, it usually can be made on the basis of the uterine contractions and other signs and symptoms (Lev03):

- Contractions occur at regular intervals;
- Intervals between contractions gradually shorten;
- Intensity of contractions gradually increases;
- Discomfort in the back and abdomen;
- Cervix dilates.

The mechanism of labor is a sequencing of events related to posturing and positioning that allows the baby to find the "easiest way out". Usually, the fetus is a passive respondent in the process of labor, while the mother provides the uterine forces and structural configuration of the passageway through which the fetus must travel. For normal labor to occur, both fetal and maternal factors must be harmonious. Understanding of these factors is essential for the obstetrician and the

midwife to appropriately intervene if the sequence of events deviates from normal (Pet00).

The sequential movements by which the fetus traverses the birth canal during labor are called cardinal movements and include engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion (Lev03). Engagement may take place as early as the last few weeks of pregnancy, or may not occur until after the commencement of labor. It consists of the fetus head touching the pelvis which is accompanied by descent, and after which the fetus starts to further descent and flexion. As a result, the fetal ovoid is transformed into a cylinder, with the smallest possible cross section normally passing through the birth canal (Lev03). Figure 2.1 presents a schematic sequence of the cardinal movements.

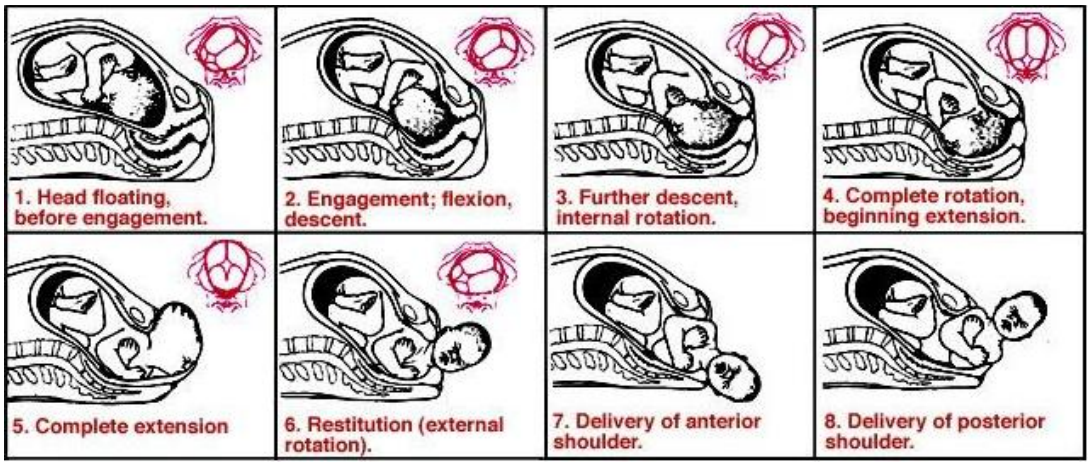

Figure 2.1: Cardinal movements during labor and delivery, left occiput anterior position (Lev03).

Stages of labor

Labor is well characterized in terms of uterine activity patterns and cervical dilation progress and state. It is considered that labor can be divided into three stages according to three major events: (1) fetal positioning and maternal promptness for delivery, (2) expulsion of the fetus, and (3) placental expulsion. As mentioned before, one of the objectives of this project is to create a model capable of reproducing spontaneous uterine activity during labor. The development of such model was based on the characterization of labor in terms of stages. A brief description of these stages is presented next.

1st stage of labor

The first stage of labor is initiated with labor onset and finishes when the cervix is completely dilated. Cervical dilation is the opening of the cervix during labor. In the early stages of pregnancy, the cervix may already have opened up to 1-3 cm (or more in rare circumstances), but during labor, repeated uterine contractions are accompanied by further widening of the cervix to about 6 centimeters. From that point on, pressure from the presenting[1] part (head in vertex birth or bottom in breech birth), along with uterine contractions, will dilate the cervix to 10 centimeters (complete dilation). Cervical dilation usually follows effacement, which is the thinning of the cervix (Lev03). Figure 2.2 presents normal evolution of cervical effacement and dilation from late pregnancy to the end of the first stage of labor.

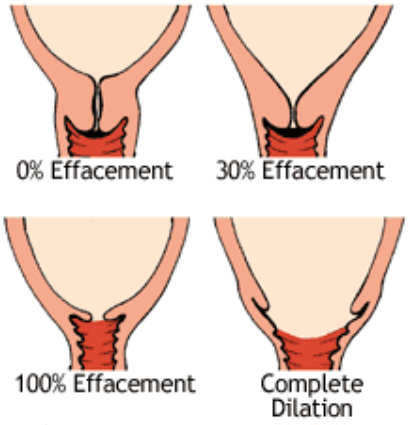

Figure 2.2: Evolution of cervical effacement and dilation from late pregnancy until the end of the first stage of labor (from the left to the right and from the top to the bottom) (Dou06).

At the same time that the cervix dilates with different rhythms along the first stage of labor, uterine contractions change pattern as well, promoting fetal positioning and posturing. Two different phases can be outlined in the first stage of labor: the latent phase, and the active phase. In the latent phase the contraction pattern is characterized by low intensity and frequency, and short duration of contractions that eventually evolve to stronger and longer contractions with higher frequency originating in the active phase. Also, in the latent phase dilation of the cervix is limited and slow, while in the active phase the major part of dilation is observed.

[1] Presentation refers to how the fetus is situated in the uterus, while the part of fetus that is closest to the cervix is termed the presenting part.

2nd stage of labor

The second stage of labor starts when the cervix is fully dilated, and therefore ready for delivery of the fetus. The woman typically begins to bear down. Uterine contractions and the accompanying expulsive forces may last 1½ minutes and recur at times after a myometrial resting phase of no more than one minute. With each contraction, the peritoneum bulges increasingly and the vaginal opening becomes more dilated by the fetal head. With the cessation of each contraction, the opening becomes smaller as the head recedes. As the head becomes increasingly visible, the vaginal outlet and vulva are stretched further until they ultimately encircle the largest diameter of the fetal head. Most often, the shoulders appear at the vulva just after external rotation and are born spontaneously. After delivery of the anterior shoulder, a finger should be passed to the neck of the fetus to ascertain whether it is encircled by one or more coils of the umbilical cord. When the fetus has been delivered the umbilical cord is cut between two clamps placed 4 or 5cm from the fetal abdomen, and later an umbilical cord clamp is applied 2 or 3cm from the fetal abdomen (Lev03).

3rd stage of labor

After delivery of the infant, the uterus maintains strong contractions, which will aid the separation of the placenta from the walls of the uterus. Usually the mother loses less than 500ml of blood but if the umbilical cord is used to tug the placenta, the blood loss will be greater. After separation of the placenta from the uterine wall, it is necessary to check if the whole placenta was expelled, because remaining parts can cause postpartum bleeding or infection (Lev03).

2.3.1 Uterine Contractility

It has become increasingly evident that the initiation of labor is not due to a single trigger, but is the culmination of a cascade of complex events that occur over days or even weeks. It is now believed that a combination of hormonal, chemical and mechanical signals interact to gradually down-regulate quiescent mechanisms and up-regulate contractile pathways as pregnancy approaches term (Tri01, Sul97, Shm06, Wra93, Zin03, Nag03, Fuc91).

During the course of a uterine contraction, the uterine wall of the upper segment of the uterus progressively thickens, attaining maximum dimension at the acme of the contraction (Figure 2.3).

As the uterus contracts, pressure within the confines of the uterus progressively increases and then gradually decreases in an uniform bell-shaped fashion, with peak pressure occurring at the acme of contraction (Kla77).

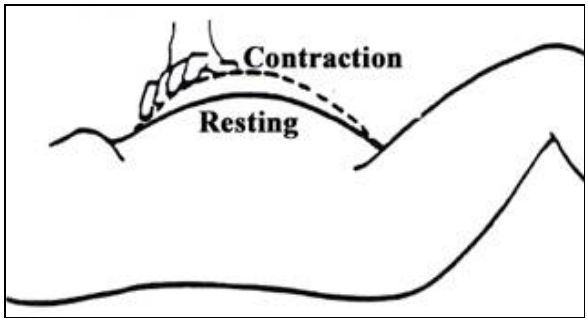

Figure 2.3: Uterine wall during contraction and resting (Ste03).

Figure 2.4 illustrates a typical cardiotocogram tracing, depicting 45 minutes of uterine activity (lower segment) and fetal heart rate (upper segment) during labor.

Uterine activity can be characterized by uterine contractility (amplitude, duration, and frequency or period), resting tone, rythmicity, and configuration. Figure 2.5 depicts the characteristic a uterine contraction curve.

The amplitude of the uterine contraction is defined as the level of intrauterine pressure at the acme of the contraction, disregarding the resting tone. Although 50-75 mmHg amplitudes are usually required to cause progressive cervical dilation and descent of the presenting part, normal labor progress may occur at amplitudes of less than 50 mmHg. Conversely, many patients will spontaneously exhibit amplitudes higher than 75 mmHg and yet not demonstrate fetal distress (Kla77). The resting tone is defined as the pressure present within the confines of the uterus between contractions, when the uterus is "at rest". The resting tone is normally 5-10 mmHg (Kla77).

With the increase in knowledge and understanding of uterine activity and the development of tocography, a need arose to quantify uterine contractions in terms other than amplitude, frequency and duration to reflect the compound of these components (Har92). Three main ways of uterine contractility quantification were developed and are commonly used. One of them is expressed in Montevideo units (MU) and is equal to the product of the average intensity of uterine contractions with the number of contractions observed during a 10-minute period (Har92). Another one is expressed in Alexandria units (AU) and is the product of the Montevideo units

with the average duration of contractions in minutes (Har92). A third uterine activity quantification unit is the uterine activity integral (UAI) and is defined as the area under the uterine contraction curves above the resting tone, measured in kPa·sec, over a 15-minute period (Har92). The quantification of uterine activity presents problems because it reflects the cumulative result of the components, hiding components changing with time, and individual contributions (Har92). However, these quantifying units are the only uterine activity measures available in most published studies.

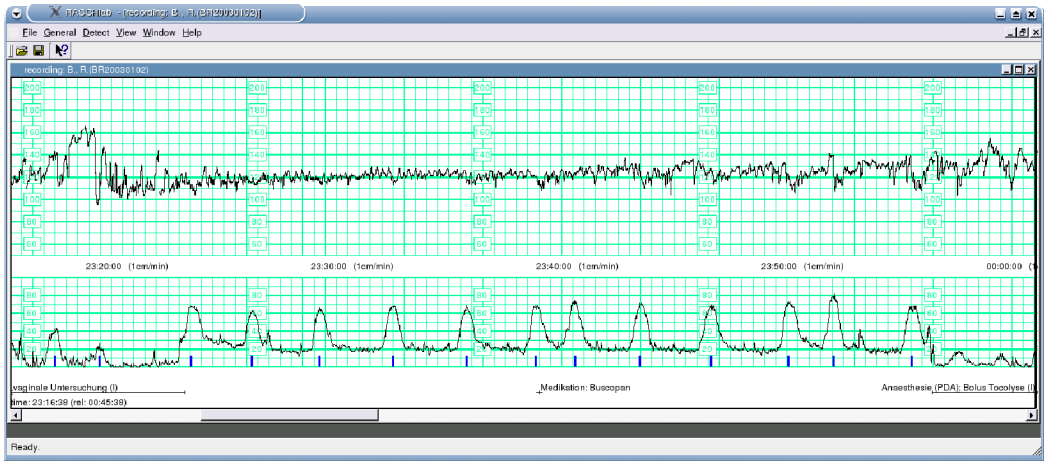

Figure 2.4: Cardiotocogram tracing recorded during labor. The tracings depict half a minute between vertical lines. (Upper segment: fetal heart rate; Lower segment: uterine contractions; Duration: approximately 45 minutes.)(Tec07)

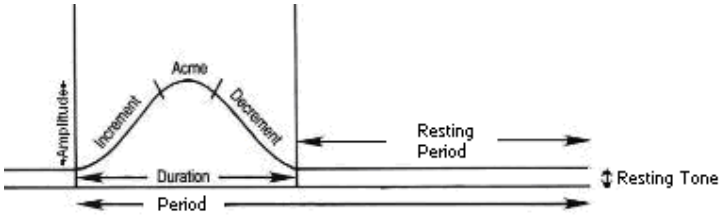

Figure 2.5: Characterization of a uterine contraction.

2.3.2 Abnormal uterine contraction patterns

Abnormalities of uterine contractility can be divided into hypotonic contractions, and uterine hyperactivity (Kla77).

Hypotonic contractions reflect a low intensity wave of uterine contractility. The resulting graphical representation of the intrauterine pressure curve during labor is that of uniform bell shaped pattern of normal uterine contractility. It is, however, of low amplitude (less than 50mmHg), short duration (less than 45 seconds), and exhibits a prolonged resting phase (less than one contraction every 5 minutes) (Kla77). This inadequate uterine activity implicates lack or slow progress of labor. The diagnosis of this uterine dysfunction in the latent phase is difficult and sometimes can be made only in retrospect. One of the common errors is to treat women for uterine dysfunction who are not yet in the active phase of labor. There have been three significant advances in the treatment of dysfunctional labor: (1) realization that undue prolongation of labor may contribute to perinatal morbidity and mortality; (2) use of dilute intravenous infusion of oxytocin in the treatment of certain types of uterine dysfunction (see section 2.5); and (3) more frequent use of cesarean delivery rather than midforceps delivery when oxytocin fails or when its use is inappropriate (Lev03).

Uterine hyperactivity relates to a pathologic increase in uterine activity, including one or all parameters of uterine activity. The graphic representation of such patterns may appear as uniform bell-shaped curves of uterine contractility exhibiting excessive amplitude, duration and/or frequency. Uterine hyperactivity may also exhibit a non-uniform slope which results in increased resting tone. These patterns are mostly seen with the use of uterine stimulants and may lead to fetal distress (Kla77). Excessive uterine activity is usually associated with fetal distress, placental abruption and uterine rupture, and, if not treated in a timely fashion, can easily lead to perinatal morbidity and mortality (Lur04, Lip85). Therefore, prompt identification of abnormal patterns of uterine activity and their influence on fetal heart rate is essential to avoid fetal compromise.

To deal with abnormal uterine activity patterns, obstetricians administer drugs that affect motility of the uterus. The next sections introduce basic aspects of pharmacology and the drugs used to modulate uterine activity during labor and delivery.

2.4 Drugs that affect uterine motility

Modern obstetrics rely on a collection of drugs either to stimulate or to suppress uterine contractions (Sul97). Such drugs are known as oxytocics and tocolytics,

respectively. These drugs facilitate the resumption to a normal progress of labor, when either idiopathic (spontaneously from an unknown cause) or iatrogenic (after an intervention) abnormal patterns occur.

2.4.1 Oxytocics

This group of drugs is responsible for inducing and augmenting labor. There are several oxytocic drugs (e.g. oxytocin, ergonovine, and prostaglandin), but oxytocin is the most widely used to induce or augment labor. It is effective when administered by any parenteral route, although it is most often given intravenously (Sul97).

Oxytocin receptors are present in the uterus in low concentrations until late pregnancy, at which time their numbers increase dramatically. Receptor levels rise during early labor to 200 times that in the nonpregnant state. Thus, at the onset of labor, oxytocin can stimulate uterine contractions at levels that are ineffective in the nonpregnant state. After parturition, the concentration of oxytocin receptors rapidly declines (Gim01). The lack of receptors in early pregnancy and in the nonpregnant uterus probably accounts for the lack of responsiveness of the uterus toward oxytocin other than during the third trimester. Possibly, the down regulation of the oxytocin receptors may be necessary to avoid unwanted contractile responses during lactation when oxytocin levels are raised (Sul97, Gim01).

Oxytocin directly stimulates uterine contractions through occupation of oxytocin receptors. Other than that, it has also been reported to cause the release of certain prostaglandins within the uterus, which can induce uterine contractions through occupation of prostaglandin receptors (Sul97, Zin03). The use of oxytocin in labor has the inherent danger of producing uterine hyperstimulation with resultant fetal distress (Lip85), since the sensitivity to this drug has a high inter-patient variability (Ste85, Bid87, Bla88, Cra91). For this reason, careful and stepwise increase of administered dose, together with continuous fetal assessment is an important aspect in the education of midwifes and obstetricians (Jam04, ACO91, Sat92, Bro91, Bla88).

2.4.2 Tocolytics

The class of tocolytic agents is most known for its therapeutic use in preterm labor, but it is also used to alleviate uterine hyperactivity during labor (Bro98, Bur89, Cha05, Ing84). Generally speaking, tocolytics are use to suppress uterine motility – this process is called tocolysis. Tocolytic agents include magnesium sulfate (Mac97,

Vig00), oxytocin antagonists (Lur04), calcium channel inhibitors (Dav97), and adrenergic beta-receptor agonists (Ari78). These different types of tocolytics are associated with rather different action mechanisms (Ing84, Wray93).

2.5 Pharmacology

Pharmacology is the study of how substances interact with living organisms in order to produce a change in function. In this section we will focus on aspects of pharmacology that are relevant to this project.

In acute care situations, drugs are most frequently administered intravenously. This permits rapid attainment of the desired drug concentration in blood in a reasonably predictable manner (Hud92, Wil01). The two most common ways to administer an intravenous drug are either by bolus or by infusion. A bolus is a single dose of drug injected over a short period of time. An infusion often keeps a constant value over a longer period of time. Administration protocols are based on knowledge concerning drug absorption, distribution, and effect. Intravenous injections bypass the absorption processes, so that therapeutic blood concentrations can rapidly be attained. This is especially advantageous when rapid onset of drug action is desired. It also facilitates titration of dosage to individual patient responses. However, the rapidity of onset also has its hazards. Should an adverse drug reaction or overdose occur, the effects are immediate and potentially severe (Hud92, Wil01). The processes that take place from drug administration until observable drug effect are usually separated in two categories, named *pharmacokinetics* and *pharmacodynamics*. These processes are explained in the next sections.

2.5.1 Pharmocokinetics

The term pharmacokinetics is derived from the Greek words for "drug" and "moving". In its broadest sense, pharmocokinetics is the quantitative analysis of the relationship between the administered drug dose and the ensuing changes in the drug concentration in blood and other tissues (Hud92). To produce its characteristic effect(s), a drug must be present in appropriate concentrations at its site(s) of action.

Although obviously a function of the amount of drug administered, the concentrations of active, unbound (free) drug attained also depend on the rates of absorption, distribution, metabolism, and excretion (Wil01, Hud92). All these processes involve drug passage across cell membranes, and therefore depend on the

mechanisms by which drugs cross membranes and the physicochemical properties of the molecules and membranes. The determining characteristics of a drug are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and non-ionized forms, and its biding to tissue proteins (Wil01).

Absorption, is related to the amount of drug in the bloodstream, and is defined by the rate at which a drug leaves its site of administration and the extent to which this occurs (Hud92, Wil01). Two different tablets containing the same amount of drug chemical may not release the same amount into the bloodstream. Also, the same amount of drug chemical administered by different routes may not release the same amount into the bloodstream.

At the same time that the drug is being absorbed it is also being cleared from the system. This process is known as *disposition*. The process of disposition can be seen as clearing the system of a dose, or disposing of the dose, where the compound or substance is distributed within the system, converted into metabolites, and finally eliminated by passing the parent compound or products of the parent compound from the system into the urine, feces, sweat, exhalation or other routes of elimination (Hud92, Wil01).

Following absorption or administration into systemic blood, a drug distributes into interstitial and intracellular fluids (*distribution*). Initially, liver, kidney, brain, and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin, and fat are slower. This second phase may require minutes to several hours before concentrations of drug in tissue are in equilibrium with that in blood.

Drugs are eliminated from the body either unchanged by the process of *excretion* or converted to metabolites (*metabolism*) (Hud92, Wil01). The kidney is the most important organ for excreting drugs and their metabolites.

Excretory organs, lungs excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds.

A fundamental hypothesis of clinical pharmacokinetics is that a relationship exists between a concentration of the drug (*e.g.*, in blood or plasma) and the pharmacological effects of a drug. The importance of pharmacokinetics in patient care is based on the improvement in therapeutic efficacy that can be attained by application of its principles when dosage regimens are chosen and modified.

The four processes – absorption, distribution, metabolism and excretion – influence the drug levels and kinetics of drug exposure to the tissues, and hence influence the performance and pharmacological activity of a drug.

The various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so via a modification of pharmacokinetic parameters. The four most important parameters are the following:

- Clearance, a measure of the body's efficiency in eliminating drug;
- Volume of distribution, a measure of apparent space in the body available to contain the drug;
- Elimination half-life, a measure of the rate of removal of drug from the body; and
- Bioavailability, the fraction of drug absorbed as such into the systemic circulation (Hud92, Wil01).

2.5.2 Pharmacodynamics

In its broadest sense, pharmacodynamics can be defined as the study of the effect of drugs on the body. Classically, pharmacologic effects have been examined with dose-response studies. Advances in drug assay techniques and methods of data analysis have made it possible to define the relationship between the drug concentration and the associated pharmacologic effect in vivo. As a result, the term pharmacodynamics has acquired a more specific definition. It is now considered to be the quantitative analysis of the relationship between drug concentration in blood, or at the site of action, and the resultant effects of the drug on biochemical or physiologic processes (Hud92, Wil01, Ell01). In theory, there must be some degree of temporal disequilibrium between plasma concentration and drug effect for all drugs with extravascular sites of action. However, for some drugs, the time lag is so short that it cannot be demonstrated (Hud92). The result of this time lag between changes in concentration and changes in effects is that the plasma concentration will only have an unvarying relationship with pharmacologic effect under steady-state conditions. At steady state, by definition, the concentration in the plasma is in equilibrium with the concentrations in all tissues, including the site of action (Hud92).

The effects of most drugs result from their interaction with macromolecular components of the organism. These interactions alter the function of the pertinent component and thereby initiate the biochemical and physiological changes that are

characteristic of the response to the drug (Ell01). The term *receptor* denotes the component of the organism with which the chemical agent interacts.

A particularly important group of drug receptors are proteins that normally serve as receptors for endogenous regulatory ligands (*e.g.*, hormones and neurotransmitters). Many drugs act on such physiological receptors which are specialized to recognize and respond to individual signaling molecules with great selectivity (Wil01). Drugs that bind to physiological receptors and mimic the regulatory effects of endogenous signaling compounds are termed *agonists* (Ell01). Other drugs bind to receptors without regulatory effect, blocking the binding of endogenous agonists. These compounds are termed *antagonists* (Ell01).

The regulatory actions of a receptor may be exerted directly on its cellular target(s), effector protein(s), or may be converted by intermediary cellular signaling molecules called *transducers*. Frequently, the proximal cellular effector protein is not the ultimate physiological target, but rather is an enzyme or transport protein that creates, moves, or degrades a small molecule metabolite or ion known as *second messenger*. Second messengers can diffuse through a cell and convey information to a wide variety of targets, which can respond simultaneously to the output of a single receptor (Ell01).

Receptors for physiological regulatory molecules can be assigned to a limited number of functional families whose members share mechanism of action and molecular structures (Ell01):

- Receptors with intrinsic enzymatic activity such as protein kinase, which exert their regulatory effects by phosphorylating diverse effector proteins at the inner face of the plasma membrane, and ligand-gated ion channels, which convey their signals by altering the cell's membrane potential or ionic composition.
- G Protein-coupled receptors include lipid signaling molecules as well as numerous peptides and protein ligands. G protein-regulated effectors include enzymes such as plasma membrane ion channels selective for Ca^{2+} and K^{+}.
- Cytoplasmatic second messengers such as the triphosphate (IP_3) that is responsible for releasing Ca^{2+} into the cytoplasm through specialized regions of the endoplasmatic reticulum.

Receptors not only initiate regulation of physiological and biochemical function but are themselves subject to many regulatory and homeostatic controls. Continued stimulation of cells with agonists generally results in a state of desensitization (also

referred as refractoriness or down-regulation), such that the effect that follows continued or subsequent exposure to the same concentration of drug is diminished.

2.6 Mathematical models

In this section we present general considerations on mathematical modeling of human physiology and pharmacology for educational simulation. This is followed by a short description of traditional pharmacokinetic and pharmacodynamic models.

2.6.1 Modeling human physiology and pharmacology for educational simulation

This subsection is based on a personal communication by supervisor Prof. van Meurs.

Rationale for model-driven acute care simulation

Models of human physiology and pharmacology, part of the simulation engine of an acute care educational simulator, provide:

- real-time, automatic, realistic, and consistent evolution of clinical signs and monitored signals and their response to therapeutic interventions, and
- a representation of the (patho)physiology of the simulated patient that can be validated and manipulated in a logical fashion.

Simulation engines

Van Meurs et al. describe the concept of a script-controlled model-driven simulation engine for acute care simulators (Van97). A time-and-event-based script is a set of commands that causes the patient simulator to operate in a specified manner. Mathematical (and sometimes mechanical) models are used to make the simulated patient evolve spontaneously, and react to one or more generally continuous-time, continuous-value simulated critical incidents and therapeutic interventions.

Model classification

A model can be defined as an abstraction of reality which accounts for those properties of a phenomenon that are pertinent to the purpose of the model (Ben98). Mathematical models of dynamic systems[2] can be classified according to their basic purpose: Descriptive, predictive, or explanatory (Cob01). A descriptive purpose may well be served by a black-box model, which is a model derived from measured input and output signals, without any information concerning internal system structure

[2] See (Van98b, Plenum) for an introduction of variables, parameters, and estimation.

and internal relations (Van94). An explanatory purpose usually requires a white-box model, which is a model derived from basic principles or descriptions of components. A predictive purpose may be served by either white-box or black-box models. Models can be further classified according to the number and types of input and output variables, for example: Discrete vs. continuous time and value, deterministic vs. stochastic, and according to general system behavior: Linear or non-linear, time-variant or time-invariant. Note that all systems considered here will be causal and dynamic; sub-systems may be static. The choice of mathematical formulation of a model, for example: Impulse response and convolution integral, transfer function, or state variable formulation, depends on a combination of system properties and model purposes.

Models of human physiology and pharmacology for educational simulations

The basic purpose of models of human physiology and pharmacology in the simulation engine of a medical educational simulator is predictive: Baseline simulated vital signs and their spontaneous evolution should be realistic and they should respond correctly to therapeutic interventions. Models in medical educational simulators usually have to represent a variety of patients and pathologies, see for example, Sá Couto et al. (SáC06), and - for pharmacologic models - a variety of drugs and effect sites (Van98a). Parameter values are obtained from the literature or via manipulation of the model by domain experts or clinical instructors. Clinical instructors may also manipulate or script model parameters and input variables to simulate critical incidents. It may be easier to find parameters for compact, descriptive black-box models, but explanatory white-box models reflecting anatomy and physiology, albeit often more complex than descriptive models, are easier to manipulate for clinical instructors. Multiple models in medical educational simulators have to interact appropriately. Although this basically depends on input-output characteristics, matching internal model structures may greatly facilitate representing such interactions.

So, models in medical educational simulators often serve multiple purposes and may be derived or adapted using a mix of input-output data and knowledge about the structure of the system. The resulting models can be referred to as "grey-box" models. The sometimes conflicting requirements - see van Meurs et al. (Van03) for an explicit list - need to be taken into account when researching and validating such models. Reflecting the diversity of biological signals and systems, types of models

found in medical educational simulators are also quite diverse. The state variable formulation is often chosen because it not limited to single-input single-output, linear, time-invariant systems, and its software implementation is straightforward.

Modeling, simulation, and validation

A white-box or grey-box model for educational simulation can be established in the following steps:

1. Study and description of physiologic or pharmacologic background information and of the clinical environment, including types of patients, health care providers, monitored signals, therapeutic interventions, pathologies, and critical incidents.
2. Formulation of model requirements. Depending on the depth and span of the project, this may take into account considerations on the trainees, simulator based educational program, simulator, simulation engine, and other physiologic or pharmacologic models. Input-output variables are identified in a general block diagram. These variables should be listed with their descriptions, symbols, units, range, and bandwidth. Target data should be obtained for baseline vitals signs, critical incidents, and responses to therapeutic interventions. If human target data is lacking, scaled animal data or data provided by domain experts are alternatives.
3. Analysis of existing models and adoption, adaptation or formulation of a conceptual model, often in the form of a detailed block diagram or analog.
4. Derivation of a mathematical model, including estimation of initial parameter values.
5. Software implementation based on a flow diagram and clearly defined data structures. The match between mathematical equations and code implementation should be carefully checked and functioning of the software should be verified via simulation of a known response, for example, an analytical solution of the model.
6. Simulation, comparison of results to target data, interpretation, model validation. Ranges of input variables for which the model is valid should be specified.
7. (Optional) integration with other models and validation of combined response, integration in an educational simulator, educational impact study.

2.6.2 Mathematical models in pharmacology

Both pharmacokinetics and pharmacodynamics play a role in the observable drug effect. The (often unobservable) concentration of drug at its effect site links the two (Nik98, Mag03).

Pharmacokinetics

The most common approach to characterize the pharmacokinetics of a drug is to represent the body as a system of compartments. In these compartmental models it is assumed that the transfers of drug between compartments follow first-order or linear kinetics in which a constant fraction of the drug is removed during a finite period of time (Hud92,Gib82). Rather than using rate constants, the rapidity of pharmacokinetic processes are often described with half-times (or half-lives) - the time required for the drug plasma concentration to decay by a factor of 2, after a single bolus administration. Another important concept in pharmacokinetics is volume of distribution, which is the pharmacokinetic parameter that quantifies the extent of drug distribution. The main physiologic factor governing the extent of drug distribution is the overall capacity for uptake by tissues, relative to blood, for that drug. Overall tissue capacity is a function of the total volume of the tissues into which a drug distributes and their average affinity for the drug (Hud92).

A simple one-compartment pharmacokinetic model (Figure 2.6), applicable to oxytocin (Gon95), depicts the body as a single homogeneous unit. This model is particularly useful for the pharmacokinetic analysis of drugs that distribute rapidly throughout the body. Immediately after iv injection, the drug is eliminated from the system. This process follows first-order kinetics and the elimination rate constant is λ_e.

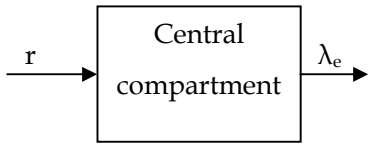

Figure 2.6: One-compartment model: r – drug dose infusion rate; λ_e – drug elimination rate constant.

Considering a one-compartment model, the system of equations that describes the change in drug concentration over time is:

$$\dot{x}(t) = -\lambda_e x(t) + r(t) \tag{2.1}$$

$$C_{pl}(t) = \frac{x(t)}{v} \tag{2.2}$$

Where:

- $x(t)$ is the drug mass at time t in blood and plasma;
- λ_e is the elimination rate constant;
- v is the volume of distribution; r(t) is the infusion rate; and
- $C_{pl}(t)$ is the drug concentration in plasma.

Figure 2.7 presents a typical concentration-time curve following first-order kinetics after a bolus injection in a one-compartmental model. Figure 2.8 presents a (somewhat stylized) concentration-time curve for drug administration as a continuous infusion. Observe that, when the infusion is stopped, concentration has a similar decay as in Figure.2.7 (Gib82).

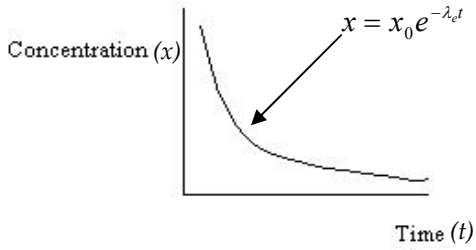

Figure 2.7: Typical concentration-time curve after bolus injection. x_0 is the initial concentration after bolus injection (Nel99).

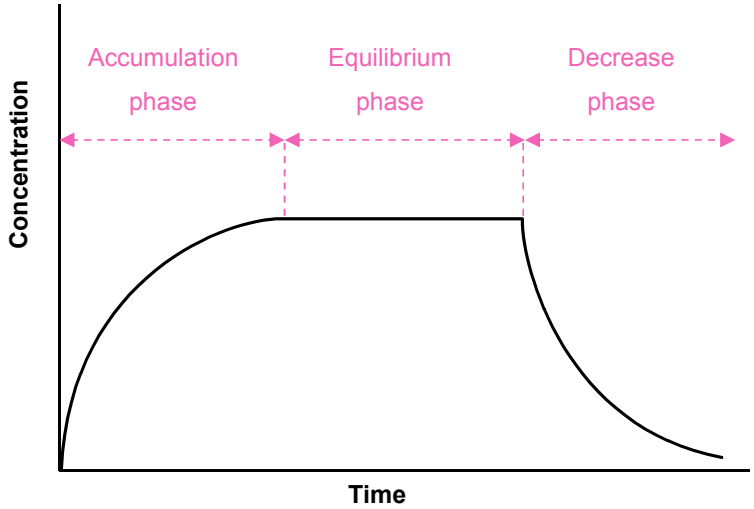

Figure 2.8: Typical concentration-time curve during continuous infusion (Ser06).

Pharmacodynamics

Pharmacodynamics has evolved from an empirical to a quantitative scientific endeavor that seeks to characterize the time course of drug effects through the application of mathematical modeling to administration, concentration, and effect data. Parameter estimation in pharmacokinetic and pharmacodynamic models is best achieved via:

- Establishing relevant pharmacokinetics;
- Understanding the mechanism of action of the drug, and appreciating the determinants of any time dependency in the response;
- Collecting a suitable array of experimental measurements as a function of dose and time.

There are many different types of pharmacodynamic models depending on mechanisms of drug action and scope of a particular study (Ear04, Mag01, Mag03, Mer95, Yao06).

A parametric sigmoidal relationship known as the E_{max} model, is commonly used for drugs that satisfy the conditions that a rapid equilibrium is obtained between plasma and biophase concentrations, and for which agonism is the relevant mechanism of action. The rationale for this approach was based on the law of mass action and classical receptor occupancy theory. Receptor occupancy theory states that drug effect is directly proportional to the fraction of occupied receptors, such that $E=a \cdot RC$ (where, E stands for Effect and RC for the number of occupied receptors). One of the forms of the E_{max} model is given by eq. 2.3:

$$E = E_0 + (E_{\max} - E_0) \cdot \frac{C_{pl}(t)}{EC_{50} + C_{pl}(t)} \tag{2.3}$$

Where:

- E_{max} is the maximal possible effect of the drug;
- E_0 is the effect when no drug is administered;
- EC_{50} is a sensitivity parameter, representing the drug concentration producing 50% of $E_{max}+E_0$; and
- $C_{pl}(t)$ is the drug plasma concentration.

Often, the E_{max} model includes an additional parameter, γ, which affects the steepness of the concentration-effect curve. This model (eq. 2.4) is usually called a sigmoidal $E_{\max}$ model:

$$E(t) = E_0 + (E_{\max} - E_0) \cdot \frac{C_{pl}{}^{\gamma}(t)}{EC_{50}{}^{\gamma} + C_{pl}{}^{\gamma}(t)} \tag{2.4}$$

Note that this is a static relationship. The effect of each model parameter on the concentration-effect curve is shown in Figure 2.9, with the excpetion of E_0 , which is kept at 0. We observe that a change in EC_{50} is associated with a horizontal translation. As mentioned above, γ defines the slope of the curve, and E_{max} reflects the maximum effect. EC_{50} is also known as the sensitivity parameter. An individual is more sensitive to a drug if half of the maximum effect is obtained with a lower drug concentration, i.e., the lower the EC_{50}, the more sensitive the patient is to the drug.

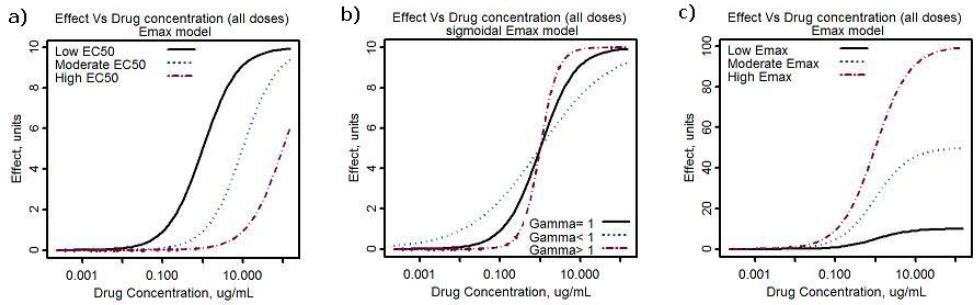

Figure 2.9: Effect of E_{max} model parameters on the concentration-effect curve: a) effect of EC_{50}; b) effect of γ; and c) effect of E_{max}.

3. Uterine activity model requirements

The requirements presented in this chapter are an important step in the development of the model, because they direct the course of this study. General requirements for mathematical models of human physiology and pharmacology part of the simulation engine of a medical educational simulator are (Van03):

- Realism of baseline vital signs and their responses to correct and incorrect therapeutic interventions;
- Parameter data reflecting different patients and pathologies should be available in the scientific literature;
- A clinical instructor should be able to manipulate the models to simulate a range of patients, pathologies, or incidents;
- Models of different aspects of physiology and pharmacology included in a simulation engine should interact appropriately.

Note, that in this chapter we will use the term "model" in the broader sense of "simulation engine". How spontaneous evolution of labor and drug responses are divided over a state machine and mathematical models is an implementation question that will be addressed in subsequent chapters.

We start with general considerations on uterine activity patterns and then focus on relevant clinical scenarios, deriving specific model requirements from there. The chapter is concluded by referenced target data for selected model responses. For later reference we maintain requirements for the effect of tocolytic agents, knowing that these will be later included in the uterine activity model and therefore taken into account in the model designed as part of this thesis. However, the development of a model for acute tocolysis is not part of this work.

3.1 General considerations for the uterine activity model

As mentioned before, labor and delivery can be divided in three stages. The uterine contractions signal, however, is usually monitored only in the first two stages of labor – from the beginning of perceived regular contractions until delivery of the fetus.

Normal contraction patterns are characterized, in the latent phase, by two to four uterine contractions with amplitudes of 20-30 mmHg during each 10 min period. In

active labor contractions generally occur every 2 to 3 minutes, last 60 seconds or more, and have an intensity of 50 to 80 mmHg. The baseline tonus is generally 10 to 15 mmHg (Par97). In the active phase of spontaneous labor, uterine activity usually does not exceed 280 MU (i.e., contractions approximately 3 minutes apart and 90 mmHg in intensity) (Lev03).

Abnormal patterns of uterine activity include hyperactivity and dysfunctional labor. Uterine hyperactivity is a well known complication of the active phase of labor (Zal90) that can result either spontaneously from an unknown cause (idiopathic) or after an intervention (iatrogenic). Hyperactive contractions are usually characterized by abnormally high values of amplitude, frequency, and/or resting tone. Tachysystolic contractions are described by a decreased period of uterine contractions that usually cause fetal distress allowing very little time for oxygen supply and removal of waste products. They are defined as 5 or more contractions every 10 minutes, with amplitudes equal to or higher than 50 mmHg (Lur04). Hypertonus is described as a rise of the resting tone to more than 15 mmHg for more than 3 minutes (Lur04). Hypertonic uterine activity is described by increased amplitude of uterine contractions.

Uterine contraction patterns change with the evolution of labor. One of the important skills, required for recognition, diagnosis, and management of certain acute obstetric situations is accurate identification of normal and abnormal uterine activity patterns by the physicians (Har92). In the presence of abnormal patterns, the therapeutic interventions consist of the administration of one or more drugs that affect motility of the uterus, either to stimulate, or to reduce or suppress uterine contractions (Sul97). Oxytocics are used to induce or augment labor, while tocolytic agents are used to achieve the opposite effect – reduction or suppression of uterine contractions.

3.2 Clinical scenarios and overall model requirements

There are a number of clinical situations that are relevant in the context of intra-partum acute care simulation. In this section, we distinguish phases of these clinical situations that are essential to identify the requirements of a uterine activity model for educational simulation of drug dependent intrauterine pressure signals during labor and delivery.

The design of an intra-partum acute care simulator incorporates a uterine activity model for the simulation of the uterine contractions signal during labor, measured

either internally (invasive, but more accurate) or externally (non-invasive, but less accurate). From the externally measured uterine pressure signal, health-care providers are able to recognize period and duration of the contractions, but not their amplitude or the resting tone. Simulated uterine activity should evolve from the beginning of labor until delivery of the fetus, and should respond appropriately to therapeutic interventions such as administration of oxytocin and tocolotytics.

Decelerations of fetal heart rate may occur during contractions; however, in a healthy fetus and in the presence of normal contractions, no complication is expected. On the other hand, if the fetus is already compromised prior to labor (like in chronic fetal hypoxia), normal contractions during the second stage of labor may induce a more severe level of hypoxia in the fetus, leading to fetal compromise.

When uterine activity is maintained within normal values throughout the progress of labor, the health-care provider is not expected to perform any intervention to change uterine contractility. However, in the presence of acute fetal distress, possibly due to cord prolapse, for example, some authorities advocate tocolysis to inhibit uterine activity, since contractions may exacerbate cord compression (Car06).

When uterine rupture occurs, the most common (and often the only) manifestations are prolonged, late, or variable decelerations and bradycardia seen on fetal heart rate monitoring (Car06, Top02). However, an abrupt decrease or arrest of uterine contractility is found to be a sign of suspicion of scar compromise (Car06). In case uterine contractions do not stop spontaneously after rupture of the uterus, it is part of the general measures to stop oxytocin administration, if any, and to administer a tocolytic agent to stop contractions.

Fetal distress caused by untreated uterine hyperactivity is usually identified by prolonged decelerations of the fetal heart rate or even bradycardia. This pattern is associated with uterine hypercontractility. Besides fetal distress due to hypoxia, excessive uterine activity may also cause uterine rupture (Top02). If placental abruption occurs, an unrelaxing uterine activity pattern with high frequency contractions may occur due to extravasation of blood into the myometrium that sets up multiple foci of irritation (Par97). However, if the health-care provider makes an accurate diagnosis of placental abruption, adequate management does not include any intervention to control uterine contractions. A common iatrogenic cause of uterine hyperactivity is the augmentation of labor with oxytocin for the resolution of a slow progress of labor due to insufficient uterine activity (one possible reason of

dysfunctional labor). A summary of possible sequential phases of uterine hypercontractility are listed below:

- Prolonged uterine hypo-activity, characterized by uterine contractions with low amplitude and frequency;
- Expected intervention: Administration of an appropriate dose of oxytocin by intravenous infusion;
- Evolution of uterine activity patterns to hyperactivity, either due to a high sensitivity to oxytocin, or to the administration of an excessive dose;
- Adequate interventions: oxytocin curtail, and in case of persistent hyperactivity, intravenous administration of a tocolytic agent;
- Cessations of uterine activity followed by resumption to normal contractions and progress of labor.

Based on the analysis above, the uterine activity model should be able to reflect:

- normal contractions and their spontaneous evolution during the first two stages of labor;
- hypotonic contractions and response to oxytocin administration;
- uterine hyperactivity and response to oxytocin curtail and to tocolytic administration.

Hyperactivity can be further subdivided into:

- tachysystole (high frequency of contractions);
- baseline hypertonus (increased resting tone);
- hypertonic contractions (high amplitude of contractions).

Within the scope of this thesis we will limit the requirements of the uterine activity model to:

- normal contractions and their spontaneous evolution during the first two stages of labor;
- hypotonic contractions and response to oxytocin administration;

We also recall the general requirement, adapted to this context:

- inter-patient variability in oxytocin sensitivity.

Any remaining requirements will be addressed in future work.

3.3 Input-output requirements

Fig. 3.1 presents the block diagram of the uterine activity model. All variable names, symbols, and units used in this project are listed in Table 3.1.

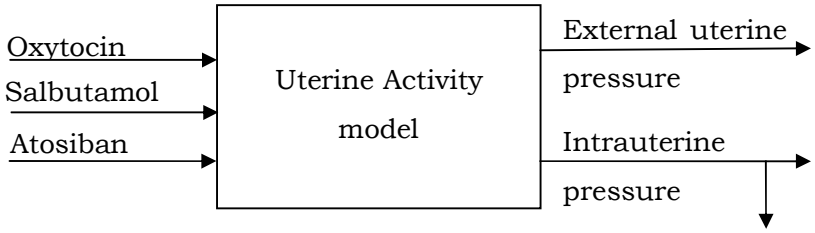

Fig.3.1: Block diagram of the uterine activity model.

3.4 Target data

This section contains referenced target values for baseline input and output variables. Referenced target data for relevant model specific validation experiments are also included. In this section, uterine contractility signal features (resting tone, amplitude, period, duration) and/or other intrauterine pressure signal quantification units will be used as measures of the intrauterine pressure signal. External uterine pressure signals are assumed to have the same contraction periods and durations as the intrauterine pressure signal. Amplitude and resting tone for externally measured signals only have a qualitative interpretation.

Normal contractions

Natural evolution

Table 3.2 presents normal mean and range values for the features of the intrauterine pressure signal for each stage of labor, until delivery of the fetus. Table 3.3 presents the mean duration of stages of labor and phases for nulliparas and multiparas.

Hypotonic contractions

Natural evolution

Slow progress of labor due to hypotonic contractions is usually defined by uterine contractions that maintain low intensity and frequency (as in the latent phase) for more than 14 hours in multiparas and for more than 20 hours in nulliparas.

Table 3.1 Input and output variables of the uterine activity model.

Name	Symbol	Unit	Type	Bandwidth	Resolution	Range
Oxytocin infusion	ot(t)	mU/min	Continuous-time, continuous-value	1Hz	0.01	0 – 100
Atosiban infusion	tlat(t)	mg/min	Continuous-time, continuous-value	1Hz	0.01	0 – 100
Salbutamol dose	tlsb(t)	μg/min	Continuous-time, continuous-value	1Hz	1	0 – 1000
Intrauterine pressure	iup(t)	mm Hg	Continuous-time, continuous-value	1Hz	1	0 – 100
External uterine pressure	eup(t)	mm Hg	Continuous-time, continuous-value	1Hz	1	0 – 100

Response to interventions

Table 3.4 presents uterine activity response to intravenous (IV) oxytocin administration (Cra91). The dose regimen considered in (Cra91) consisted of initiating oxytocin at 1mU/min. Before oxytocin administration, a monitoring period of at least 60 min was recorded.

Table 3.2: Normal mean and range values of intrauterine pressure features for the first and second stages of labor (Kla77, Par97, Lev03).

	First Stage		Second Stage
	Latent Phase	**Active Phase**	
Resting Tone (mmHg)	8 (5-10)	11 (5-15)	13 (10-15)
Amplitude (mmHg)	25 (≤30)	60 (50-75)	65 (50-80)
Frequency (contractions per 10min)	2 (2-3.3)	3.3 (2-5)	4 (3.3-5)
Duration (sec)	60 (40-90)	80 (60-90)	85 (60-90)

Table 3.3: Mean durations of labor phases and stages (Par97).

	First Stage		Second Stage
	Latent Phase	**Active Phase**	
Nulliparas	7h	4h	50min
Multiparas	4h	2h	20min

Table 3.4: Response to oxytocin administration in a population of 10 patients (mean (and SD) values) (Cra91).

	Oxytocin infusion rate (mU/min) and administration period (min)	
	0 (≥60)	**1 (110)**
Alexandria Units	132(61)	199(64)
Montevideo Units	97(48)	145(58)

Table 3.5 presents results of labor augmentation with oxytocin, using different protocols (Bid87a, Bid87b). To assess uterine activity from several labors of varying lengths the test period was divided into quarters by time and uterine activity averaged for each quarter.

Table 3.5: Uterine Activity Integral (UAI) in kPas/15 min (mean (SD)) by group and quarters of labor (Bid87a, Bid87b).

Time period	Group 1	Group 2	Group 3
Control	947 (489)	848 (440)	900 (463)
Quarter1	1038 (460)	1069 (494)	1529 (515)
Quarter2	1074 (474)	1100 (485)	1758 (594)
Quarter3	1245 (583)	1321 (440)	1733 (579)
Quarter4	1291 (621)	1344 (452)	1770 (131)

Group 1. N=20, mean infusion rate 1.98 mU/min (range 0-18.5), mean total dose 0.52 U (range 0-3.89);
Group 2. N=21, mean infusion rate 3.0 mU/min (range 0-16.82), mean total dose 1.34 U (range 0-12.36);
3. N=19, mean infusion rate 9.46 mU/min (range 0.28-28.9), mean total dose 2.43 U (range 0.11-9.98);

Hyperactivity

Natural evolution

A hyperactivity pattern results from one or more uterine contractility features increasing beyond the normal range. Table 3.6 lists diagnostic criteria for different types of uterine hyperactivity, when only one parameter exceeds its normal range. Note that a combination of these patterns is likely to occur.

Table 3.6: Hyperactivity patterns.

	Affected signal feature	First Stage Active Phase	Second Stage
Baseline hypertonus (Lur04)	**Resting Tone (mmHg)**	>15	>15
Hypertonic contractions (Kla77).	**Amplitude (mmHg)**	>75	>80
Tachysystole (Lur04)	**Frequency (contractions per 10 min)**	>5	>5

Response to adequate interventions

In case of uterine hyperactivity associated with fetal distress, the physician is expected to curtail oxytocin administration, if any, and possibly administer tocolytic agents if the fetal condition does not show signs of improvement. Since there are a high number of tocolytic agents available, two were selected in the scope of intra-partum acute care simulation, according to their use world-wide: Salbutamol (mostly in Europe) and atosiban (new and increasingly used oxytocin antagonist). Magnesium sulfate was excluded because nowadays the application of this tocolytic to treat intra-partum uterine hyperactivity is very rare.

Oxytocin curtail

When uterine hyperactivity is caused by oxytocin administration, it is mandatory to stop the oxytocin infusion. This procedure alone is in many cases sufficient to recover normal uterine activity. Usually, if hyperactivity is not alleviated within 5-10 minutes (Lur04, Zal90), a tocolytic agent is given. The adequate timing to intervene may also depend on the severity of fetal distress. Table 3.7 presents the responses to 10 minutes of oxcytocin curtail after 110 min infusions of 1mU/min and 2mU/min of oxytocin, respectively.

Table 3.7: Response to oxytocin curtail (Cra91).

	1 mU/min		**2mU/min**	
	During infusion	**10 min interruption**	**During infusion**	**10 min interruption**
Alexandria Units[1]	199±64	142±21	240±64	214±37

[1].Mean(SD) of a 10 patients population.

Salbutamol

In MacDevitt et al. (McD75) salbutamol (5.0 mg in 500 ml of 5.0% dextrose solution) was infused intravenously in eight patients. An initial rate of 10 μg/min was administered on average for 4.9 minutes, followed by a 20 μg/min infusion rate, with a mean duration of 5.25 min. All patients in this study had normal baseline contractility and were in the first stage of labor (at term). Baseline contractility was recorded for 30 minutes. Table 3.8 presents the average baseline uterine activity, dose regimen and response to Salbutamol infusions (mean±SE). Using the definition of Alexandria units (see Chapter 2), it is possible to derive the period for each case.

Table 3.8: Response to Salbutamol (McD75).

	Salbutamol (μg/min)		
	0	**10**	**20**
Resting Tone (mmHg)	10.4±1.4	10.3±1.3	9.8±1.2
Amplitude (mmHg)	45.0±5.3	37.8±5.7	26.1±4.4
Duration (sec)	106.6±8.8	97.6±10.3	104.5±13.9
Alexandria Units	277.0±65.3	129.4±28.1	80.5±25.7

Atosiban

Lurie *et al*. reported that 93% of uterine hyperactivity cases were alleviated within minutes after bolus administration of atosiban. When hyperactivity was noted, the woman was turned to the left lateral decubitus position, oxygen was given by mask,

oxytocin administration was stopped in those women who were receiving it, and intravenous clear fluids were given. If hyperactivity was not alleviated within 5 minutes, Atosiban was given as a single intravenous bolus dose of 6.75 mg in 0.9 ml of isotonic sodium chloride solution. Alleviation of hypertonus (or tachysystole) was defined as decline of uterine tonus (or attenuation of frequent contractions) within 3 minutes. In the treatment of idiopathic tachysystolic contractions, uterine activity took (on average) 25 minutes to resume (i.e., appearance of regular contractions), ranging from 15 to 30 minutes. In the treatment of oxytocin-induced tachysystolic contractions, resumption of normal uterine activity took on average 23 minutes. In the treatment of oxytocin-induced hypertonus, regular contractions took 25 minutes to appear. Table 3.9 presents median and range times for resumption of normal uterine activity after alleviation of tachysystole or hypertonus within 3 minutes after the administration the bolus of atosiban.

Table 3.9: Time (min) to resumption of normal uterine activity after atosiban administration (bolus dose – 6.75mg in 0.9mL isotonic sodium chloride solution) (Lur04)

	Cause		
	Idiopathic	**Oxytocin**	**Any**
Median	30	20	25
Range	15-30	20-30	15-30

4. Critical evaluation of previous developments

The purpose of this chapter is to evaluate the uterine activity models previously developed at the *Instituto de Engenharia Biomédica* (INEB) by Ana Raquel Pereira, Luísa Ferreira Bastos, and Pedro Sá Couto and other published models for the simulation of uterine contractions signals. To do this, we describe the existing models, their validation, and their application to intra-partum acute care simulation, taking into account the uterine activity model requirements described in Chapter 3. The critical evaluation of the existing models concludes with a proposal for further developments.

4.1 Simulation engine developed at INEB

This section presents a description and analysis of the previously implemented uterine activity model. This model is composed of three major parts (1) an intrauterine pressure generator; (2) a script-driven spontaneous uterine activity engine; and (3) an oxytocin pharmacological model. The latter can be further subdivided into a pharmacokinetic model and a pharmacodynamic model.

For each part we present in Appendix 1 a detailed description of the following:

- Block diagram;
- Model equations;
- The flow diagram and essential data structures of software implementation.

The following section presents the integration of the parts in a block diagram, followed by the flow diagram that explains their code implementation.

4.1.1 Integrated uterine activity model

With the previously developed uterine activity model it is possible to simulate intrauterine pressure signals from uterine contractility features: amplitude, period, duration, and resting tone. These uterine contractions waveform features are generated according to an initial condition which determines the type of spontaneous labor (normal, hypotonic, or hypertonic). Administration of oxytocin will affect the uterine contraction waveform features: amplitude and period. This is achieved via the integration of three models: oxytocin pharmacokinetics, oxytocin pharmacodynamics, and Alexandria unit decomposition. This decomposition block converts uterine activity quantified in Alexandria units into uterine contractions

waveform features: amplitude and period. The block and flow diagrams in Figures 4.1 and 4.2, respectively, describe the integration of the three major blocks: intrauterine pressure generator; script-driven spontaneous uterine activity; and oxytocin pharmacological model.

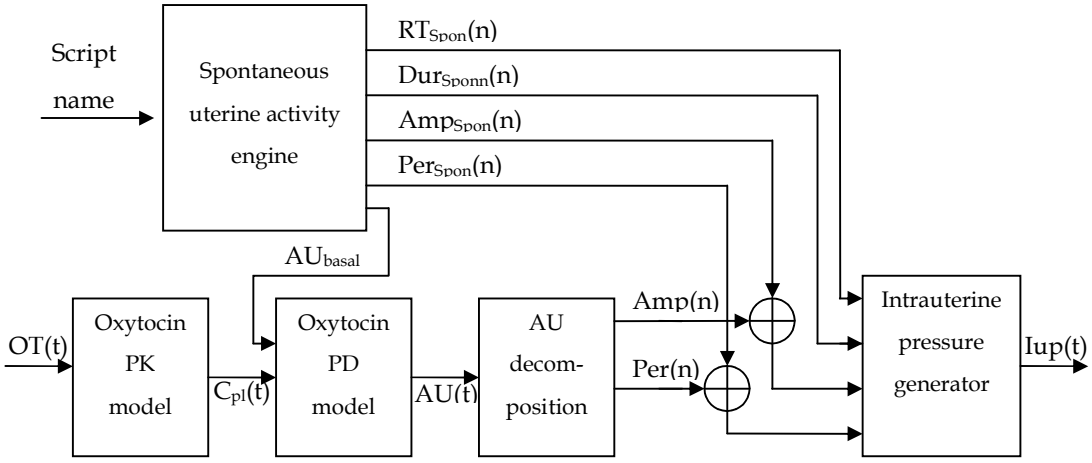

Figure 4.1: Block diagram of the previously implemented uterine activity simulation engine. The symbol "⊕" represents a disjunction; amplitude and period are generated either in the spontaneous uterine activity block, or in the AU decomposition block.

4.2 Published models and data

The literature review presented in this section covers models and relevant information related to uterine motility, concerning either simulation of uterine contractions or oxytocin pharmacology (both pharmacokinetics and pharmacodynamics).

4.2.1 Models for simulation of uterine contractions

There are several published models for the simulation of uterine contractions (And95, You97, Vau00, Vau03). These models are based on physiologic aspects of intracellular events that happen during uterine contractions. The models found in the literature consider contractile elements (myometrium cells) as the basis for uterine activity.

Andersen *et al.* (And95) modeled the uterus as a hollow ovoid composed of nine cells. Each cell contacts with eight surrounding cells and propagates impulses iteratively from cell to cell. Contraction pressure is the sum of the tension

contributions by contracting cells. Contraction waveforms were generated based on various numbers of cells organized in the ovoid with long and short axis ratios, and with one or two pacemakers at varying positions.

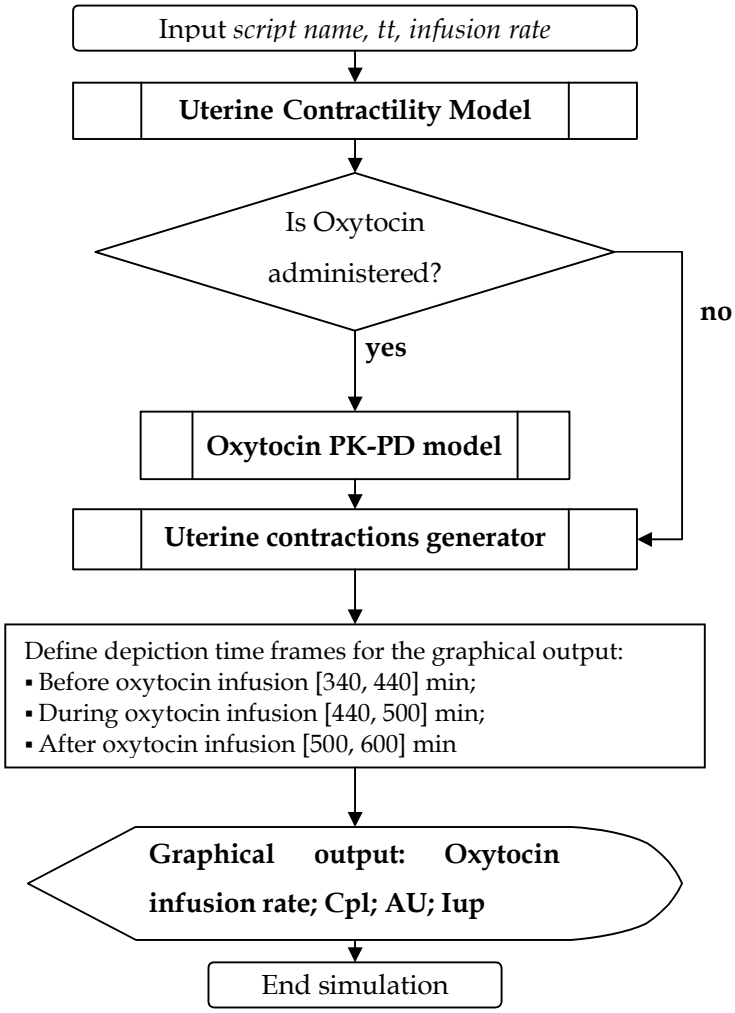

Figure 4.2: Flow diagram of the previously implemented uterine activity simulation engine.

Another model was presented by Young *et al.* (You97). This model results from the combination of two known mechanisms of intercellular communication. These mechanisms consist of action potentials throughout the uterus and of calcium waves within the tissues.

Vauge et al. (Vau00, Vau03) suggested a mathematical model for uterine dynamics and its application to human parturition. This model is based on three physiological states of the myometrium cells, associated with the contractility of the uterus during human parturition. The model is composed by a set of contractile elements (the myometrium smooth muscle cells), which experience one of three states (quiescent, contracted or refractory) at a given time.

The applicability of these models in the context of intra-partum acute care simulation will be discussed below (see section 4.3).

4.2.2 Studies of uterine activity and the effect of oxytocin

Even though few models were found for the simulation of uterine contractions signals, and none for the simulation of the effect of oxytocics and tocolytics on uterine activity, many studies have been carried out in an attempt to explain the mechanisms involved in these processes. This section summarizes the most relevant studies found in the context of this project.

Uterine activity

One early study was presented by Barclay *et al.* (Bar77). The authors suggest the use of the Hill model of muscle dynamics and a modified cardiac model to analyze certain aspects of uterine contractility and uterine function of parturition. In this analysis, five parameters were computed: (1) the maximum developed pressure, (2) the maximum rate of pressure rise with respect to time, (3) the extrapolated maximum muscle velocity (Vmax), (4) the slope of the linear regression line used to determine Vmax, and (5) the standard deviation of points used in defining the regression line. Additionally, relationships between labor patterns and maternal and fetal outcomes, dysfunctional uterine activity, and use of drugs are discussed with reference to the computed parameters.

Kruse *et al.* (Kru86) reviewed the pharmacology and the proper clinical use of oxytocin in the augmentation of labor. They concluded that:

- In addition to increasing the intensity and frequency of contractions, oxytocin facilitates the correction of ineffective or irregular uterine contractions during labor.
- If used improperly, oxytocin can lead to such complications as uterine hypercontractility, associated with fetal distress, uterine rupture, maternal

hypotension, and others. With proper dosages of oxytocin and with careful fetal and maternal monitoring these complications can be avoided.

Seitchik *et al.* (Sei76) identified similarities and differences between uterine contractions in patients with spontaneous labor, oxytocin-corrected hypocontractility, and oxytocin-induced hypercontractility. These differences were identified with measurements of specific characteristics of the intrauterine pressure waveform, including pressure, rate of change of pressure, and duration.

Oxytocin effect on uterine motility

Several studies address the pharmacokinetics of oxytocin (Sei84, Per96, Lea80, Gon85). All conclude that the pharmacokinetics of oxytocin can be represented by a first order process in a single compartment pharmacokinetic model. Clearance values range from 11.2 to 32.5 ml/kg/min, and half-time from 2.7 to 20 min.

The collected studies of the effect of oxytocin administration on uterine activity don't provide enough elements for the pharmacodynamic description of this drug.

Oxytocin dose-response studies include Steer *et al.* (Ste85) and Bidgood *et al.* (Bid87a and Bid87b). They evaluated uterine activity, cervix dilation and caesarean section rate in women with slow progress of labor that were treated with oxytocin. Uterine activity was measured in Montevideo units, uterine activity integral, and uterine contraction waveform features (amplitude and frequency). The relationship between uterine activity integral and uterine contraction waveform features was also studied by these authors. In (Ste85) the dose was titrated as a function of observed response, hence low doses were used when a sensitive uterus responded with a large increase in uterine activity integral, whereas high doses were only used in an attempt to produce an adequate response from a less sensitive uterus. In (Bid87a, Bid87b), the positive correlation between dose and uterine activity integral is based entirely on the high-dose group, where oxytocin was given regardless of response (unless hyper-stimulation occurred). Crall and Mattison (Cra91) evaluated the uterine response to long infusions of oxytocin, finding a period of tolerance to the drug. All authors highlight inter-patient variability in response to oxytocin.

Summarizing, these articles support that the response of the uterus to oxytocin appears to be dependent on dose, on the underlying spontaneous uterine activity, and on myometrial sensitivity to oxytocin.

4.3 Discussion

In this section we discuss the value of the presented existing models for application in educational intra-partum acute care simulation. In Chapter 3, we concluded that the uterine activity model has to be able to simulate, at least, the following intrauterine pressure patterns:

- Normal contractions in the latent phase;
- Normal contractions in the active phase;
- Normal contractions in second stage labor;
- Prolonged uterine hypocontractility;
- Uterine hyperactivity.

Note that these patterns are directly related to uterine contractility waveform characteristics (amplitude, frequency, resting tone, etc.). This is a nomenclature that health-care providers are comfortable and familiar with. Since they are most likely to be the ultimate users of medical simulators (not only as trainees, but also as instructors), it is essential to make the simulation engine as intuitive as possible. In this sense, the physiological models found in the literature revealed difficult to manipulate for the simulation of the listed patterns. Conversely, the empirical intrauterine pressure generator developed at INEB, together with the spontaneous uterine activity script-driven engine, allows for the simulation of the previously listed patterns simply by choosing the adequate script. The intrauterine pressure signals are described in terms of the uterine contraction waveform features: amplitude, frequency, duration, and resting tone, which allows for the instructor to program different scripts, if necessary.

The scripts included in the spontaneous uterine activity generator were set based on literature data (Cra91, Har92, Kla77) and underwent preliminary validation by a clinical expert.

The goal of the oxytocin pharmacokinetics-pharmacodynamics model is to simulate the effect of intravenous administration of oxytocin on uterine motility. In the literature review we did not find any model that completely fulfills this purpose. However, relevant information and considerations on oxytocin pharmacokinetics and pharmacodynamics were found.

The choice of the pharmacokinetic model in the previously developed work at INEB was based on data from Gonser (Gon95). The model parameters were obtained from Gonser, and Seitchik *et al.* (Gon95, Sei84). In our simulations, we verified that

approximately 40 minutes are needed to reach steady-state after initiation of infusion, as reported in (Sei84, Gon95). Also, simulated oxytocin concentration at steady-state is within the range reported by Leak *et al.* (Lea80). Assuming that the time to reach steady-state concentration is less than or equal to the time to reach steady-state uterine activity, the evolution of the plasma concentration during a constant infusion is in agreement with the descriptions in Crall *et al.*, Gonser, and Seitchik *et al.* (Cra91, Gon95, Sei84). In the first 10-20 minutes, the effect of oxytocin suffers a rapid increase after which this proceeds at a much slower rate, stabilizing after 40 minutes (Cra91, Ama70). Altogether, the simulated oxytocin pharmacokinetics are in agreement with the published data. Note, however, that we were not able to find population plasma concentration profiles for this drug. Therefore, the derived model was considered to be satisfactory for medical educational simulation applications, but further study is required to determine if it reflects the oxytocin pharmacokinetics of an average patient.

The pharmacodynamic model was designed based on Crall et al. (Cra91), and the model parameters were estimated with data from this same article. An attempt was made to reproduce the results presented in (Cra91). However, this was not achieved, due to the use of a lower baseline uterine activity. When correcting the basal uterine activity (as reported in Cra91, in the control period) the oxytocin effect was excessive and extreme (see Figure 4.3), when compared with the data in Cra91.

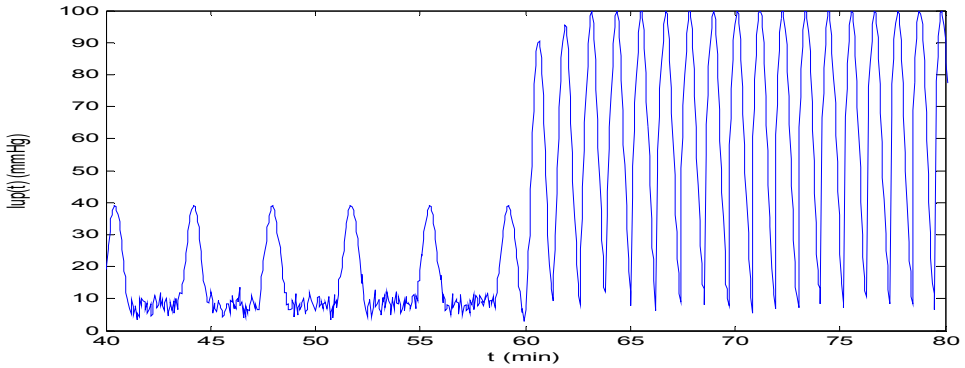

Figure 4.3: Simulated intrauterine pressure response to oxytocin from a patient derived from Cra91. After 60 minutes (control period) oxytocin is administered at a rate of 1mU/min.

New references obtained during the development of this thesis brought to our attention aspects that influence the response to oxytocin that were not included in the previously developed pharmacodynamic model (Bid87a, Bid87b, Ste85). These

aspects were: sensitivity to oxytocin, and influence of underlying uterine activity on oxytocin effect. Therefore, we considered that the oxytocin pharmacodynamics model should be redesigned.

Since the output of the pharmacodynamic model was the quantification of uterine activity in Alexandria units, this response needed to be decomposed in uterine activity features (input variables of the uterine contractions generator). This decomposition was based on the definition of Alexandria units and an empirical relationship, estimated from a single uterine activity pattern. However, Bidgood et al. (Bid87b) have shown that the relationships between these characteristics may be non-linear. Furthermore, to guarantee that intrauterine pressure reflects oxytocin effect, Alexandria units before decomposition and after intrauterine pressure generation had to remain the same. This condition could not be verified for all simulation results (see appendix 1). This points to another shortcoming in the previous work.

Until now, our analysis separated spontaneous uterine activity and oxytocin effect. The integration of both blocks in the previously developed uterine activity engine was done as follows: when oxytocin is administered, the script-driven spontaneous uterine activity stops, and it is replaced by the pharmacokinetic-pharmacodynamic model. After infusion stops and plasma concentration drops to zero, the uterine contractions amplitude and frequency are still simulated by the oxytocin pharmacodynamic model. One problem with this approach is that uterine activity will be simulated disregarding any pre-existing or spontaneously evolving uterine activity. Therefore, the integration of the uterine activity simulation engine blocks has to be carefully revised.

Besides the previous comments on the models, we make the following suggestions for improvement of the code implementation:

- The parts described separately in this document (appendix 1) were implemented in a single function. To allow a simple update and integration of other models, the implementation needs to be segmented and structured.
- The software implementation described in this chapter does not support real-time simulation of intrauterine pressure signals. The possibility to run the model in real-time is essential for its integrated use in intra-partum acute care simulation (see Chapter 3).

Drug infusions are not programmable in time or duration. However, the model should permit any oxytocin administration regimen in an educational environment.

5. Model development

Based on the general requirements for a simulation engine for educational simulation of uterine activity (Chapter 3) and the discussion of existing models (Chapter 4) we formulate the following global objectives for a new simulation engine. This engine should be able to:

- reproduce uterine contraction patterns associated with spontaneous evolution of labor,
- represent the response to oxytocin, taking into account underlying and possibly evolving spontanous uterine activity, and
- match patient variability in both spontaneous evolution and oxytocin response.

The first section of this chapter presents the uterine activity simulation engine design. The second section describes model equations and estimation of model parameters.

5.1 Uterine activity model design

The new uterine activity model proposed here results from the integration of previous work at INEB with elements based on literature data (Bid87, Ste85). The general block diagram (Figure 5.1) is somewhat simplified as compared to the previous model presented in section 4.1. Also, the oxytocin pharmacodynamics model was redesigned in order to:

- take into account that the oxytocin effect depends on spontaneous uterine activity;
- include parameters allowing to adjust patient sensitivity to the drug;
- model oxytocin effects directly (and separately) for each uterine contraction waveform feature.

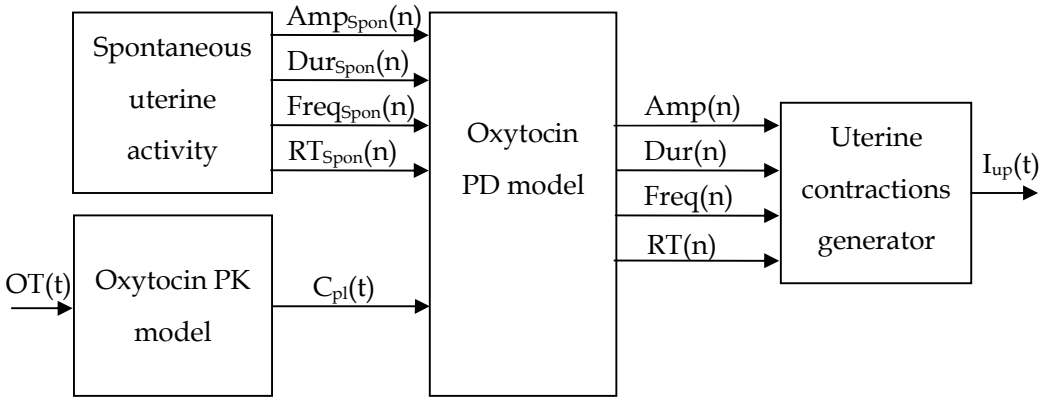

Figure 5.1: Block diagram of the uterine activity model. See the main text for symbols.

The continuous time intrauterine pressure $I_{up}(t)$ is generated by the uterine contractions generator based on the waveform features Amp(n), Dur(n), Freq(n), and RT(n) (one value per contraction cycle n). These features are scripted, describing different pre-programmed spontaneous uterine activity patterns, and may undergo a modification if oxytocin is administered. An oxytocin infusion at rate OT(t) will cause the plasma oxytocin concentration $C_{pl}(t)$ to rise according to the oxytocin pharmakinetics (PK) model. Uterine contraction features will reflect both spontaneous uterine activity and plasma concentration of exogenous oxytocin, according to the oxytocin pharamacodynamics (PD) model.

A basic function of the uterine activity simulation engine is to simulate spontaneous uterine activity. The second function is to simulate the effect of oxytocin on uterine motility. This guideline was very helpful to set intermediate objectives and to think of the uterine activity simulation engine not as a whole but as a composition of smaller parts that have to interact appropriately.

Both the uterine contractions generator and the spontaneous uterine activity engine were maintained from previous work, since they provided a high degree of flexibility in simulating spontaneous contraction patterns, corresponding to various clinical situations. Variability in uterine contraction waveform features is introduced via addition of uniformly distributed random variables in the uterine contractions generator. Statistical parameters were set empirically by model developers.

The previously developed oxytocin pharmacokinetics model was included in this new engine. As mentioned earlier in Chapter 4, this is a very simple model consisting of only one compartment. Rather than introducing an effect site, we maintained this simplification because, according to the literature (Gon85, Cra91), the time lag between the plasma concentration and the site effect concentration is very short.

Due to some inconsistencies in design and validation of the previous model (see Chapter 4 for details), the oxytocin pharmacodynamics model was redesigned. We propose to elaborate on a traditional pharmacodynamics model known as the E_{max} model (see section 2.6.2). With this new approach, we intend to integrate some characteristics of oxytocin effects as described in the literature (Bid87, Ste85). Moreover, instead of considering the effect on a global uterine activity quantifier (Alexandria Units) we will consider the effect of oxytocin on each uterine contraction waveform feature, separately. The next section elaborates on the new oxytocin pharmacodynamics model.

5.2 Oxytocin pharmacodynamics model

According to several authors (Ste85, Bid87), the response to oxytocin depends on the underlying uterine activity. It has been demonstrated (Bid87a, Bid87b) that for a given dose of oxytocin, its effect will be more pronounced when spontaneous uterine activity is lower (and vice-versa). Furthermore, oxytocin effect is positively correlated with dose, so that, for the same underlying uterine activity in a given patient, a higher dose will produce a higher effect. Finally, two different patients with the same underlying uterine activity, treated with the same oxytocin dose, may experience different effects. This is due to the inter-patient variability in sensitivity to oxytocin.

To construct a model that takes in to account the above, we adapted an E_{max} model (reflecting dose-dependency only, as described in section 2.6.2), as follows:

- Provide three concentration effect relationships – one for each uterine contraction waveform features: Amplitude, duration, and frequency (number of contractions per 10 min). To our knowledge, the literature does not contain data for oxytocin effect on resting tone. For now, the model will ignore any such effects.
- Replace the minimum effects E_0 (one for each feature) by the spontaneous uterine contraction waveform feature; this assures that in absence of drug, the engine tracks scripted spontaneous activity, and will make the model react differently to different levels of (underlying) spontaneous uterine activity.
- Allow for the modification of the parameters EC_{50} (one for each feature) to simulate patients with different sensitivity to oxytocin (the smaller its value, the more sensitive a patient is).

By considering the effect of oxytocin on the uterine contraction waveform features separately, the redesigned pharmacodynamic model will contribute to:

- Avoiding using non-objective relationships between global uterine activity measures and uterine contraction waveform features.
- Future integration of other pharmacologic effects directly on measurable waveform features (e.g. tocolytic agents).

Note that the E_{max} model only enables the simulation of a monotonically ascending or monotonically descending dose-effect relationship. The effect of oxytocin on uterine contractions waveform features could be bi-phasic, i.e. some uterine contraction waveform features may have a dose-effect relationship characterized by a rise followed by a decrease. Until such phenomena can unambiguously be attributed to pharmacodynamics, we will ignore them in the model. It is known that uterine activity

is positively correlated with oxytocin concentration/dose. Both amplitude and frequency have ascending monotonic relationships with rising uterine activity (Bid87). The E_{max} model therefore seems adequate to represent the oxytocin effect on these two uterine contraction waveform features. To our knowledge, the relationship between uterine contraction duration and oxytocin concentration or uterine activity is not described in the literature. Therefore, the application of the E_{max} model to this uterine contraction waveform feature is hypothetical for now.

5.2.1 Model equations

Following the above considerations the pharmacodynamics model consists of the following equations:

$$Freq(n) = Freq_{spon}(n) + (F_{\max} - Freq_{spon}(n)) \cdot \frac{C_{pl}(t)^{\gamma}}{FC_{50}^{\gamma} + C_{pl}(t)^{\gamma}} \tag{5.1}$$

$$Amp(n) = Amp_{spon}(n) + (A_{\max} - Amp_{spon}(n)) \cdot \frac{C_{pl}(t)^{\gamma}}{AC_{50}^{\gamma} + C_{pl}(t)^{\gamma}} \tag{5.2}$$

$$Dur(n) = Dur_{spon}(n) + (D_{\max} - Dur_{spon}(n)) \cdot \frac{C_{pl}(t)^{\gamma}}{DC_{50}^{\gamma} + C_{pl}(t)^{\gamma}} \tag{5.3}$$

$$RT(n) = RT_{spon}(n) \tag{5.4}$$

With input variables:

- $Freq_{Spon}(n)$, $Amp_{Spon}(n)$, $Dur_{Spon}(n)$, $RT_{spon}(n)$, waveform features of spontaneous uterine contraction n = 1, 2, 3, ...;
- $C_{pl}(t)$, plasma concentration of exogenous oxytocin at time t, corresponding to the start of uterine contraction n.

model parameters:

- F_{max}, A_{max}, D_{max}, value of the uterine contraction waveform feature at maximum drug effect;
- FC_{50}, AC_{50}, DC_{50}, concentrations associated with 50% of maximum effect in each contraction waveform feature (at any given spontaneous activity);
- γ, curve slope, for now, assumed identical for all three features.

and output variables:

- *Freq(n), Amp(n), Dur(n), RT(n)*, waveform feature of uterine contraction n

From equations (5.1)-(5.3) it is clear that if no oxytocin is being administered (*Cpl(t) = 0*), the pharmacodynamics model will not modify the spontaneous uterine activity features, i.e.:

$Freq(n) = Freq_{Spon}(n)$,
$Amp(n) = Amp_{Spon}(n)$,
$Dur(n) = Dur_{Spon}(n)$.

5.2.2 Parameter estimation

The model parameters are F_{max}, A_{max}, D_{max}, FC_{50}, AC_{50}, DC_{50} and γ. To estimate the parameter values, different methods were used. This section is subdivided in two subsections. The first one presents the estimation of parameters reflecting maximal oxytocin effect (F_{max}, A_{max}, D_{max}). The second subsection describes the methods used to estimate the sensitivity parameters (FC_{50}, AC_{50}, DC_{50}) and curve slope (γ).

5.2.2.1 F_{max}, A_{max}, D_{max}

The parameters F_{max}, A_{max}, D_{max} can be interpreted as the uterus' limit to contract. In other words, it is expected that – for a general population – the intrauterine pressure signal will not exhibit a frequency of contractions above F_{max}, contractions intensity higher than A_{max}, and duration of contractions higher than D_{max}. These parameters were estimated based on real tracings of intrauterine pressure with hyperactivity and completed by expert opinion, considering the simulation engine requirements described in Chapter 3.

A_{max} was set to the upper limit of the monitoring scale - 100 mmHg - also the limit to intrauterine pressure in available tracings. F_{max} was set to the highest frequency observed in clinical practice by a clinical expert: approximately 7 contractions per 10 minutes. Figure 5.2 depicts a 10-minute section of a real tracing of intrauterine pressure presenting 7 contractions.

D_{max} was set to the maximum duration expected in the relevant clinical phases established in Chapter 3. Note, that in some cases contractions can last as much as 7 minutes. Simulation of these patterns is currently not part of model requirements. Therefore, taking into account the objectives of this work, the maximum duration was

taken from the clinical phases: Normal contractions and Hyperactivity: 1.5 minutes. In the future D_{max} may be changed to include other contraction patterns.

Summarizing, the parameters values are:

- F_{max} = 7 contractions per 10 min;
- A_{max} = 100 mmHg;
- D_{max} = 1.5 min.

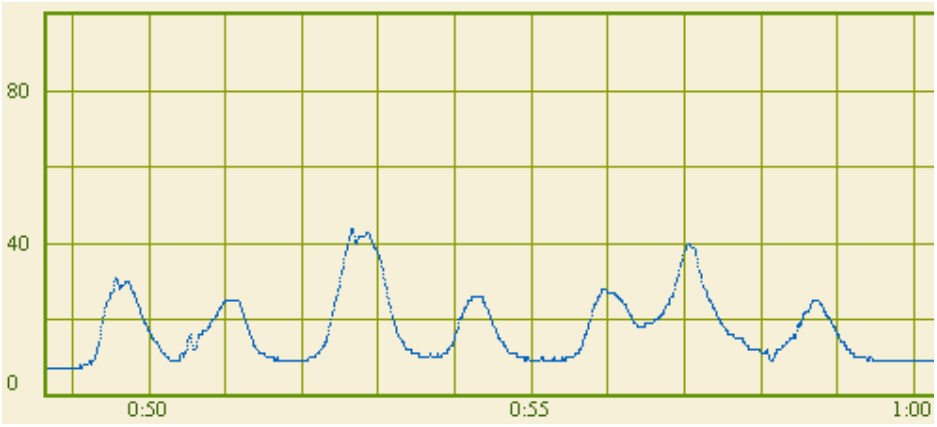

Figure 5.2: Section of a real tracing of intrauterine pressure: the 10-minute section presents 7 contractions.

5.2.2.2 FC_{50}, AC_{50}, DC_{50} and γ

Data from Crall *et al.* (Cra91) were used to estimate the parameters FC_{50}, AC_{50}, DC_{50} and γ, using nonlinear least-squares regression. In this study the authors evaluated the uterine response to fixed doses of oxytocin (1-3 mU/min) over long infusion periods in 10 patients with secondary arrest of dilation. The uterine activity was measured in Alexandria units and averaged in intervals of 60 minutes, if possible. Table 5.1 presents the average results from the 10 patients.

Table 5.1: Oxytocin dependent uterine activity in Alexandria units for a 10-patient population (Cra91), Mean ± SD.

	Oxytocin infusion rate (mU/min)		
	0	1	2
Alexandria Units	132 ± 61	199 ± 64	240 ± 64

We used a least-squares optimization method, which solves a problem in the following form:

$$\text{Min } \underset{x}{sum}(f(x)^2) \tag{5.5}$$

In our case *f(x)* is:

$$f(AC_{50}, FC_{50}, DC_{50}, \gamma) = AU_{Cra} - AU_{Sim} \tag{5.6}$$

With:

- AU_{Cra}, data from Cra91 in Alexandria units;
- AU_{Sim}, simulated Alexandria units following the baseline and dosages described in Cra91.

Although the uterine contraction features are not explicit in eq. 5.6, the Alexandria units result from a known combination of uterine contraction waveform features (see section 2.3.1).

The algorithm is iterative, starting with an initial set of values for the parameters to be estimated. This initial set has to be chosen carefully, because it will determine if the results will converge to a valid solution. We point to the literature for a detailed description of the used nonlinear least-square algorithm (Lev44, Mar63).

The estimated parameters for the population average are:

- FC_{50} = 18.5 µg/ml
- AC_{50} = 5.34 µg/ml
- DC_{50} = 5.54 µg/ml
- γ = 0.760

According to the estimated values, the effect of oxytcin on amplitude and duration of contractions will be observed at lower concentrations as compared to the effect of contraction frequency. This means that after infusion of oxytocin, the first uterine contraction waveform features suffering augmentation are amplitude and duration. Unfortunately, there are no published clinical data corroborating these observations.

The curve slope (γ) has a relatively small value, which means that even at a very low dose the effect of oxytocin is felt. This seems reasonable for uterine activity (Wiq62). So far, we did not encounter data confirming that the use of a single γ for all features is reasonable. We will come back to this issue in Chapter 7.

We also alert to the fact that the estimated DC_{50} remained equal to the initial value, and this for a number of initial values. This can possibly be attributed to the fact that the baseline duration is close to D_{max}, making the objective function of the optimization problem (in Alexandria units) insensitive to duration.

5.2.3 Model verification

In order to evaluate the parameter estimation, we check if the resulting values can simulate the data the estimation was based on. This procedure is called model verification (as opposed to *validation* with independent data). Figure 5.3 illustrates the performance of the model in simulating an average patient of the population from Crall *et al*. (Cra91). The green open circles together with the black lines represent the population average and standard deviation described in Table 5.1. The blue asterisks represent the simulation results. Via graphical inspection we verify that the model with the estimated parameters can simulate the data used for estimation.

As Bidgood and Steer observe (Bid87b), the range of responses within dose groups is much larger than the differences between dose groups. This supports the hypothesis that the sensitivity of the uterus is the most important factor in the response to oxytocin stimulation. Therefore, to simulate different patients, the sensitivity parameters (FC_{50}, AC_{50}, DC_{50}) are adjustable.

In the next chapter we present several simulation results that test not only the oxytocin pharmacokinetic-pharmacodynamic model, but also its integration with the spontaneous uterine activity engine, as well as the capability of the combined models to simulate a wide range of patients.

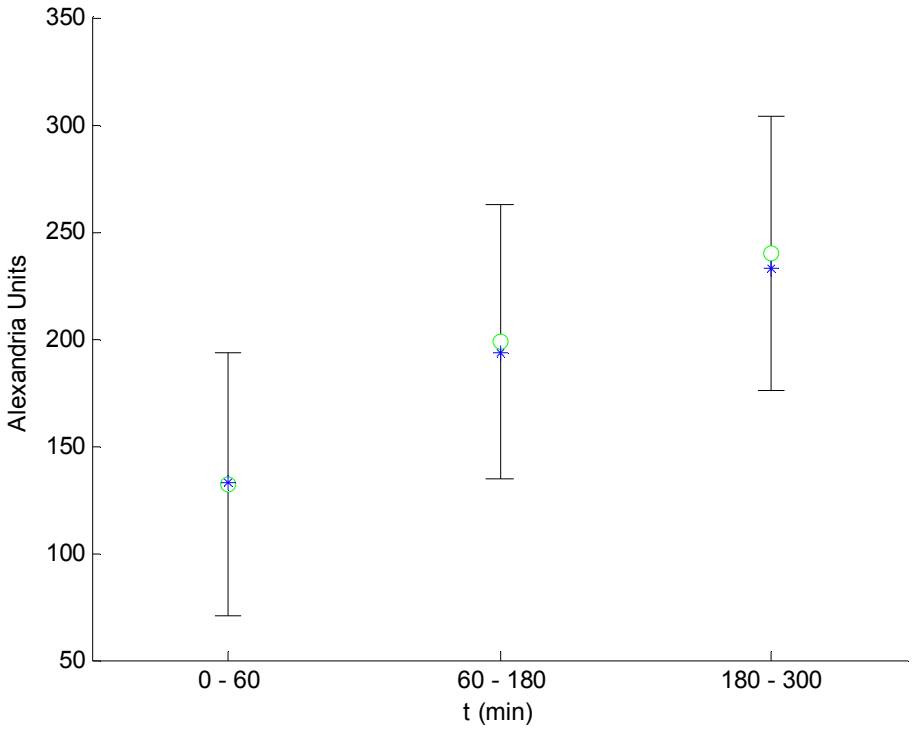

Figure 5.3: Mean (o) ± SD (–) Alexandria units from Crall et al. (Cra91) and simulation results(*).

6. Results

Referring to Chapter 3 and the introductory section of Chapter 5, the requirements of the uterine activity model include correct representation of evolution of uterine activity from the beginning of labor until delivery of the fetus, as well as adequate responses to the administration of pharmacologic agents that augment uterine contractility. The simulated signals and responses should be realistic and the model should be able to reflect multiple patients. The presentation of results in this chapter was structured in order to illustrate the realism of the output signal ($I_{up}(t)$) for both spontaneous and augmented labor, and to demonstrate manipulation of model parameters to reflect different patients. We hope to show that the simulated intrauterine pressure signals are realistic enough for educational simulation of various patients and clinical situations. Different simulations are obtained with different scripts, or by adjusting oxytocin sensitivity parameters.

The chapter is divided in four sections. The first section focuses on spontaneous uterine activity, while the second and third sections focus on the uterine response to oxytocin administration. In these first three sections, simulated contraction patterns are compared to published target data. In the fourth section we present a pilot study in which independent clinical experts evaluated selected simulated tracings. This small, relatively subjective evaluation is presented as a step towards further model validation.

Each simulated tracing is depicted in one or more 40-minute strips, where 5-minute periods are represented with bold green vertical lines and 1-minute periods are represented within thin lines. Tracings depict only those segments considered necessary and sufficient for evaluation of a given clinical situation. Time in minutes is shown on the left side of each strip, as well as on the horizontal axis. In some tracings the symbol "|…|" marks time elapsed between strips.

6.1 Spontaneous evolution of labor

Although spontaneous evolution of labor was a simulation engine feature developed and validated previously, it is important to present it in this chapter because its implementation is crucial for the response to oxytocin.

Taking into consideration the main scope of this work (see section 3.2.1), the spontaneous uterine activity patterns presented in this section are: normal

contractions from the latent phase until second stage of labor, and hypotonic contractions.

6.1.1 Normal progression of labor

Figure 6.1 shows simulated normal contractions. This simulation was obtained using the developed model without drug administration (OT(t) = 0) and script name ”normal” (see section 3.4 for a detailed description of data underlying this script). The figure represents segments from the entire course of labor from beginning (minute 0) until delivery (minute 600). The different phases/stages of labor are marked with different colors.

We verify that average uterine contractions waveform features reflect target data in Table 3.2. We observe that uterine activity increases through phases and stages, but transitions between labor phases and stages are too sudden, and could be improved by using scripts with interpolation of waveform features. We will present a more detailed discussion of these and other results in the next chapter.

6.1.2 Hypotonic labor

Figure 6.2 shows simulated spontaneous hypotonic labor. The script prescribes short contractions with low intensity, occurring at a low frequency, and for a prolonged period of time. We again verify that scripted uterine contractions waveform features reflect target data for hypotonic labor (see section 3.4 for a detailed description of data underlying this script).

6.2 Response to oxytocin

In the presence of slow progress of labor, oxytocin is commonly administered to promote labor augmentation. Although uterine activity is the main factor for adequate cervical dilation and an important indicator of slow progress of labor, some patients experience good cervical dilation with low uterine activity. For this reason progress of labor can only be evaluated by regular vaginal examination.

(0-40)

(340-380)

(520-560)

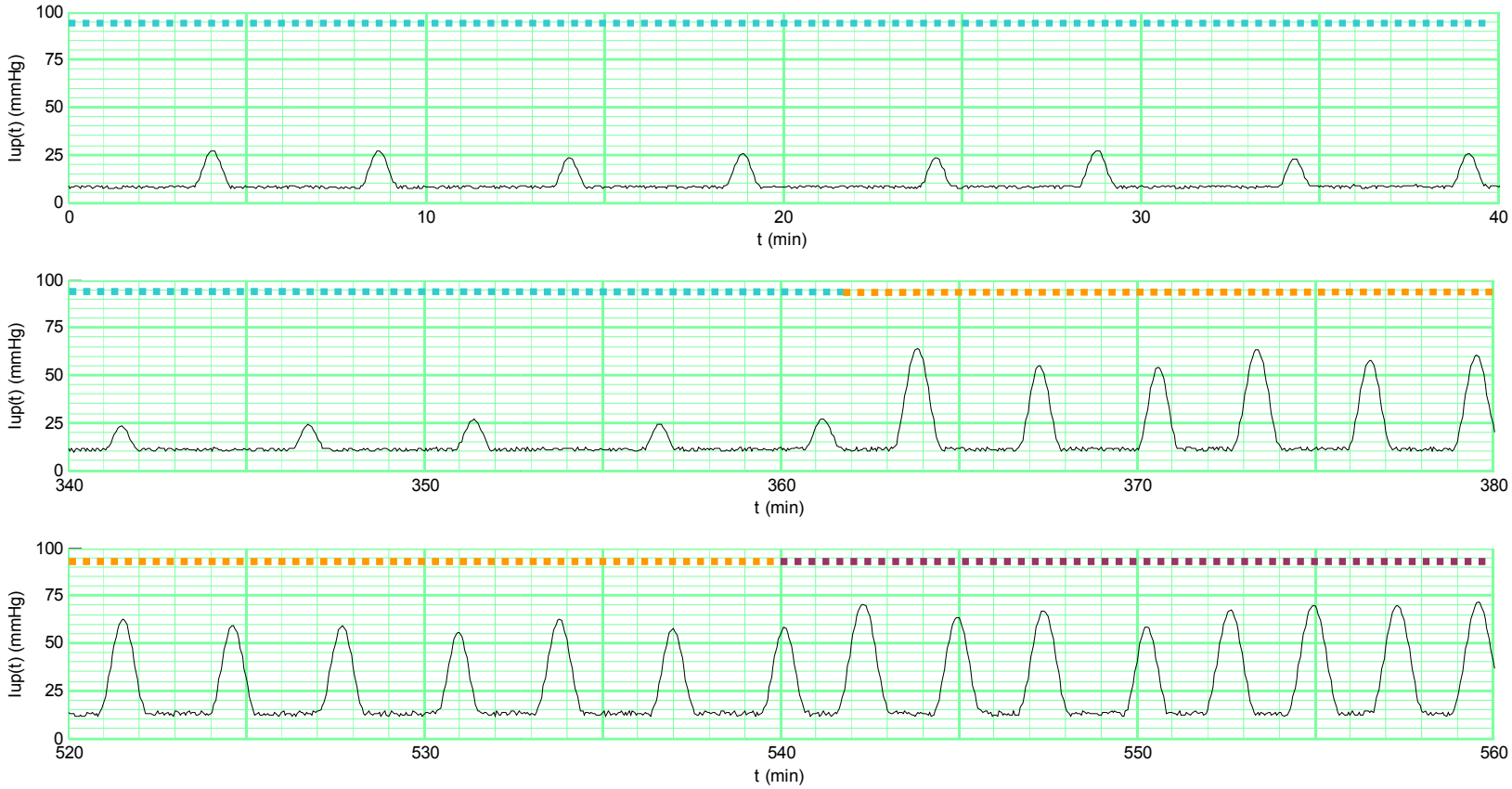

Figure: 6.1 Simulated spontaneous labor with normal progression: (-) latent phase; (-) active phase; (-) second stage. (Fig. continued on next page)

(560-600)

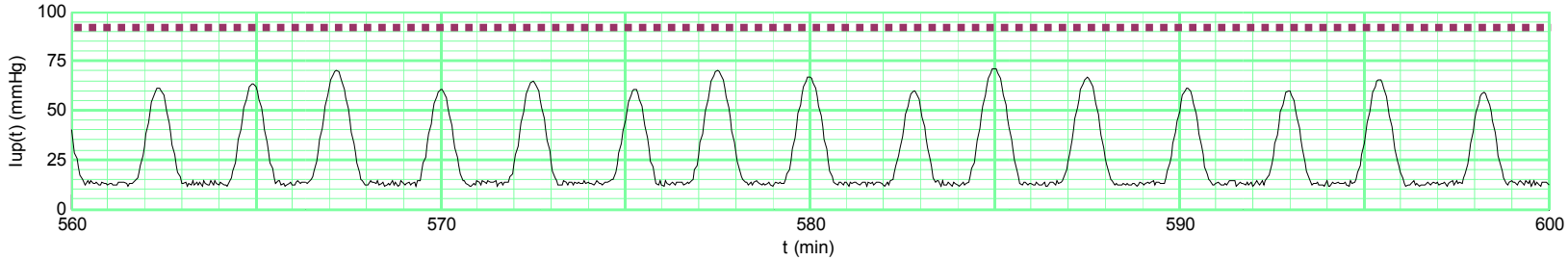

Figure 6.1: Simulated spontaneous labor with normal progression: (-) latent phase; (-) active phase; (-) second stage. (cont.)

(0-600)

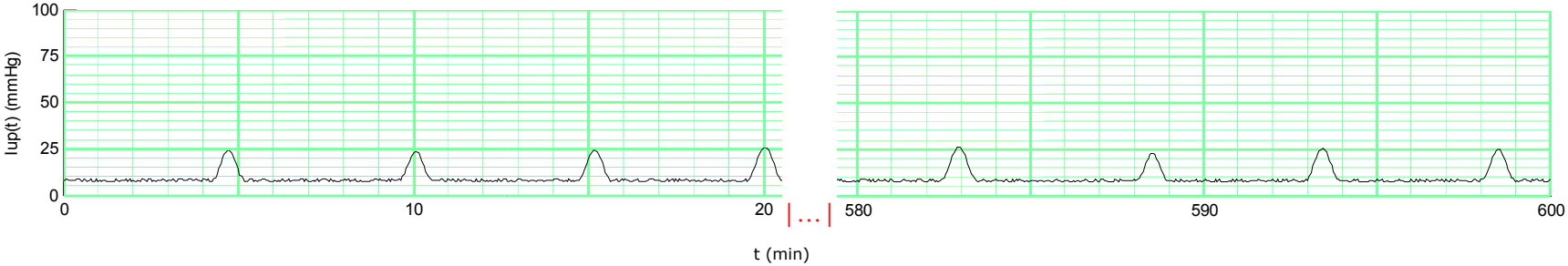

Figure: 6.2 Simulated spontaneous hypotonic labor.

Crall *et al.* (Cra91) presented a study with 10 patients in secondary arrest of dilation, where the responses to fixed doses of oxytocin over long infusion times were recorded. In this section, we simulate several patients from this publication. Since the preprogrammed script for hypotonic contractions failed to describe these patients, new scripts were created to simulate underlying uterine activity (i.e., spontaneous uterine activity observed before oxytocin administration). For each simulated patient, the oxytocin sensitivity parameters AC_{50}, FC_{50}, and DC_{50} were estimated. The parameter estimation procedure was described in the previous chapter. To simulate the responses to oxytocin, the drug administration profiles for each patient were mimicked. These administration profiles had small deviations from the protocol established beforehand (Cra91): A constant infusion rate of 1 mU/min for 110 minutes, followed by a 10 minute pause, and a 2 mU/min infusion rate for another 110 minutes.

The results presented in this section were carefully chosen to allow for verification and validation of different aspects of the uterine activity model. We start with (1) the simulation of a single patient without spontaneous evolution of labor and average drug sensitivity; followed by (2) the simulation of multiple individual patients without spontaneous evolution of labor and with different drug sensitivities.

We believe that assuming constant uterine activity for spontaneous labor without normal evolution may not be adequate for every patient, even with hypotonic labor. However, it is not always possible to separate activity due to spontaneous evolution and to exogenous oxytocin effects. We use constant baseline spontaneous activity for the simulation of several patients from Cra91. For the remaining patients, section 6.3, we consider spontaneous evolution of labor in combination with labor augmentation.

6.2.1 Patient with average drug sensitivity

In Figure 6.3 we present a simulated intrauterine pressure signal for an average patient, from an initial control period (60 minutes prior to oxytocin administration) until delivery. Oxytocin infusion rates are indicated in the figure. Consider the average patient as the population average in the study by Crall *et al.*.

We verified that the simulated tracings reflect the oxytocin effect, as measured in Alexandira units, published by Crall *et al.* In the discussion sections we will come back to the fact that this does not constitute a model validation, as data from the same publication were used to estimate selected model parameters.

6.2.2 Individual patients with different drug sensitivities

Taking into account the educational importance of inter-patient variability, the oxytocin pharmacodynamic model allows for the simulation of different patients by adjusting the sensitivity parameters (AC_{50}, FC_{50}, DC_{50}).

Figure 6.4 presents the simulated intrauterine pressure signal from control period until delivery of the fetus, for a specific patient derived from patient 4 in Crall *et al.*. For the simulation of this patient, the oxytocin pharmacodynamic sensitivity parameters were altered. We verified again that the simulation results correctly reflect uterine activity quantifications presented in Crall *et al.* for this particular patient.

Here we presented simulation results for one specific patient. Note, however, that contraction profiles of 5 out of 10 patients could be reproduced simply by adjusting the oxytocin pharmacodynamic sensitivity parameters AC_{50}, FC_{50}, and DC_{50}. Even to the untrained eye, the tracings for patient 4 differ considerably from the average patient, especially after the 2mU/min infusion starts. The fact that the model can reproduce such educationally relevant distinct cases with relatively simple parameter adjustments constitutes the most important result of this section. In the following section we suggest another procedure to simulate the remaining patients.

6.3 Combined spontaneous evolution of labor and response to oxytocin

In previous chapters we discussed that the effect of oxytocin depends on (1) the amount of oxytocin being administered, (2) uterine sensitivity to oxytocin, and (3) underlying uterine activity (Bid87).

In this section we present simulated intrauterine pressure signals that undergo spontaneous evolution under labor augmentation with oxytocin. This is illustrated via the simulation of a patient from (Cra91) - patient 1 - that showed an atypical response to oxytocin.

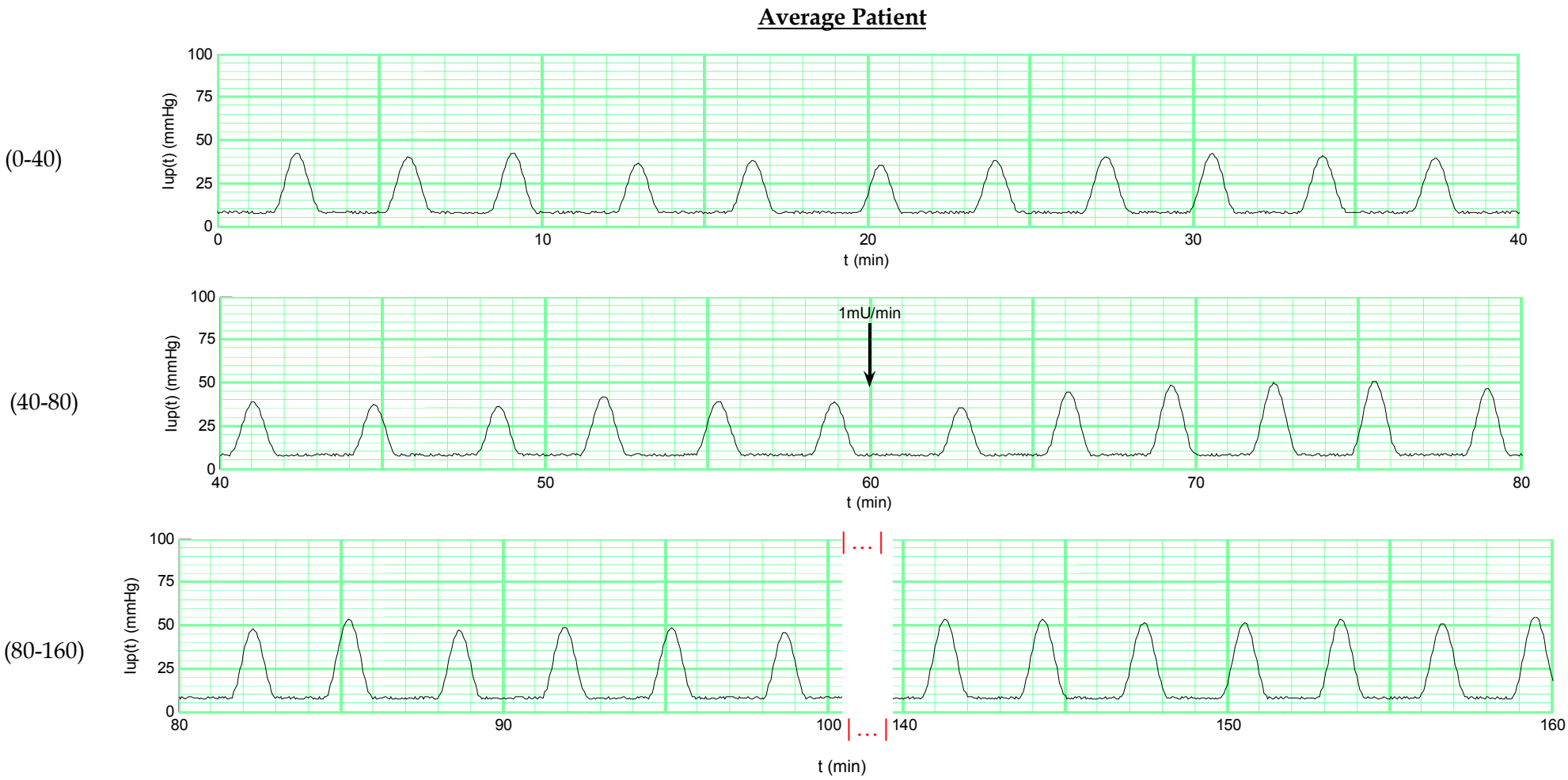

Figure 6.3: Simulated intrauterine pressure response to oxytocin for an average patient derived from the average population of Crall *et al.*.(Fig. continued on next page)

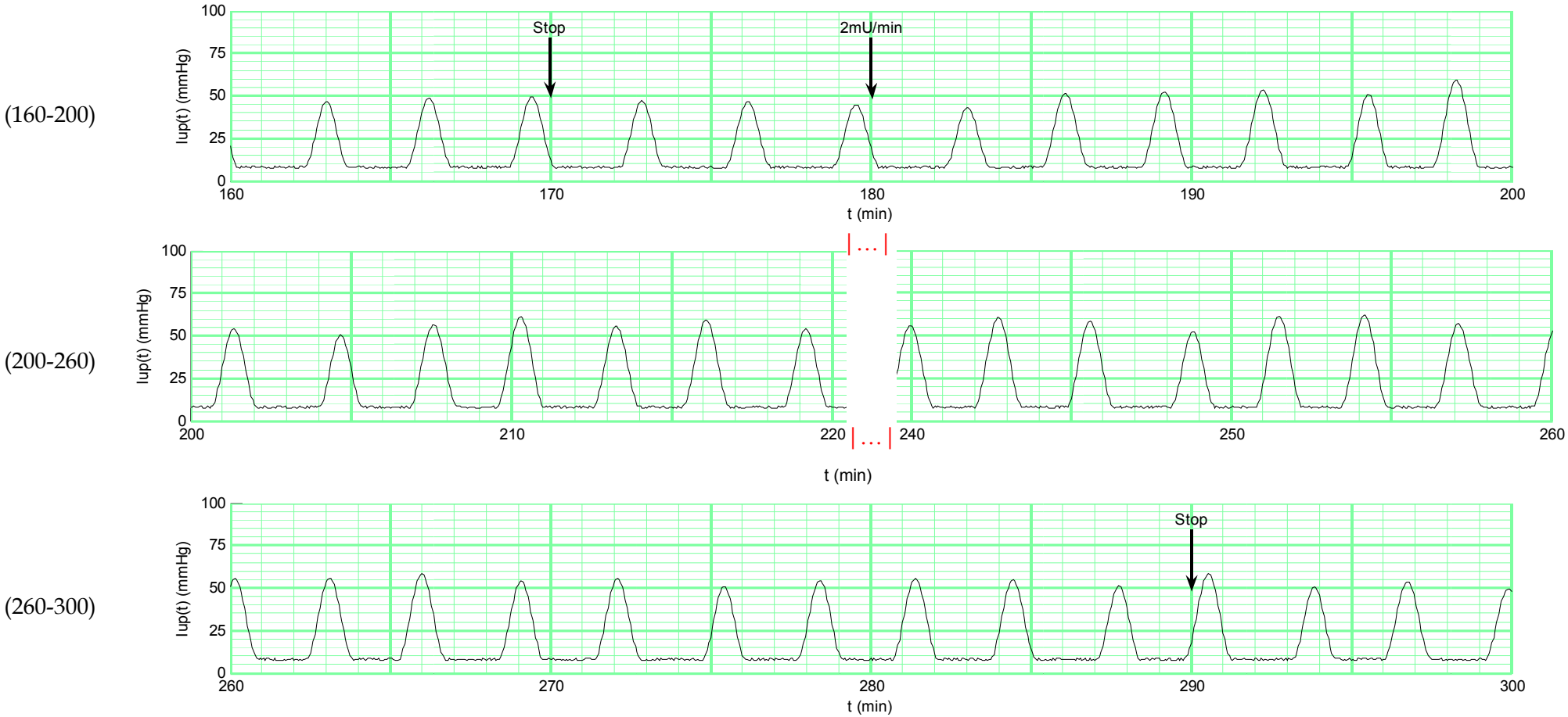

Figure 6.3: Simulated intrauterine pressure response to oxytocin for an average patient derived from the average population of Crall *et al.*. (cont.)

Patient No 4

(0-40)

(40-80)

(80-160)

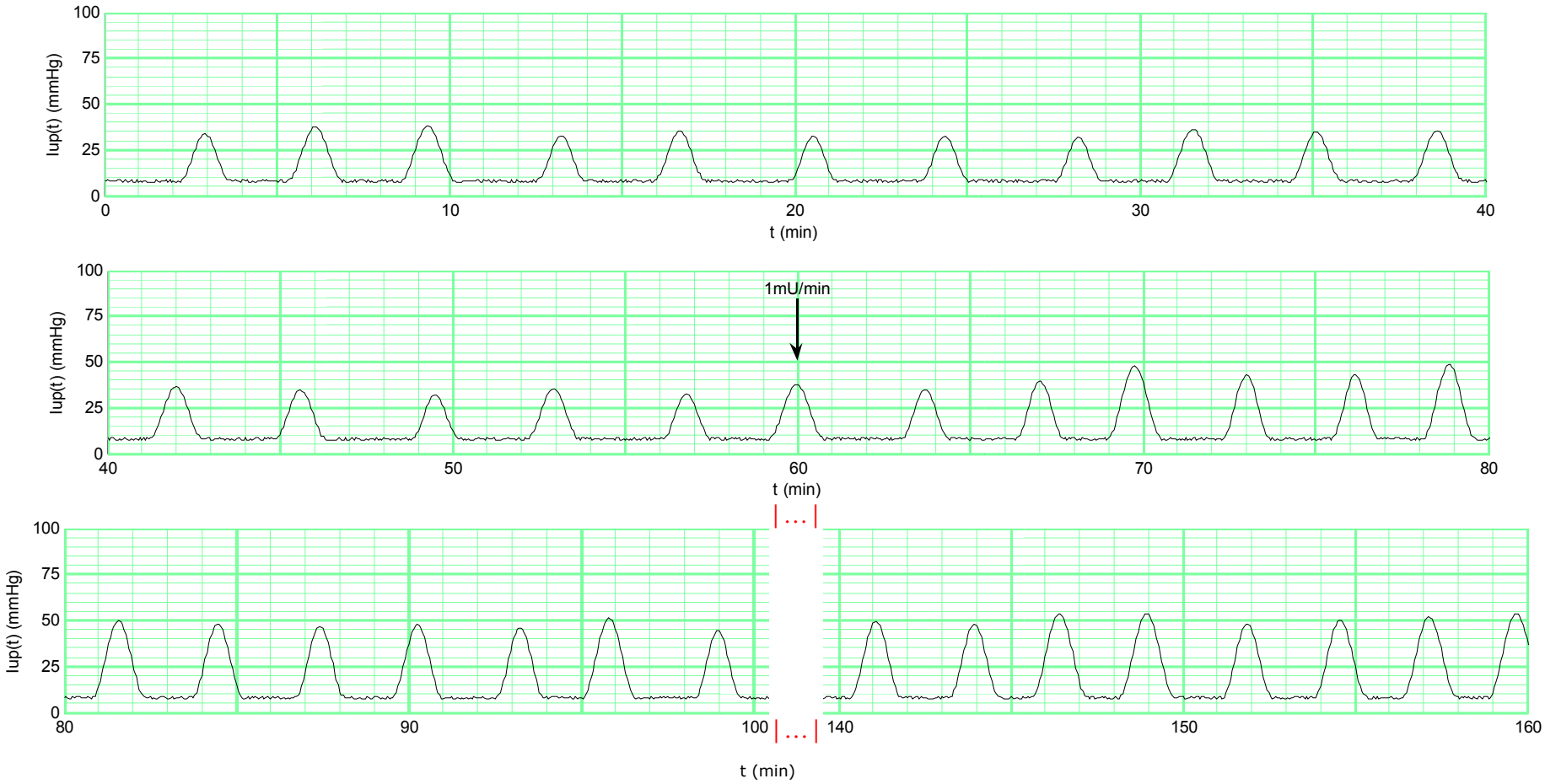

Figure 6.4: Simulated intrauterine pressure response to oxytocin for a patient derived from patient 4 (Cra91). (Fig. continued on next page)

(160-200)

(200-260)

(260-290)

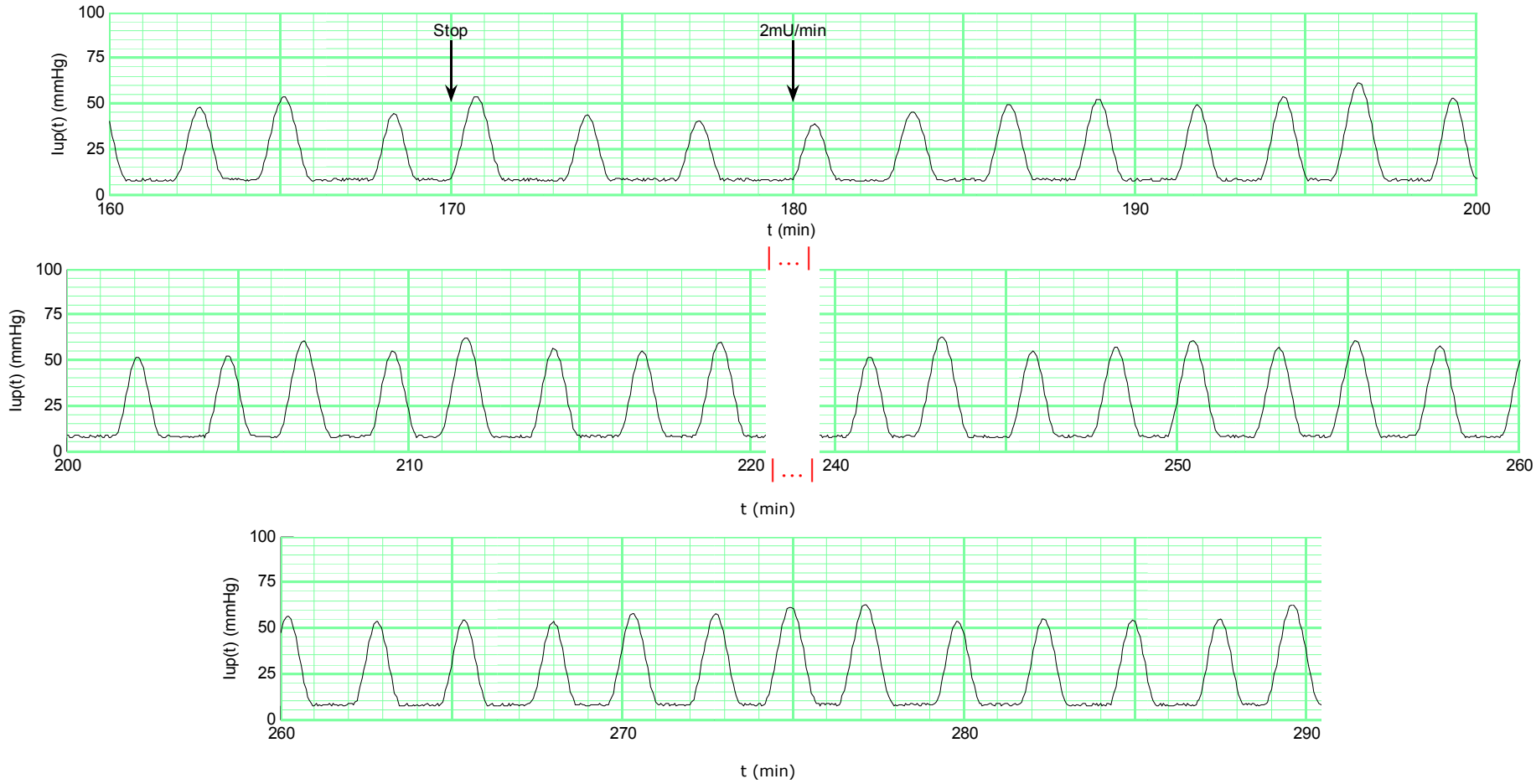

Figure 6.4: Simulated intrauterine pressure response to oxytocin for a patient derived from patient 4 (Cra91). (cont.)

In the population of 10 patients presented in Crall *et al.*, 5 patients showed at some point in time a decrease in uterine activity while oxytocin was being administered. Therefore we allowed scripts to show an evolution of uterine activity consistent with this behavior. This procedure began with establishing a first provisory script followed by estimation of oxytocin pharmacodynamic sensitivity parameters (AC_{50}, FC_{50}, DC_{50}). If the simulation results didn't verify the published data, an improved script was created until verification was successful.

In Figure 6.5 we present the simulated intrauterine pressure signal, based on data for patient 1 from Crall *et al.* (Cra91). Figure 6.6 provides quantification of the signal in Figure 6.5 in Alexandria units. The red line shows the simulated underlying spontaneous uterine activity, the black line the simulated response to exogenous oxytocin, and the blue line the combined spontaneous evolution and the response to labor augmentation with oxytocin, including variability. The simulated results are in accordance with the published data for patient 1.

In the previous section we showed that adjusting the oxytocin pharmacodynamic sensitivity parameters was sufficient to simulate five out of ten patients of the population in (Cra91). Using the script engine to reflect assumed underlying spontaneous evolution of uterine activity under labor augmentation, we were able to simulate the remaining five patients.

We used the same source for parameter estimation and verification of simulation results (Cra91). We need an independent source to validate our results. Since we did not find independent published target data to validate the model output in terms of its morphology and evolution and variability of features, we designed a pilot study to obtain clinical expert opinion about the simulated signals. This study and its results are presented in the next section.

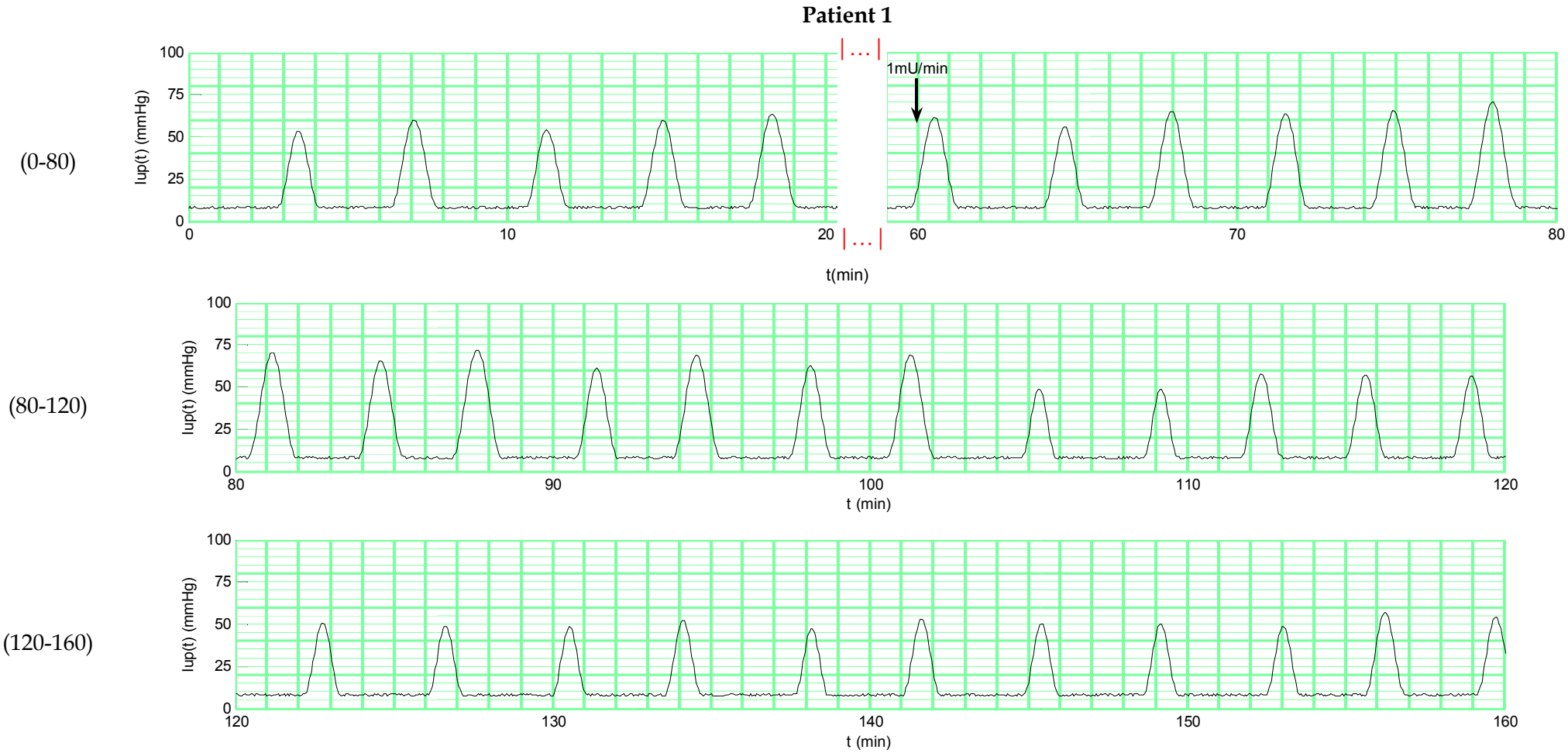

Figure 6.5: Simulated intrauterine pressure response to oxytocin for a patient derived from patient 1 (Cra91). (Fig. continued on next page)

(160-200)

(200-280)

(280-330)

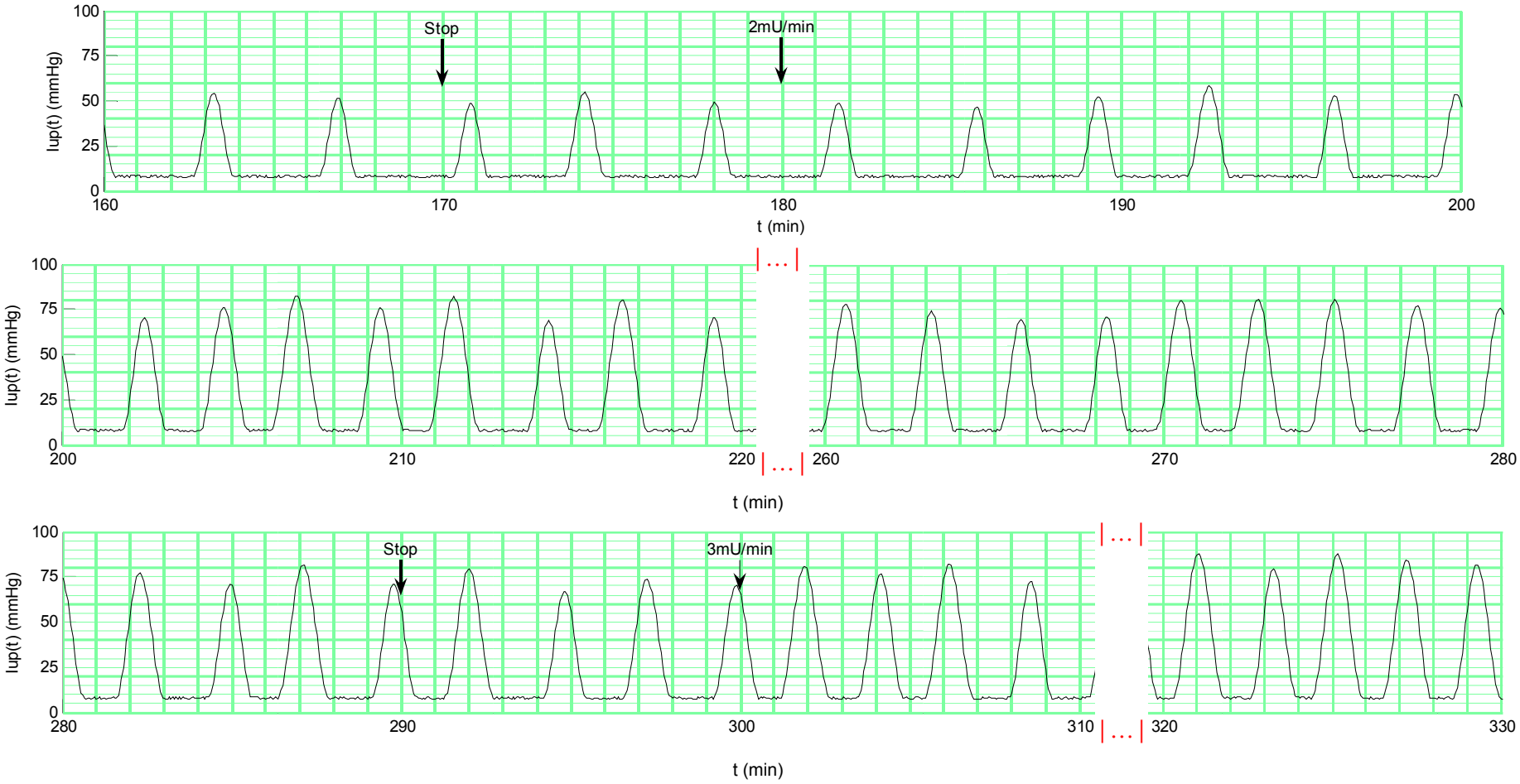

Figure 6.5: Simulated intrauterine pressure response to oxytocin for a patient derived from patient 1 (Cra91). (cont.)

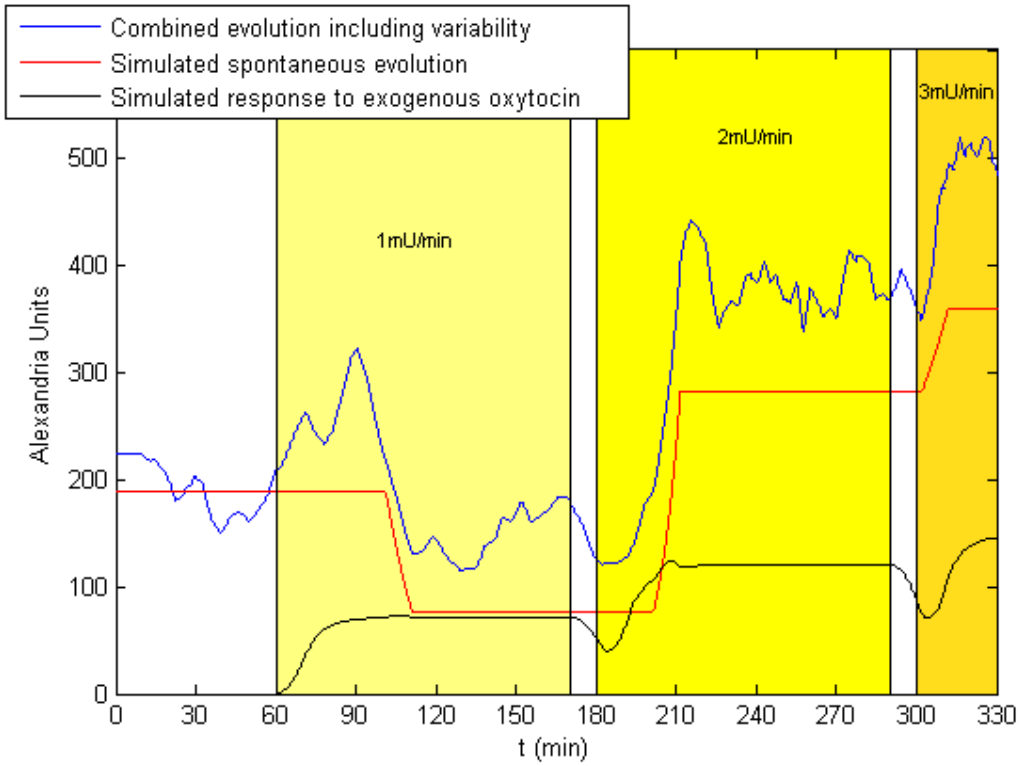

Figure 6.6: Simulated uterine activity in Alexandria Units from a patient derived from patient 1 (Cra91): (-) simulated spontaneous evolution; (-) simulated response to exogenous oxytocin; and (-)combined evolution including variability. White bands represent periods were no oxytocin was administered and yellow bands with different shades represent periods were oxytocin was administered at different dose rates (1, 2 and 3mU/min).

6.4 Clinical expert evaluation

We established a questionnaire for clinical experts to evaluate the realism of the simulated intrauterine pressure signals. The aspects addressed by this questionnaire were (1) realism of the uterine contraction waveform morphology; (2) realism of the evolving uterine contraction waveform features (amplitude, frequency, duration and resting tone); and (3) overall realism, using a scale from 1 to 4 (1-unrealistic, 2-substantial differences from real tracings, 3-negligible differences from real tracings, 4-cannot be distinguished from real tracings). The clinicians participating in this study were also encouraged to provide additional comments on the simulated tracings and explain their classification. In this section we present the answers of two independent clinical experts (see appendix 3 for the questionnaire and classifications).

When presented with Figure 6.1, the two clinicians had somewhat diverging opinions on overall realism of the simulated intrauterine pressure signal during the latent phase of labor (classifications 2 and 3). In the active phase, the tracing was

classified as 3 and 4, respectively. In the second stage both experts classified the tracing as 2, mainly due to the morphology of contractions. The transitions between phases and stages were classified as 1 and 2. Additional comments to these tracing highlighted (1) the unnatural regularity of the latent phase and (2) the sudden changes between phases and stages.

Figure 6.2 again obtained the somewhat diverging classifications 2 and 3, with a similar comment on the regularity of the uterine contractions for classification 2, and its apparent realism for classification 3.

The third tracing included in the questionnaire presented the same oxytocin administration profile and sensitivity parameters used for the simulation in Figure 6.3, but the underlying spontaneous uterine activity was as in Figure 6.2. The objective of this figure was to evaluate the transition from a hypotonic pattern to normal contractions, using the same administration protocol of the other simulations (see Figure 6.3). In general, features and morphology were classified as 3. However, frequency and duration were classified as 2 by one of the experts, and as 4 by the other. The overall realism was classified as 2 and 3, respectively.

In Figure 6.5, almost every aspect of the tracing was classified as 2 or 3. The additional comments point out the low variability of amplitude, duration and morphology of contractions, especially with higher levels of uterine activity.

We will present a more detailed discussion of these results in the next chapter.

7. Discussion, conclusions, future work

In this thesis we provide a critical evaluation of existing models for the simulation of drug dependent uterine contraction signals and propose an original simulation engine for educational simulation of spontaneous and augmented labor. Model requirements, specifically established for educational simulation of intra-partum acute care, guided evaluation and developement.

In this chapter we return to the model requirements (Chapter 3) and results (Chapter 6) to (1) discuss to what extent the proposed model meets the requirements, and (2) evaluate the realism of the simulated signals. For the latter, two methods were used: (1) an objective evaluation comparing simulation results with published data; and (2) a more subjective evaluation consisting of the opinion of two independent domain experts answering a structured questionnaire.

This chapter is divided into four sections. In the first and second we discuss the simulation results for spontaneous and augmented labor. In the third section we present our conclusions. In the fourth section we present envisioned future work on the uterine activity model.

7.1 Educational simulation of spontaneous labor

The results presented in Figures 6.1 and 6.2 show that the developed simulation engine is able to simulate spontaneous labor with a normal progression and spontaneous hypotonic labor, respectively.

For the simulation of these results we used a previously developed spontaneous uterine activity engine with several preprogrammed scripts. This approach allows for the incorporation of new scripts, depending on educational needs. Scripts define the evolution of the uterine contraction waveform features: Amplitude, frequency, duration, and resting tone – familiar concepts to the health care provider in obstetrics.

We verified that the preprogrammed scripts fulfill the model requirements, allowing for simulation of all specified clinical phases. The spontaneous uterine activity target data presented in Chapter 3, only provided mean (and sometimes range) of a subset of the uterine contraction waveform features or were presented in Alexandria units, Montevideo units, or as a uterine activity integral. Even though these global measures are important to characterize the uterine contractions signal, they do not

characterize shorter-time signal evolution, feature variability, and morphology of the signal. The pilot clinical expert study, described in section 6.4, gave us a first indication of the realism of the simulated intrauterine pressure signals during spontaneous labor with normal and hypotonic contractions – the two clinical phases considered within the scope of this thesis.

The average values of uterine contraction waveform features were scripted based on published data. In the pilot clinical expert evaluation study, the variability of signal features (especially during the latent phase of labor or hypotonic labor) and morphology (especially during the second stage of labor) were considered to be substantially different from real tracings. This should be improved in a future version of the simulation engine. It may be possible to obtain variability estimates from analysis of real intrauterine pressure signals, or by empirically tuning corresponding model parameters with the help of domain experts.

7.2 Educational simulation of labor augmentation and patient variability

Labor augmentation with oxytocin is an important and common procedure. Oxytocin administration and careful monitoring of the uterine contractions signal are two important aspects addressed in educational simulation of labor augmentation. Therefore, the developed uterine activity engine was expanded with a pharmacologic model describing the transport and effect of oxytocin.

The pharmacologic model is divided into a pharmacokinetic model that describes the drug distribution in, and elimination from, the body, and a pharmacodynamic model that describes the effect of the drug on the uterine contraction waveform features. The pharmacokinetic model was previously developed at INEB. It consists of a traditional compartmental model, with parameter values established based on literature data.

In our opinion, one of the two main contributions of the presented work consists of an oxytocin pharmacodynamic model. To our knowledge, this is the first mathematical model that describes the effect of oxytocin on uterine contraction waveform features. Other attempts to modeling oxytocin pharmacodynamcis were published in the literature. Multiple aspects make this a challenging task:

- ethics of studies in pregnant women;

- multiple mechanisms of regulation of uterine activity – many of them still under research;
- endogenous production of oxytocin, not all of which can be detected in blood plasma;
- physiologic changes during pregnancy, especially at term.

Our approach overcomes part of these difficulties by taking into account evolving underlying spontaneous uterine activity and inter-individual variability in sensitivity to the drug.

In order to narrow the number of parameters to estimate we have considered only one parameter for three different curve slopes. There is no evidence that oxytocin will affect all three uterine activity waveform features according to the same curve slope. For this reason, in further developments of the pharmacodynamic model, we will consider three different curve slopes, γ_A, γ_D, γ_F, instead of one, γ.

In our opinion, the second main contribution of the presented work consists of the structure of the uterine activity simulation engine, which combines script-driven prescription of spontaneous uterine waveform features with mathematical models of oxytocin pharmacokinetics and pharmadodynamics, and an empirical waveform generator. The result of this combination is illustrated in Figure 6.5 with the simulation of a patient derived from (Cra91). This structure allows for the simulation of multiple scenarios and patients, thus meeting an essential requirement for educational simulation in general and of labor augmentation in particular.

Using the developed uterine activity simulation engine, we were able to simulate the responses to oxytocin of a population of 10 patients from a published study. We verified that simulation results correctly reflect published global signal quantifiers. As the same data were used to estimate model parameters, this verification does not constitute a true validation. To expand the validation of our model, we designed a pilot study to obtain expert opinions about the simulated signal and responses to oxytocin administration. The results presented in the previous chapter show some divergence of opinions between the two experts participating in this study (see appendix 3 for clinical experts' classifications). The open comments state a favorable opinion on the simulated effect of oxytocin, especially on the response to 2mU/min of oxytocin presented in Figure 6.5. Challenges for expert validation studies include: Inter-patient variability, differences in protocols between institutions, and inter-observer variability.

In this study we choose to focus on inter-patient variability and on the clinical expert validation, and did not further explore model validation using target data presented in Table 3.5..

7.3 Conclusions

Like other areas of acute care medicine, patient safety during labor and delivery could benefit from simulation-based training using realistic full-body, model-driven educational simulators. In the work presented here:

- We formulated requirements for a uterine activity simulation engine, explicitly referring to the envisioned educational application.
- Elaborating on previous work, we present an original simulation engine, which combines script-driven evolution of spontaneous uterine waveform features with mathematical models of oxytocin pharmacokinetics and pharmacodynamics, and an empirical waveform generator.
- Referring to the general goals set in the introductory section to Chapter 5 and the results presented in Chapter 6 and discussed in this chapter, we verified that this engine is able to:
    - reproduce various uterine contraction patterns associated with spontaneous evolution of labor,
    - represent the response of an average patient to oxytocin, and
    - match patient variability by adjusting a limited number of pharmacodynamic parameters or by combining such adjustments with patient specific scripts for spontaneous evolution of labor.

Full validation of such an engine is complicated by the scarcity and type of available target data. For this reason, we expanded our analysis with a pilot expert validation study, with the preliminary conclusions that:

- Many features of the simulated waveforms were considered to have negligible differences from real tracings, and are therefore acceptable to be used in educational simulations, but
- Specific features, including waveform variability and simulation of transitions between phases and stages should be improved.

7.4 Future work

The developed simulation engine globally meets the specified requirements, but – as pointed out in previous chapters and sections - a number of components and procedures could benefit from a more elaborate analysis in the future.

Scripted spontaneous evolution of uterine contractions

- Modeling and validation of variability in uterine contraction waveform features, using real tracings and clinical expert opinion.
- Smooth transition of simulated waveform features between phases and stages of labor. Presently, only the resting tone has a progressive evolution.

Pharmacokinetic model

- The oxytocin pharmacokinetic model was evaluated as part of the presented work, but a more in-depth study of pharmacokinetic data presented in the literature could shed some light on inter- and intra-patient variability and help choose one or more sets of pharmacokinetic parameters.

Pharmacodynamic model

- A more formal analysis of pharmacodynamic parameter estimation, taking into account all pharmacodynamic parameters and establishing a careful separation of scripted spontaneous and modeled drug dependent evolution of waveform features.
- Modeling of tocolytics.

Uterine contractions waveform generator

- We used a generator for the information rich invasive uterine contractions signal. A generator for a (simpler) externally measured signal still needs to be developed and validated.

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Appendix 1: INEB's related developed work: models description

In this appendix is described with detailed information the uterine activity simulation engine previously developed at INEB. This section is subdivided into three subsections, each concerning the main parts of the uterine activity model: (1) intrauterine pressure generator; (2) script-driven spontaneous uterine activity; and (3) oxytocin pharmacological model.

A1.1 Uterine contractions generator

The uterine contractions generator allows the simulation of intrauterine pressure signals, based on parameters of uterine contractility: amplitude, period, duration, and resting tone (see Figure A1.1).

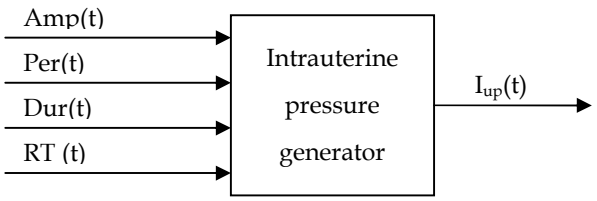

Figure A1.1: Input/output block diagram of the uterine contractions generator. Amp(t) is the contractions amplitude; Per(t) is the period of contractions; Dur(t) is the duration of the contractions; and RT(t) is the resting tone.

The generator models the intrauterine pressure signal using the following equation for each contraction *n*:

$$I_{up}(t) = \begin{cases} RT(t), & t \in [(n-1)\cdot Per(t), n\cdot Per(t) - Dur(t)[\quad \text{(A1.1)} \\ (Amp(t) - RT(t))\sin^2(u(t)) + RT(t), & t \in [n\cdot Per(t) - Dur(t), n\cdot Per(t)[\quad \text{(A1.2)} \end{cases}$$

with

$$u(t) = \frac{t - (n\cdot Per(t) - Dur)}{Dur(t)}\cdot \pi, \quad n \in N$$

Figure A1.2 presents the flow diagram of the previous implementation of the intrauterine pressure generator.

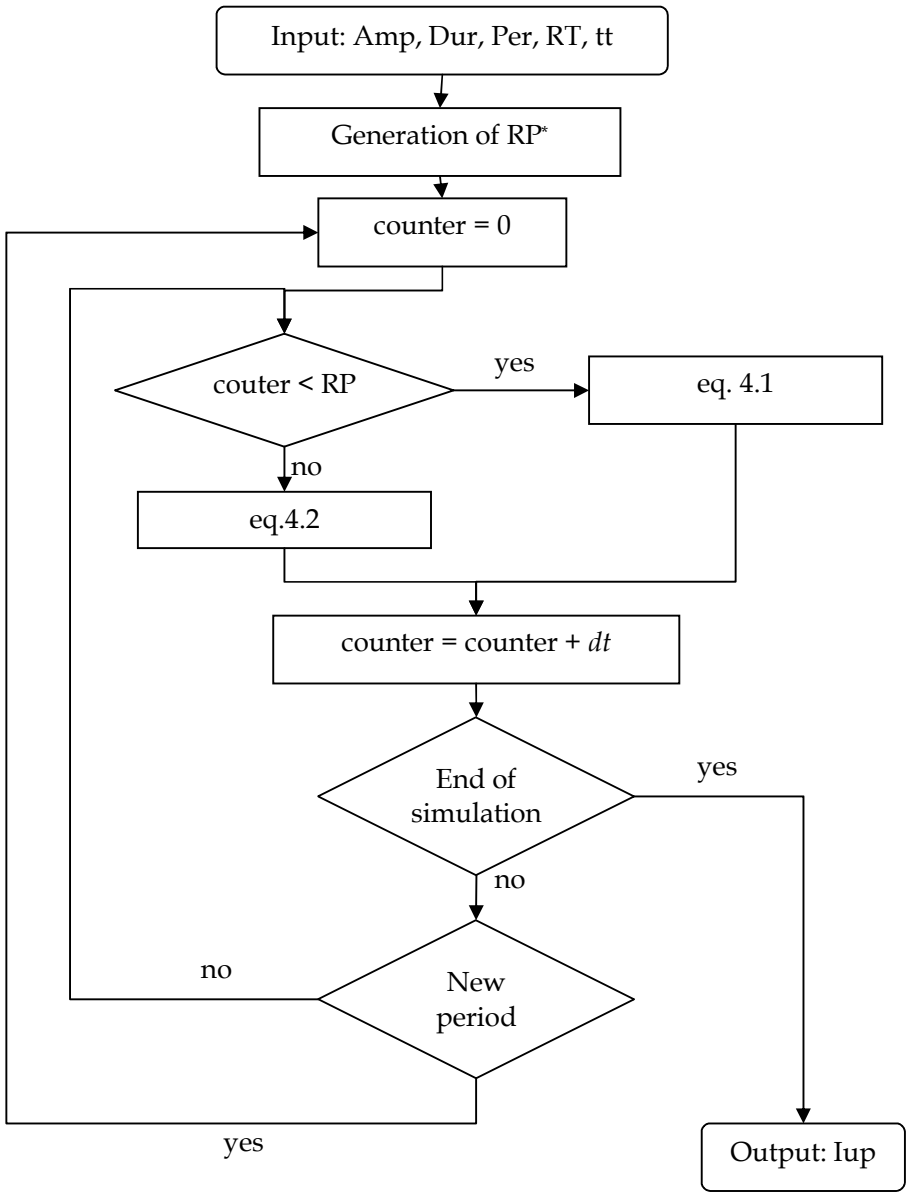

Figure A1.2: Flow diagram of the implementation of the uterine contractions generator. RP stands for resting period which is the recovery time between contractions. For each contraction, the duration of this resting period is Per-Dur.

A1.2 Script-driven spontaneous uterine activity

The scripts included in this model combine the following predefined patterns (see Chapter 3): normal contractions, hypotonic labor, baseline hypertonus, tachysystolic contractions, and hypertonic contractions. These names define the scripts that can be chosen by the user. Depending on the chosen script, the system will generate the time dependent values of the uterine contractility parameters for the first and second stages of labor, as follows:

- Per(t) changes with the phases and stages of labor; during one phase or stage, it remains constant.
- Dur(t) and Amp(t) change each period; for each uterine contraction that arises, the values of these parameters change around a mean value and according to an established standard deviation.
- RT(t) has an intra-phase/stage point to point variability, and it increases between sages and phases.

The pre-established standard deviation and point-to-point variability were settled empirically and validated with expert opinion. Figures A1.3 and A1.4 present the block diagram and the flow diagram, respectively, of the previous implementation of the script-driven spontaneous uterine activity.

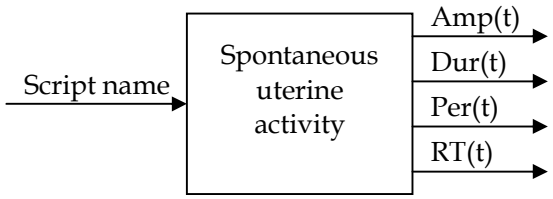

Figure A1.3: Block diagram of the script-driven model of spontaneous intra-partum activity.

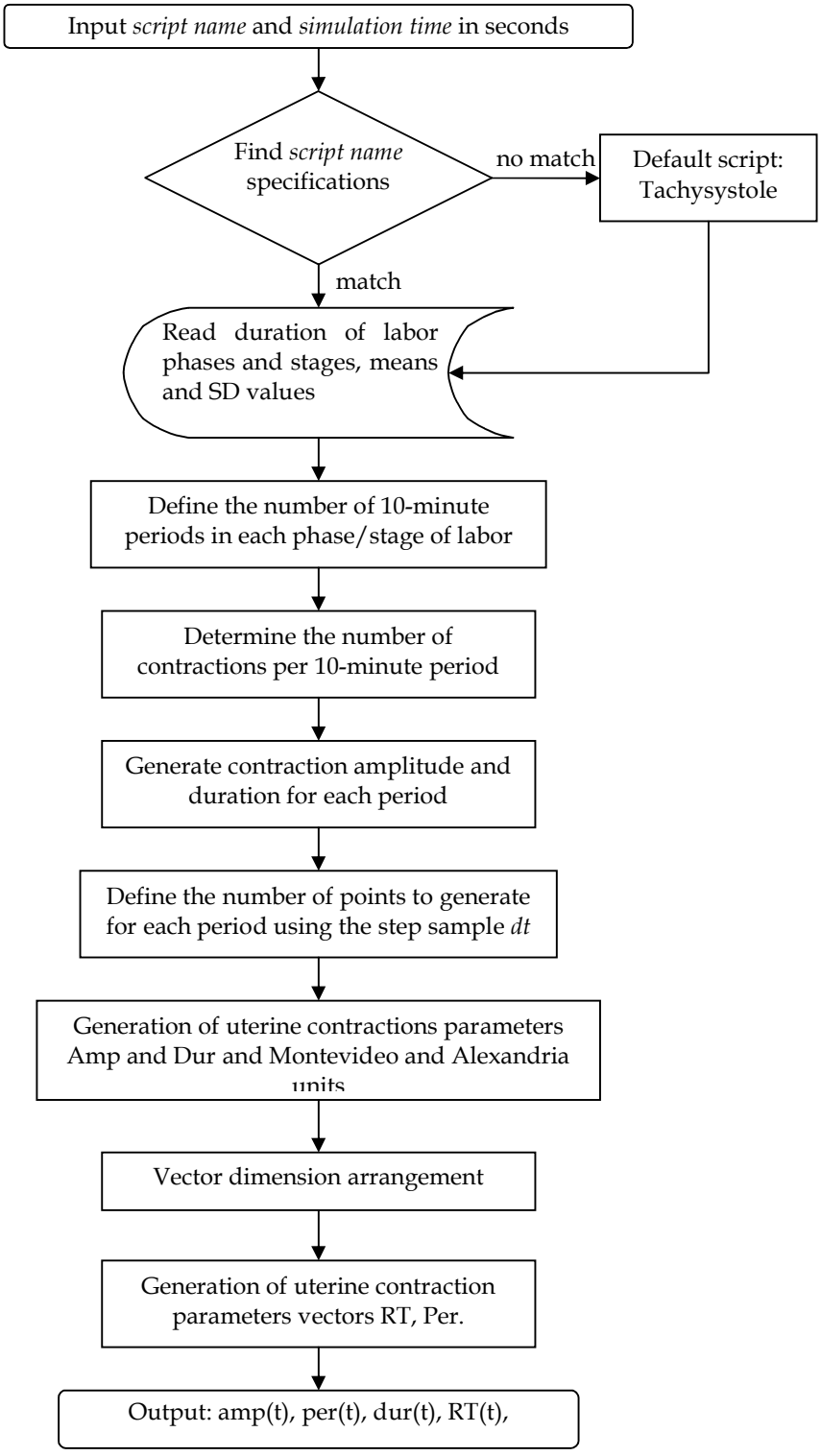

Figure A1.4: Flow diagram of the implementation of the script-driven spontaneous labor.

A1.3 Oxytocin pharmacokinetic-pharmacodynamic model

The oxytocin pharmacokinetic-pharmacodynamic (PK-PD) model simulates the effect of labor augmentation on the uterine activity. The input variables of this model are the infusion rate being administered and the basal uterine activity, in Alexandria Units, observed just before the initiation of the oxytocin administration. The output variables are the uterine contraction features amplitude and period (see Figure A1.5).

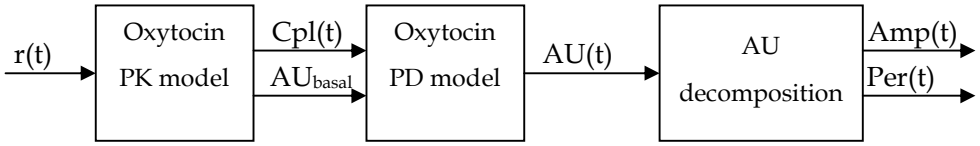

Figure A1.5: Oxytocin PK-PD model block diagram.

The following equations describe the Oxytocin PK-PD model:

Pharmacokinetic model

$$\dot{x}(t) = -\lambda_e x(t) + r(t) \tag{A1.3}$$

$$C_{pl}(t) = \frac{1}{v} \cdot x(t) \tag{A1.4}$$

where:

- $x(t)$ is the oxytocin mass in the blood plasma;
- $C_{pl}(t)$ is the concentration of oxytocin in the blood plasma;
- $r(t)$ is the oxytocin infusion rate;
- λ_e is the disposition rate constant of the drug;
- v is the volume of distribution.

The PK model is derived from one compartmental model, according the pharmacokinetic studies available in the literature (Gon95, Sei83, and Sei84).

Based on the available data from the literature (Sei84), the disposition rate constant (λ) and the volume of the distribution (v) are calculated using the following equations as presented by Gibaldi and Perrier (Gib82):

$$\lambda_e = \frac{\ln 2}{T_{1/2}} = \frac{\ln 2}{5} \tag{A1.5}$$

$$v = \frac{Cl_s}{\lambda_e} \tag{A1.6}$$

From the PK study of Seitchik *et al*. (Sei84), the pharmacokinetic parameters values were collected: oxytocin half-life ($T_{1/2}$) is 5 minutes and clearance rate (Cl_s) is 1247.33

ml/min. Using these two values and equations A1.5 and A1..6, the values of the PK model parameters are:

- $\lambda_e = 0.1386 s^{-1}$
- $v = 8998\ ml$

Pharmacodynamic model

The pharmacodynamic model was derived from data presented by Crall *et al.* This paper reports the response to labor augmentation with oxytcin, in 10 patients with a slow progress of labor. The oxytocin doses were fixed to 1 and 2 mU/min over 110 min.

According to Crall *et al.* (Cra91) the response to oxytocin is a mechanism that depends not only on the concentration of the drug in the blood, but also on the duration of the drug infusion. Actually, they demonstrate that the uterine motility decreases its tolerance to oxytocin concentrations after a long period of infusion. To incorporate these mechanisms in the PD model, the effect was described by two systems of equations (eq. A1.7 and A1.8). The first one describes the relationship between oxytocin plasma concentration and uterine activity quantified in Alexandria units (AU). The second one describes the time dependent tolerance to oxytocin.

$$AU(C_{pl}) = \begin{cases} AU_{base}, & if \quad 0 < C_{pl} < \dfrac{AU_{base} - b(t)}{85.67} \\ 85.67 C_{pl} + b(t), & if \quad \dfrac{AU_{base} - b(t)}{85.67} \le C_{pl} \le \dfrac{AU_{\max} - b(t)}{85.67} \\ AU_{\max}, & if \quad C_{pl} > \dfrac{AU_{\max} - b(t)}{85.67} \end{cases} \tag{A1.7}$$

where:

- AU is the uterine work in Alexandria Units;
- AU_{base} is the observed uterine activity (measured in Alexandria units), immediately before the drug administration;
- AU_{max} is the contractile capacity of the uterus, calculated with the mean maximum values of the uterine activity parameters ($AU_{\max} = 90 mmHg \cdot 7 \cdot 1.42 min = 894.6$);
- *b(t)* reflects the tolerance to long oxytocin infusions, according to the following expression:

$$b(t) = \begin{cases} b_{base}, & t \le 90 \\ -2.838 \cdot t + b_{base} + 255.42, & t > 90 \end{cases} \tag{A1.8}$$

where:

$b_{base} = AU_{base} - 85.67C_{pl\,\min}$, and $C_{pl\,\min}$ is the limit of oxytocin plasma concentration below which no effect is observed $(C_{pl\,\min} = 0.0055)$.

The equations coefficients were derived from the data available in *Crall et al*..

Alexandria units decomposition

Once the output of the Oxytocin PD model is in Alexandria Units, there was the need to "decompose" this measure into the uterine contractility parameters used to simulate the intrauterine pressure signal. As it has been reported that the effect of oxytocin is mainly reflected in the amplitude and the period of contractions, the decomposition of AU was only applied to these parameters. This was achieved by estimating a set of proportions as presented below in equations A1.9 and A1.10.

$$Amp(t) = p_{amp} \cdot AU(t) \quad \text{(A1.9)}$$

$$Freq(t) = p_{freq} \cdot AU(t) \quad \text{(A1.10)}$$

The proportions were calculated considering the normal values in the latent phase of labor.

Figure A1.6 describes the oxytocin PK-PD model implementation.

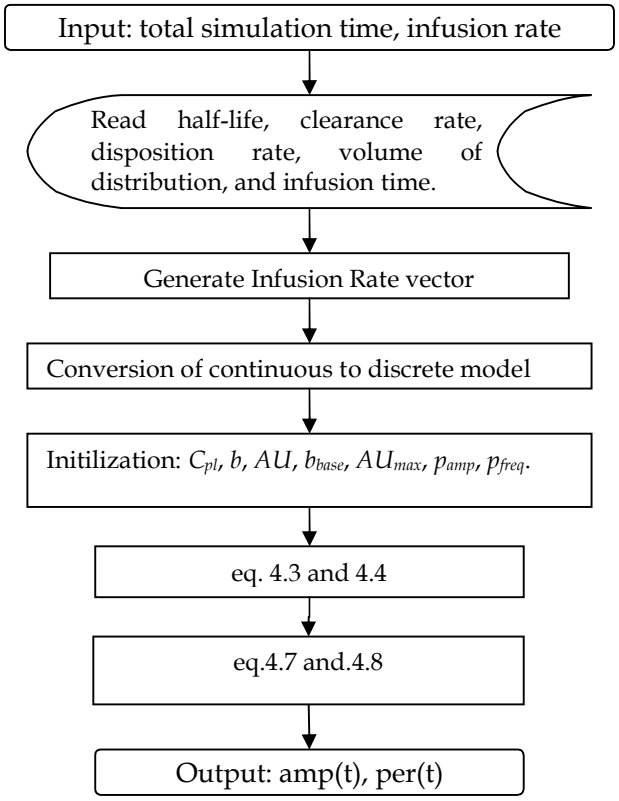

Figure A1.6: Flow diagram of the previously implemented Oxytocin PK-PD model.

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Appendix 2: Results comparison with published data from Crall *et al.*

The content of this appendix is related with the uterine activity model verification. The graphics presented here compare the simulations results of both average and specific patients showed in chapter 6 with the original data from Crall *et al.*

The uterine activity in Alexandria units was averaged for the same intervals described in (Cra91) so that blue dots represent the simulations results, green open circles the mean values the results presented in Crall et al. and black lines are the error boundaries for each interval.

Average patient

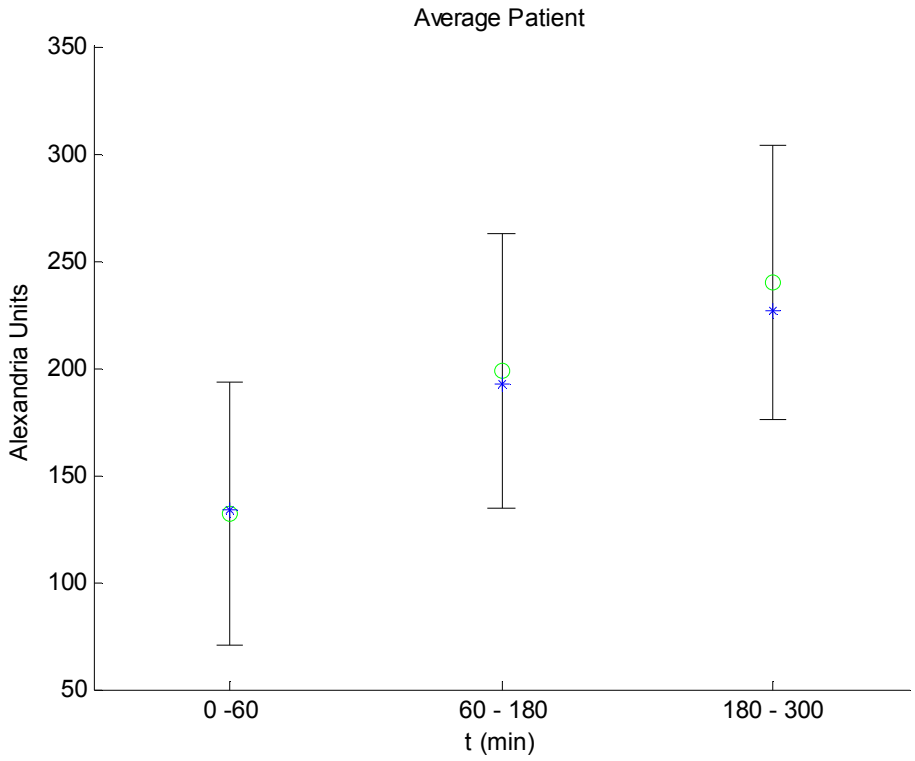

Figure A2.1: Simulation results from average patient (in Alexandria units) averaged in 60-minutes intervals: comparison between simulation (.) results and Cra91 (o).

Patient 4

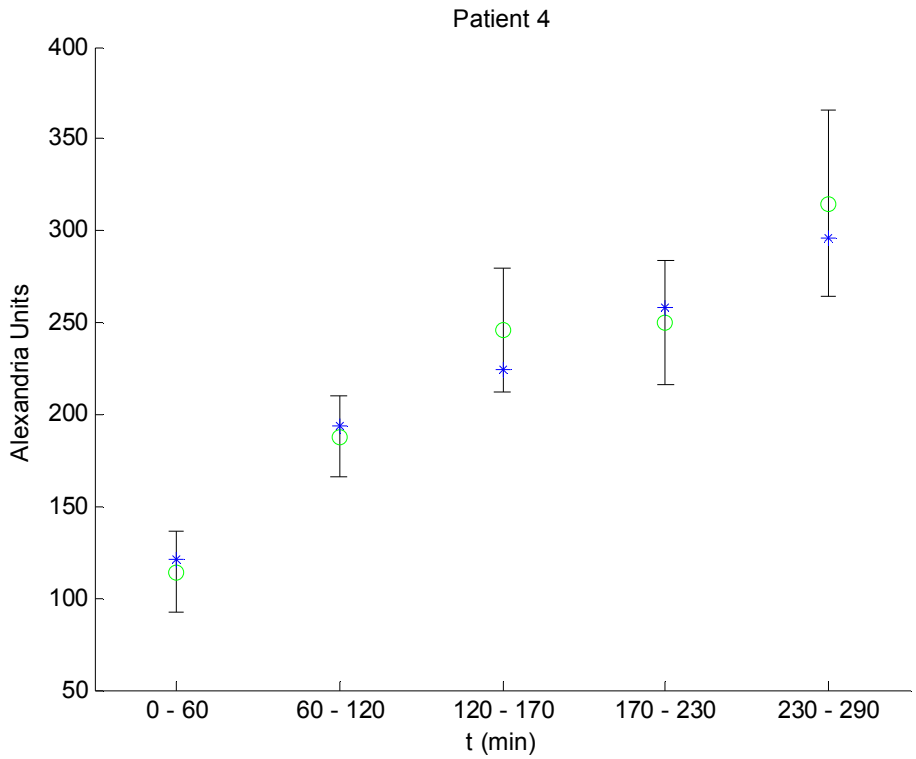

Figure A2.2: Simulation results from patient 1 (in Alexandria units) averaged in 60-minutes intervals: comparison between simulation (.) results and Cra91 (o).

Patient 1

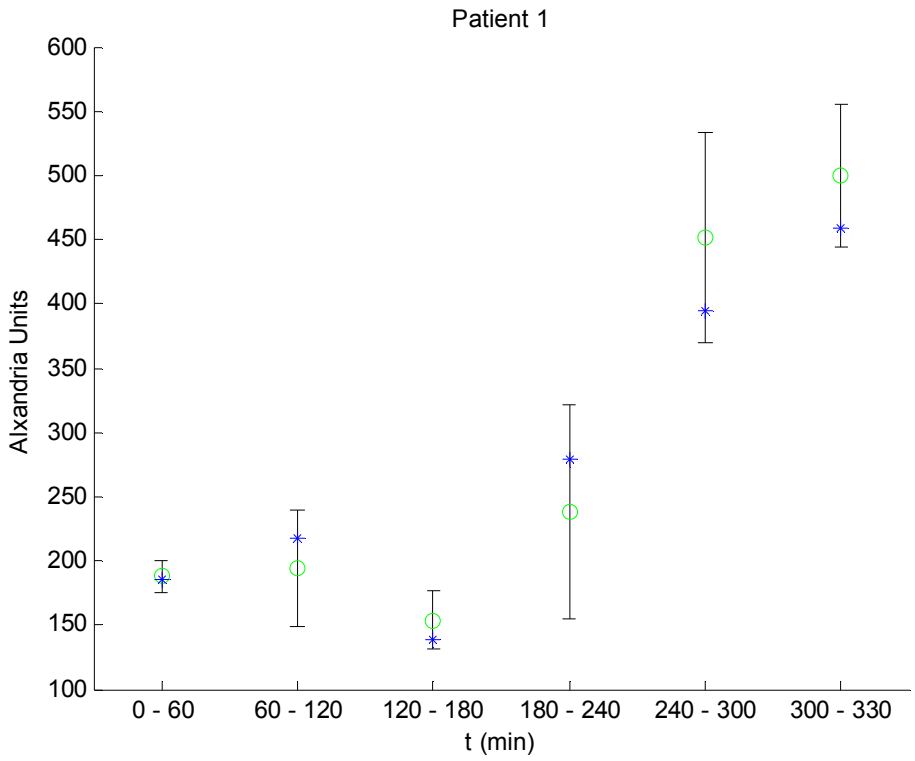

Figure A2.3: Simulation results from patient 1 (in Alexandria units) averaged in 60-minutes intervals: comparison between simulation (.) results and Cra91 (o).

Appendix 3: Pilot clinical expert evaluation study – Questionaire

In this appendix we present the questionnaire given to independent clinical experts for a preliminary evaluation of the simulation results realism. Because intrauterine pressure simulations presented in this questionnaire were already presented in Chapter 6 these will not be presented here again, only referenced.

Classifications and comments are presented in this appendix using a different color for each expert.

Intrauterine pressure activity model evaluation

Mariana Lobo, Luísa Ferreira Bastos, Diogo Ayres-de-Campos, Willem van Meurs

Questionnaire

The purpose of this questionnaire is to evaluate the realism of a series of computer simulated **intrauterine pressure** tracings for post-graduate healthcare education of labor and delivery. The opinion of clinical experts is important for validation of medical simulation engines, before their use in education and training.
The four intra-partum tracings below reflect clinical situations under spontaneous or augmented labor. Each tracing is depicted over one or more 40-minute strips, where 5-minute periods are represented within bold green vertical lines and 1-minute periods are represented within thin lines. Tracings depict only those segments considered necessary and sufficient for evaluation of a given clinical situation. Time in minutes is shown on the left side of each strip, as well as in the horizontal axis. Minute zero is considered the beginning of labor. In some tracings the symbol "|…|" marks time elapsed between strips.
For labor augmentation, oxytocin is administered intravenously (one 10 U ampoule in 1000 ml of isotonic solution) at rates varying between 6 and 18 ml/h.

Please qualify the realism of each simulated tracing using the following scale:

- Unrealistic,
- Substantial differences from real tracings,
- Negligible differences from real tracings,
- Cannot be distinguished from real tracings,

by typing an "**x**" in the corresponding field (one per row).

Additional comments are very welcome.

After answering the questionnaire, please save the changes in the document and re-sent it via e-mail to nanalobo@gmail.com. This should take no more than 15 minutes.
Thank you for your collaboration in the evaluation of these simulated intrauterine pressure signals. We hope that the results of this questionnaire will contribute to improve medical simulation in obstetrics.

Tracing 1. This tracing represents normal uterine contractions from the beginning of labor until delivery, therefore including simulation of the latent phase (···), the active phase (···), and the second stage (···). These different stages and phases are marked above the tracing.

Please see Figure 6.1

Please classify the following characteristics in each stage/phase

Latent phase		**Unrealistic**	**Substantial differences from real tracings**	**Negligible differences from real tracings**	**Cannot be distinguished from real tracings**
Amplitude of contractions:			x	x	
Frequency of contractions:				xx	
Duration of contractions:				xx	
Resting tone	Level:		x	x	
	Morphology:			xx	
Morphology of contractions:			x	x	
Overall realism			x	x	

Active phase		**Unrealistic**	**Substantial differences from real tracings**	**Negligible differences from real tracings**	**Cannot be distinguished from real tracings**
Amplitude of contractions:					xx
Frequency of contractions:				x	x
Duration of contractions:					xx
Resting tone	Level:			x	x
	Morphology:			xx	
Morphology of contractions:				x	x
Overall realism				x	x

Second stage		**Unrealistic**	**Substantial differences from real tracings**	**Negligible differences from real tracings**	**Cannot be distinguished from real tracings**
Amplitude of contractions:				x	x
Frequency of contractions:			x	x	
Duration of contractions:			x	x	
Resting tone	Level:			xx	
	Morphology:			xx	
Morphology of contractions:		xx			
Overall realism			xx		

Please classify the following transitions of stage/phase

	Unrealistic	**Substantial differences from real tracings**	**Negligible differences from real tracings**	**Cannot be distinguished from real tracings**
Transition from latent phase to active phase:	x	x		
Transition from active phase to second stage:	x	x		

Comment:

The resting tone is too homogenous.
Second stage: The morphology is unrealistic. There should be a plateau (active pushing)
The transition from one stage to the other is too sudden.

Contractions in the latent phase are a somewhat too regular and it seems somewhat unrealistic although I can not say exactly what it is.
Th transition from latent phase to active phase is unrealistic, because suddenly contractions are much stronger.

Active phase is allright.

In the second stage you normally see that the woman is pushing, I don ‘t see anything of these amplitudes reaching high pressures.
Therefore transition from active phase to second stage is unrealistic.

I am used to registrations at 2 cm/min, so it is somewhat difficult for me to classify these registrations at 1 cm/min.

Tracing 2. This tracing represents a case of hypotonic labor, with insufficient uterine activity for normal progress to occur. No therapeutic intervention is performed.

Please see Figure 6.2

	Unrealistic	Substantial differences from real tracings	Negligible differences from real tracings	Cannot be distinguished from real tracings
Please classify the overall realism of Tracing 2		**x**	**x**	

Comment:

I would expect more irregular contractions in poor progress.
The amplitude is ok. But more variety in amplitude would make it more realistic.

(By the way, contractions with a low amplitude do not necessarily lead to poor progress. Progress can only be evaluated by regular vaginal examination. It's additional information that you cannot extract from the intra-uterine pressure. But of course that's not new to you.)

Although it is unrealistic that you see such a pattern for 10 hours, the registration seems realistic.

Tracing 3. The following tracing represents a patient with hypotonic labor that was treated with oxytocin. Oxytocin infusion start and stop times as well as the dose rate administered are marked on the tracing with black arrows.

Please see Figure 6.3
The following classifications refers to the same oxytocin administration profile and sensitivity parameters used for the simulation in figure 6.3, but the underlying spontaneous uterine activity was the same as in figure 6.2.

Please classify the following characteristics regarding the effect of oxytocin

		Unrealistic	**Substantial differences from real tracings**	**Negligible differences from real tracings**	**Cannot be distinguished from real tracings**
Amplitude of contractions:				**xx**	
Frequency of contractions:			**x**		**x**
Duration of contractions:			**x**		**x**
Resting tone	Level:			**xx**	
	Morphology:			**xx**	
Morphology of contractions:				**xx**	
Overall realism			**x**	**x**	

Comment:

Nice tracing regarding to the effect of oxytocin. See comment on tracing 2 for overall realism of the beginning of the trace.

The augmentation of contractions after starting oxytocin could be more slowly.

Morpholgy and amplitude of the contractions, also as a result of oxytocin, seem allright.

The frequency of the contractions is not changing, only 2 per 10 minutes after administration of oxytocin, that is unrealistic. I'm not sure the effect of starting and stopping oxytocin is as quick as you show here.

Tracing 4. This tracing presents another patient treated with oxytocin. Infusion start and stop times, as well as the dose administered are marked on the tracing with black arrows.

Please see Figure 6.5

Please classify the following characteristics regarding the effect of oxytocin

		Unrealistic	Substantial differences from real tracings	Negligible differences from real tracings	Cannot be distinguished from real tracings
Amplitude of contractions:			x	x	
Frequency of contractions:				xx	
Duration of contractions:			x	x	
Resting tone	Level:		x	x	
	Morphology:			xx	
Morphology of contractions:			x	x	
Overall realism			x	x	

Comment:

You want to simulate this high frequency of contractions, I suppose.
It is realistic that the frequency of contractions increases at a stable dose of 12 ml/h. Very goed!

I miss some variety in duration, amplitude and morphology compared to a real tracing.

This registration is more realistic than the third one. It would expect the resting tone to go up after the oxytocin wa increased to 18 ml/hour, because there is hardly any pause between the contractions (probably the duration of the contractions is somewhat long).