Mathematical models for educational simulation of uterine contractions during labor

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To Lurdes and Mário,

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To Cristina,

for showing me the mirror to my soul

To Ricardo,

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Abstract

The use of simulation as a tool for teaching diagnostic and therapeutic skills in acute care medicine has increased over the last few years. It provides a controllable environment for training healthcare providers in rare, life-threatening situations, without any risks to real patients. Labor and delivery is a potentially hazardous process for both mother and fetus, and can benefit from educational simulation to increase patient safety and further improve outcomes. However, available obstetric simulators and training programs lack realism and capabilities, impeding fully immersive training of obstetric emergencies.

In developed countries, intrapartum monitoring in high-risk cases involves continuous evaluation of the fetal heart rate and uterine contraction signals. A prompt detection of abnormalities in these signals is essential for a timely resolution of potentially harmful situations. Uterine contraction signals provide information on the onset and progress of labor, and assist in the diagnosis of obstetric emergencies, such as placental abruption and uterine rupture. They also aid in the evaluation of the relevance of certain fetal heart rate abnormalities. For example, fetal oxygenation may be compromised by uterine hyperstimulation following labor augmentation with oxytocin. In severe cases this can cause long-term neurological sequelae or fetal death. Immediate oxytocin curtail and rapid administration of drugs that inhibit contractility (tocolysis) are the best approaches to rapidly reverse the situation.

This thesis presents an essential component of a high-fidelity simulator for normal and critical situations in labor and delivery: a set of interacting mathematical models for the simulation of uterine contraction signals. These models include a signal generator, scripts of evolving signal features, and continuous-time models of pharmacokinetics and pharmacodynamics of oxytocin and salbutamol. The model underlying the signal generator is a truncated Gaussian curve with programmable contraction amplitude, frequency, duration, and resting tone. Natural variability of these features and of the baseline pressure are approximated by deterministic trends and stationary stochastic processes. Time-and-event based scripts consist of linear interpolations between feature values at given points in time. These values are set based on data published in the scientific literature and/or in accordance with specific educational needs. The pharmacokinetic models for oxytocin and salbutamol consist of independent first order

differential equations for drug concentrations normalized to infusion rate. The oxytocin pharmacodynamic model consists of an original adaptation of the traditional Emax model. It takes simulated spontaneously evolving contraction waveform features as a starting point, adding the effect of exogenous oxytocin. The salbutamol pharmacodynamic model consists of an original adaptation of the traditional inhibitory Emax model. It inhibits simulated spontaneously evolving and possibly augmented contraction waveform features in a multiplicative way. The combined models allow for the simulation of spontaneous evolution of uterine activity, labor augmentation with oxytocin, and tocolysis with salbutamol. The variability of simulated uterine contraction signals, spontaneous evolution and drug sensitivities can be normal or abnormal, allowing the simulation of uterine contractions that corresponds to different patterns, patients and clinical situations.

In addition to model validation with independent target data, other methods were adopted for the evaluation of simulated clinical signals using expert opinion. In a "blind" evaluation of uterine contraction signals, experts attributed similar realism scores to simulated and to real tracings. In a side-by-side comparison of real and simulated signals, experts judged simulated signals to be indistinguishable or negligibly different from real tracings. In the identification of underlying situations, experts identified correctly the simulated situations in all tracings and considered them to be "good" or "excellent" representations of reality. Validation results suggest that the combined models are able to simulate realistic uterine contraction signals during labor, for different patients, pathologies, and evolving clinical situations. They also respond realistically to drugs that affect uterine motility.

In our opinion, the methods presented in this thesis have more general applicability in the design and validation of models for medical educational simulation.

Combined with a fetal-heart-rate generator, the presented models can be incorporated in a screen-based simulator where individual healthcare providers can practice the identification of critical situations and develop certain aspects of clinical decision making. It can also be incorporated in a full-body, model-driven simulator, contributing to an immersive simulation environment for training healthcare teams in the technical and non-technical skills required for the management of obstetric emergencies.

Sumário

A utilização da simulação como uma ferramenta para o desenvolvimento de capacidades de diagnóstico e terapêuticas em emergências médicas tem aumentado nos últimos anos. Esta ferramenta permite treinar estudantes e profissionais de saúde em situações raras, graves e agudas, num ambiente controlado, sem qualquer risco para pacientes reais. O trabalho de parto é um processo potencialmente perigoso tanto para a mãe como para o feto e pode beneficiar com a utilização da simulação educacional para aumentar a segurança e para melhorar os desfechos clínicos. Contudo, os simuladores obstétricos e os programas de treino existentes ainda carecem de realismo e de certas capacidades que impedem o treino imersivo das situações de emergência.

Em países desenvolvidos, a monitorização do trabalho de parto de risco envolve a avaliação contínua dos sinais da frequência cardíaca fetal e das contracções uterinas. A detecção rápida de padrões suspeitos é essencial para a resolução atempada de situações potencialmente perigosas. Os sinais das contracções uterinas fornecem informação sobre o início e a progressão do trabalho de parto, para além de auxiliarem no diagnóstico de algumas emergências obstétricas, como o descolamento da placenta e a ruptura uterina. Estes sinais assistem também na avaliação de padrões suspeitos da frequência cardíaca fetal. A oxigenação fetal pode ser comprometida por uma excessiva estimulação uterina, devida por exemplo à aceleração do trabalho de parto com ocitocina. Em casos graves, esta situação pode levar a sequelas neurológicas a longo prazo ou mesmo à morte do feto. A suspensão imediata da administração de ocitocina e a rápida administração de um fármaco que inibe a contractilidade uterina (tocolítico) são as melhores abordagens para reverter rapidamente a situação.

Esta tese apresenta uma componente essencial de um simulador do trabalho de parto de alta-fidelidade para situações normais e críticas: um conjunto de modelos matemáticos interactivos para a simulação dos sinais de actividade uterina. Estes modelos incluem um gerador de sinais, cenários da evolução das características do sinal e modelos em tempo contínuo da farmacocinética e da farmacodinâmica da ocitocina e do salbutamol (um agente tocolítico). O modelo subjacente ao gerador de sinais consiste numa curva Gaussiana truncada com características programáveis: amplitude, duração e frequência das contracções e o tonus basal. A variabilidade natural destas características e da linha de

base é aproximada por tendências determinísticas e por processos estocásticos estacionários. Os cenários pré-programados consistem na interpolação linear entre valores das características em determinados instantes de tempo. Estes valores são estabelecidos de acordo com dados publicados na literatura científica e/ou de acordo com necessidades educacionais específicas. Os modelos farmacocinéticos da ocitocina e do salbutamol consistem em equações diferenciais de primeira ordem, independentes para concentrações normalizadas dos fármacos nas taxas de infusão. O modelo farmacodinâmico da ocitocina consiste numa adaptação original do modelo Emax tradicional. Tendo como ponto de partida a evolução espontânea das características das contracções, o modelo adiciona o efeito da ocitocina exógena. O modelo farmacodinâmico do salbutamol consiste numa adaptação original do modelo Emax inibitório tradicional. De forma multiplicativa, o modelo inibe as características das contracções resultantes da evolução espontânea ou da aceleração do trabalho de parto. A integração destes modelos permite a simulação da evolução espontânea da actividade uterina, a aceleração do trabalho de parto com ocitocina e a sua inibição com salbutamol. A variabilidade dos sinais simulados das contracções uterinas, da sua evolução espontânea e da sensibilidade aos fármacos pode ser normal ou anormal, permitindo a simulação de contracções uterinas que correspondem a diferentes padrões, pacientes e situações clínicas.

Os modelos foram validados com dados independentes da literatura ou utilizando a opinião de especialistas clínicos. Numa avaliação de sinais de contracções uterinas em que foram incluídos traçados simulados e reais, os especialistas atribuíram graus de realismo semelhantes a ambos. Numa comparação lado-a-lado de sinais reais e simulados, os especialistas consideraram que os sinais simulados não eram distinguíveis ou eram negligenciavelmente diferentes dos traçados reais. Na identificação das situações clínicas subjacentes aos sinais simulados, os especialistas identificaram correctamente todas as situações e consideraram que eram representações "boas" ou "excelentes" da realidade. Os resultados de validação sugerem que os modelos integrados são capazes de simular sinais realistas das contracções uterinas durante o trabalho de parto para diferentes pacientes, patologias e situações clínicas evolutivas. Estes modelos respondem também realisticamente a fármacos que afectam a actividade uterina.

Na nossa opinião, os métodos apresentados nesta tese têm uma aplicabilidade mais geral no desenho e na validação de modelos para simulação educacional.

Combinados com um gerador da frequência cardíaca fetal, os modelos apresentados poderão ser incorporados num simulador de ecrã de computador, onde os profissionais de saúde podem praticar individualmente a identificação de situações críticas e desenvolver alguns aspectos da tomada de decisão clínica. Os modelos poderão também ser incorporados num simulador em manequim de tamanho real, contribuindo para um ambiente de simulação imersivo para o treino de equipas de saúde nas capacidades técnicas e não-técnicas necessárias para a resolução de emergências obstétricas.

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Chapter 1

Introduction

In this chapter we first present an overview of the clinical and educational context that pushed forward modeling and simulation in healthcare, with a special reference to Obstetrics. The second section presents background information on labor and monitoring of uterine contractions, as well as the objective of the thesis and the modeling requirements. The thesis is outlined in the last section.

Modeling and simulation for healthcare education and training

In 2000, the Committee on Quality of Health Care in America published a book entitled "To Err Is Human: Building a Safer Health System". This book includes a broad reflection on the numbers and causes of medical errors. It was estimated that between 44.000 and 98.000 deaths per year in the USA were due to medical errors. However, these numbers were considered an underestimation of the occurrence of preventable adverse events, because these studies: (1) considered only patients whose injuries resulted in death; (2) imposed a high threshold to determine whether an adverse event was preventable or not; and (3) included only errors that were documented in patient records[1]. From this and other publications[2-6], estimates were established on a report of the National Patient Safety Agency of the UK, from 2005. This report states that preventable adverse events are likely to have occurred in about 5% of hospital admissions, and in about 0.5% of those admissions preventable adverse events resulted in death or severe injuries[7]. This signifies that from an estimation of 30.000.000 hospital admissions per year in the USA, 1.500.000 patients are likely to have been victims of preventable adverse events, and approximately 150.000 patients died or suffered severe injuries. Similar estimates can be presented for the European Union (25 states), where 225.000 patients per year are thought to be victims of death or severe injuries due to medical errors. But what are the causes of these errors?

Medical errors are not only caused by individual mistakes, but can also be due to poor team performance and system faults[8,9]. Individual mistakes can occur due to lack of adequate professional development or overwork. Team performance can be compromised by inefficient communication, clashing motivations, and poor interpersonal skills – also known as non-technical skills. System faults can occur with equipment failure or lack of training with new equipment, with inadequate resource allocation, unclear protocols, lack of evidence-based practice and inadequate information technology for staff[9-12]. Even though many of these problems can be overcome with reforms at the organizational and administrative levels, others can only be solved with efficient training[1,10,12]. However, training in the clinical environment with real patients has its shortcomings[13-17]. For one, patients' currently shorter hospital stays and clinical visits, and limited trainees' working hours may lead to inefficient training and an uncontrolled educational program[18-22].

Furthermore, even certified physicians may not be prepared to recognize or manage life-threatening emergencies, especially in rare situations[23]. Additionally, the ethical appropriateness of using real patients as training resources has become increasingly questionable[1,24].

Simulation-based training provides a controlled educational environment to achieve and maintain competency in the management of life-threatening, often low-frequency events, with no risk to real patients[23,25,26]. Simulation is being widely adopted throughout the world, in several areas of medicine, and spanning from undergraduate studies to postgraduate training. This led to the development of medical simulation environments that integrate a wide diversity of tools, and targets a wide variety of audiences and application areas[27-30]. These environments provide the means to acquire knowledge and skills at different proficiency levels[24,31]. Depending on the training needs, educators chose a more or less immersive simulation environment. For example, immersion may be unnecessary when training basic technical skills alone. However, it may become important when evaluating team performance in acute and life-threatening situations. Along the same lines, simulator fidelity can be adapted to the training needs. A patient-actor may be adequate to train general patient-doctor communication skills. However, to train drug administration for general anesthesia, one may need a model-driven simulator with physiological and pharmacological functions that automatically react to trainees' interventions.

The distinction between technical and non-technical skills plays an important role in the development of simulation environments. Technical skills are the knowledge and proficiencies required in the accomplishment of a specific task. Non-technical skills are cognitive, social, and behavioral skills. There is a consensus in the recent scientific literature about the importance of these two types of skills to ensure the proficiency of a healthcare provider[32-36]. Furthermore, note that an immersive simulation environment does not necessarily include the use of high-fidelity simulators. Below is a list of some examples of simulation environments, with different levels of immersion and simulator fidelity:

- An actor-based simulation setting may provide an immersive environment for individual training of general practitioners; in this environment, training may include the acquisition of technical and non-technical skills in general practice.

- A high-fidelity surgical virtual reality simulator can provide an accurate representation of the relevant functional anatomy and allows for individual training of surgeons; in this environment, training includes the acquisition of technical skills.
- A screen-based simulator provides a non-immersive environment for individual training of physicians, nurses, residents, or undergraduate students; this environment may allow for cost-effective acquisition of knowledge and training of technical skills, such as identification of different clinical situations and decision making.
- A full-body model-driven simulator can contribute to an immersive environment for individual or team training of residents, physicians and nurses; this environment usually provides the possibility for advanced training of both technical and non-technical skills.

Simulators in healthcare range from simple anatomical parts to complex combinations of anatomic, mechanical, and *in silico* models[37-40]. Part-task trainers consist of 3D representations of body parts and/or internal organs used to practice clinical tasks or procedures. Examples of part-task trainers are:

- A plastic arm that can be used to puncture veins for fluid administration or collecting a blood sample.
- An airway management head to practice assisted ventilation via a face mask, or insertion of an endotracheal tube.
- A male or female pelvis with a urethral opening to practice the process of inserting a urinary catheter.
- A female pelvis with gynecological organs to allow the practice of the pelvic exam.

Some part-task trainers include user feedback systems that can aid in the assessment of trainees' performance, such as the measure of exerted force.

Another type of simulator is the instructor-driven simulator, which consists of a combination of partial or full-body anatomic models with script- and/or instructor-controlled physiologic functions. They are frequently used to train interventions and procedures in different clinical scenarios. Since they are not programmed to be reactive to

the user, an instructor adjusts the relevant vital signs to reflect patient responses to trainees' interventions. Examples of instructor-driven simulators are:

- The Anaesthesia Computer Controlled Emergency Situation Simulator (ACCESS) system, designed to simulate anesthetic emergencies with the objective of improving the training of junior doctors[34,41].
- HAL® (Gaumard®, Miami, FL, U.S.A.), a wireless PC-controlled manikin, designed primarily for training of pre-hospital on-site care, followed by patient transport and in-hospital follow-up.
- SimMan® (Laerdal, Stavanger, Norway), a full scale patient simulator that allows the training of advanced life support skills in different clinical scenarios. Trend curves on the instructor's panel control how the physiological parameters will change over time[34,42].

Full-body model-driven simulators typically include mannequins that mimic the evolution of human physiology in normal and pathological situations, and react automatically and realistically to medical interventions. Examples of full-body model-driven simulators are:

- The Human Patient Simulator - HPS® (METI®, Sarasota, FL, USA), which integrates physiologic models for the cardiovascular and respiratory systems and includes pharmacologic models for approximately 50 intravenous drugs and 5 inhalational agents. Standard medical devices can be used to monitor and treat the patient.
- i-Stan® (METI®, Sarasota, FL, USA), a wireless portable manikin with an internal skeleton that allows for more lifelike motion. It also includes reactive models of human cardiovascular and respiratory systems.

Computer screen-based simulators may include reactive models of physiological signs and signals. Simpler versions of this type of simulator do not include reactive models, but commented scripted scenarios or real physiological data. Depending on the models and data incorporated in such simulators, they may allow for independent training of diagnosis and decision making. Examples of this type of simulators are:

- The Transcranial Doppler Simulator (Hemodynamic.com, Bern, Switzerland) that models cerebral circulation, related pathologies, and the ways to monitor them. Educational content includes background, mathematical equations and

derivations, monitor placement, and details on pathophysiologic and traumatic states. Selected physiological variables are adjustable in real-time.

- GasMan® (MMSI, Boston, MA, USA), a pharmacologic modeling program that allows the user to enter gaseous anesthetic agents, calculate and graph dose-effect, and see how the drug equilibrates through multiple compartments. It also takes into consideration the breathing circuit when calculating uptake.

Virtual reality simulators use computer models to re-create 3D environments that mimic a part of human functional anatomy. These models are reactive to interventions and, in addition to *in silico* anatomical and physiological models, may also include physical and haptic (sense of touch) models. These simulators typically include post-performance feedback, which allows for debriefing and performance evaluation, based on objective data. Examples of such simulators are:

- The EYESI system (VRmagic, Mannheim, Germany) that uses computer generated images seen through a stereo microscope, haptic feedback and realistic instruments to allow trainees to practice intraocular surgery.
- The Minimally Invasive Surgery Training system – MIST™ (Mentice, Gothenburg, Sweden) that combines non-anatomic and anatomic modules allowing the acquisition of technical skills in minimally invasive surgery. These skills range from single-handed object manipulation to complex suturing tasks.

The diversity of available environments and simulators provide the opportunity to train a wide variety of healthcare personnel without putting patients at risk, and therefore contribute towards patient centered care[1,43]. Furthermore, trainees have the possibility to train rare and life-threatening events as many times as necessary (repetitive practice) in a short period of time. This provides the opportunity to follow controlled training programs, with levels of difficulty adjusted to previous experience, leading to more efficient training. Some simulators and simulation environments provide the possibility to assess performance and debrief after a simulation exercise, based on objective or subjective data. Such features enhance educational feedback beyond what is generally possible in clinical practice[27,43]. Along with the understanding of the causes of preventable adverse outcomes, educators have recently given more attention to team training and training non-technical skills, aspects that can be adequately trained in many simulation environments.

This may help to avoid communication problems within the team and with patients, in addition to mastering technical skills[1,27,44].

It has been shown that simulation-based training may improve performance in shorter training periods than traditional clinical training[45-47]. Realism of the simulation setting is important for an effective transfer of some competencies to the professional environment[43]. Note, however, that realism may be limited to the feeling of the needle puncturing the vein for drug administration or it may be as broad as seeing a patient losing his/her vital signs on the operating room, because of failure to intubate after general anesthesia. Need for realism is often balanced with the need for affordable simulators.

In silico models are an important component of healthcare simulators when human physiology or pharmacology, or clinical signs or signals need to be represented in a realistic fashion for the training environment, and when the use of real data is not an adequate solution. Computer modeling methodologies will be addressed in the modeling chapters of this thesis (chapters 2, 3, 4, and 5). In the last chapter, we will discuss some perspectives and directions that are being proposed for simulation in healthcare education and training. For the remainder of this section, we will address the status of simulation-based training in Obstetrics.

Educational simulation in the specialty of Obstetrics was promoted after the success of simulation-based training in other areas of healthcare[48]. In 1997, the report of an independent organization in the United Kingdom, set up to perform a confidential evaluation of fetal and infant deaths (Confidential enquiries into stillbirths and deaths in infancy - CESDI 4th Annual Report), concluded that of the 873 intrapartum-related deaths that occurred in the years 1994 and 1995, 52% had received suboptimal care. The latter was defined as the situation where "different management would reasonably have been expected to have made a difference to the outcome"[49]. Similarly, reports on maternal deaths from 1998 and 2007 conclude that about half of adverse outcomes would probably be preventable with better care[50-52]. These data led to the recommendation from several committees to promote simulation-based training to improve management of obstetric emergencies[49-53].

Currently, there are several commercially available simulators for the management of labor, for example:

- FetalSim™ (Advanced Medical Simulations, Binghamton, NY, U.S.A.) is a computer-based simulator that does not incorporate reactive models. It provides fetal heart rate and maternal uterine contraction data for the simulation of electronic fetal monitoring (EFM) also known as cardiotocography (CTG), with the possibility of display in a compatible EFM system. This simulator allows training of recognition and interpretation of EFM patterns, and allows programming of different scenarios. It is mainly used for individual training.
- The Prompt Birthing simulator (Limbs & Things, Bristol, UK) is a part-task trainer developed for the acquisition of technical and non-technical skills required for the management of normal labor and delivery as well as selected obstetric emergencies. It includes a bony pelvis, pelvic floor musculature and an articulated baby with a force sensor system on the neck, and anatomical landmarks (e.g. fontanelles, clavicles and scapulae).
- SimOne™ (3B Scientific®, Hamburg, Germany) is an advanced part-task trainer with haptic feedback for the training of vacuum or forceps delivery. It includes a computer screen with information on the progress of labor and EFM tracing, an anatomic model of the female abdomen and pelvis, and a fetal head with sagittal suture and fontanelles.
- The Noelle® birthing simulator (Gaumard®, Miami, FL, U.S.A.) is an instructor-driven simulator with full-body mannequins of a pregnant woman and a fetus that descends and rotates as it moves down the birth canal. Monitoring includes EFM and other maternal and fetal signs and signals.

Several studies have indicated that simulation in this area can improve neonatal outcomes[54-59]. Common features of effective training are the inclusion of nearly all labor ward staff, multi-professional training of obstetric emergencies, using realistic environments and simple teaching/training algorithms[60].

Background information, thesis objectives and model requirements

Human error has been documented to play a significant role in adverse outcomes in Obstetrics[49-51,61] (please see previous section). Simulation-based training in the

management of obstetric emergencies is recommended by several organizations to improve this situation[15,49-51]. Following such recommendation, simulation environments have been used for the training of emergencies and their effectiveness has been investigated[54-60,62]. Even though high-fidelity environments have been proven to augment the effectiveness of simulation-based training[60,63], available simulators in this field are still of low to intermediate fidelity[48]. The simulation technology available for training obstetric emergencies lacks automatic and realistic reactions to interventions. This restricts training program design and assessment. In such conditions, objective assessment of training is difficult, due to the inability to use and record objective pathophysiological data. Such information is necessary, for example, in the analysis of accuracy of task performance, completion times, and efficiency of interventions[64,65]. We will come back to this issue in chapter 6. The modeling and simulation program of INEB – Institute of Biomedical Engineering – aims to develop a full-body model-driven simulator with clinical monitoring of fetal and maternal signs and signals, to improve the automaticity and thereby the realism of simulation environments in labor and delivery.

Labor and delivery can be divided in four stages. The first stage is subdivided in two phases: the latent phase, and the active phase. The latent phase starts with the onset of labor, which is defined as the point at which the mother perceives regular contractions that lead to observed changes in the uterine cervix. This phase is accompanied by progressive, albeit slow, cervical dilation, and ends at 4 cm dilatation. The active phase of the first stage of labor is generally accepted to begin when cervical dilatation exceeeds 4 cm, in the presence of uterine contractions. It ends with full cervical dilation. The second stage of labor begins at this time and ends with fetal expulsion. The third stage begins after delivery of the infant and ends with the delivery of the placenta. The first hours after delivery are critical because of the risk of hemorrhage, and this period has been designated by some as the "fourth stage of labor"[66-69].

Clinical monitoring during labor and delivery, at least in high-risk cases, relies on two major signals: the fetal heart rate and the uterine contraction signals[70-74]. The acquisition system of these signals is commonly called the cardiotocograph (CTG) or the electronic fetal monitor (EFM). Accurate appraisal of uterine activity is an essential component of the electronic fetal monitoring system. Uterine activity data reflects the degree and timing of stress being delivered to the fetus, and this data is important to assess the fetal response[75-

[77]. Furthermore, the proper utilization and interpretation of uterine activity enables the obstetrician, midwife, or resident to assess the progress of labor and to diagnose abnormal or ineffective labor patterns[78-81].

Uterine contractions are detected either by a catheter inserted transcervically into the uterine cavity and attached to a strain-gauge transducer, or by an external device, termed tokodynamometer, which is placed on the maternal abdomen and which recognizes the tightening of the uterus during a contraction. With the invasive (and more accurate) measurement method the intrauterine pressure signal is recorded. With the non-invasive (and less accurate) method, a transabdominal uterine activity signal is acquired. As the uterus contracts, pressure within the confines of the uterus progressively increases and then gradually decreases in a uniform bell-shaped form, with the peak pressure occurring at the acme of the contraction. Uterine contractions can be defined by their amplitude, duration, period (or frequency), and resting tone (Figure 1.1). These parameters help healthcare providers to quantify and qualify uterine activity during labor and delivery[66,78,82].

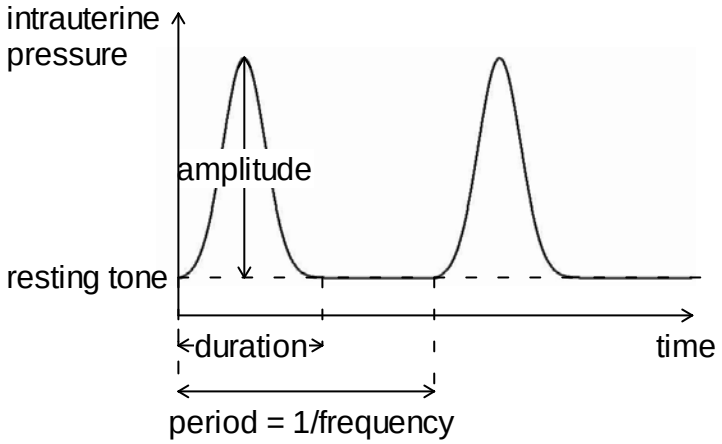

Figure 1.1. Uterine contractility parameters.

There are a number of methods of combining the contraction frequency and amplitude in order to obtain a simplified quantification of uterine activity[66,67,74,83]. The simplest and most widespread method is that of the Montevideo units (MU). The latter are the product of the number of uterine contractions in 10 minutes multiplied by the mean amplitude of contractions in millimeters of mercury (mm Hg). Another technique for quantifying

uterine activity is the calculation of Alexandria units (AU). This measure also takes into account the duration of contractions. Alexandria units are defined as the average amplitude multiplied by the average duration multiplied by the number (or frequency) of contractions in 10 minutes. More complex quantification measurements include: (1) the uterine activity integral (UAI), which is defined as the area under the uterine contraction curve minus the baseline pressure; and (2) the mean active pressure (MAP), which reflects the mean value of active pressure per second. These quantifying techniques and the uterine contractility parameters are useful to identify different uterine activity patterns, such as, normal contractions, dysfunctional contractions, and hyperactive contractions[84-87]. Both dysfunctional contractions and uterine hyperactivity can compromise fetal oxygenation. Furthermore, signs of a sudden decrease or increase in uterine activity, or uncoordinated patterns may be caused by an emergency situation, such as uterine rupture or placental abruption. In the presence of abnormal patterns, obstetricians rely on a collection of drugs that affect uterine motility, either to stimulate or to reduce uterine contractions[88]. Uterine-stimulating agents, also called oxytocic drugs, are used when labor augmentation or induction is thought to be necessary, and also to prevent or treat maternal hemorrhage after delivery of the fetus. Labor induction is usually adopted when the risk of continuing the pregnancy is higher than the risk of immediate delivery and pharmacological induction[89]. Such circumstances include situations such as premature rupture of membranes, maternal complications of pregnancy and mild fetal compromise. Labor augmentation is usually indicated when there are hypotonic contractions or a very prolonged latent phase, and where there is a significant arrest in cervical dilatation or fetal decent. Both in cases of labor induction and augmentation, a physician should be immediately available and continuous fetal and maternal monitoring should be in place, due to the risk of uterine hyperstimulation. If the latter occurs, oxytocic administration needs to be discontinued immediately. Potential complications of hyperstimulation are uterine rupture and compromised fetal oxygenation, due to the decrease or loss of placental gas exchange. In the third stage of labor – after the delivery of the fetus – it is desirable to have a firm and contracted uterus to avoid post-partum hemorrhage. Therefore, it is common practice in developed countries to administer a uterine-stimulant immediately after delivery. The most commonly used drug for labor induction and augmentation and for the management of the third stage of labor is oxytocin. Other drugs

like protaglandins are also used for labor induction and ergot alkaloids are still employed in some countries for the management of the third stage of labor[89,90].

Uterine activity inhibitors are called tocolytic agents. During labor, tocolytics are used to reduce uterine contractions:

- When oxytocin curtail does not alleviate acute fetal oxygen deprivation due to uterine hyperstimulation;
- Where temporary suppression of uterine activity is necessary, before an emergency cesarean section, to alleviate fetal oxygen deprivation.

During these intrapartum emergencies, the administration of a tocolytic agent is commonly named acute tocolysis[91-95].

Accurate identification of normal and abnormal uterine activity is an important aspect for the management of several obstetric emergencies[66,83].

The objective of this thesis fits within the overall framework of a full-body model-driven simulator for immersive simulation of clinical management in normal labor and delivery and obstetric emergencies. It specifically targets modeling and simulation of the intrauterine pressure signal. Given the rather complex dynamics and multiple dependencies of this signal, an instructor-driven system or data-base approach cannot provide the level of realism and automaticity required for the envisioned immersive simulations. In this context, consider, for example, the very large range of tocolytic administration protocols used in developed countries. Specific model requirements are as follows: first, the model should be able to simulate realistic intrauterine pressure signals, with natural feature variability and possibly corrupted by measurement noise. Second, the model needs to be able to simulate spontaneous evolution of uterine activity throughout labor. Besides normal progression, it should be able to simulate abnormal progression, such as:

- Slow progress;
- Sudden decrease in rate and intensity;
- Sudden increase in rate and intensity;
- Appearance of ineffective patterns.

Further programming of evolution patterns by clinical instructors should be possible, in order to adapt the model to specific educational needs. Third, the model needs to react

appropriately to the administration of drugs that affect uterine motility – oxytocic and tocolytic agents. Such drugs are not usually administered simultaneously, but a second drug may be administered while a first one is still present in the blood stream. Therefore, a model that includes the effect of both an oxytocic and a tocolytic needs to be able to simulate the interaction effect of these drugs. Inter-patient variability in the response to oxytocin should be programmable. The commonly used tocolytic drug salbutamol, was chosen as a modeling example.

Outline of the thesis

The thesis consists of six chapters. This introduction gives an overview of the application area for the modeling and simulation work developed in the thesis – healthcare education and training – provides general background information on the subject of uterine activity and establishes the objectives and requirements for the work. Chapter 2 – "An intrauterine pressure generator for educational simulation of labor and delivery" – presents a first component of a model for the educational simulation of drug-dependent uterine contractions signals. This component is able to simulate intrauterine pressure signals with natural variability of uterine contraction features and of baseline pressure. A preliminary evaluation of simulated tracings was carried out by experts. Chapter 3 – "A model for educational simulation of the evolution of uterine contractions during labor" – presents a model that combines the signal generator in chapter 2 with literature-based pre-programmed scripts for educationally relevant scenarios. This integration provides an intuitive method for programming different patients, pathologies and clinical situations, based on literature data and/or in accordance with specific educational scenario requirements. Clinical experts evaluated the realism of simulated tracings for different intrauterine pressure patterns. Chapter 4 – "A model for educational simulation of the effect of oxytocin on uterine contractions" – presents what is, to our knowledge, the first model of the effect of oxytocin on uterine contraction features, which allows the programming of patients with different sensitivities to the drug. Expert evaluation was carried out to determine the realism of specific simulated clinical situations. Chapter 5 – "A model for educational simulation of the effect of salbutamol on uterine contractions" – presents a model for the simulation of acute tocolysis with salbutamol. This model

includes the interaction of spontaneous uterine activity, the effect of oxytocin and the effect of salbutamol on uterine activity. Chapter 6 – "Conclusions and perspectives" – starts with the description of the achievements, innovations, and the envisioned use of the work presented in this thesis. The last section presents some perspectives for the future of simulation for healthcare education and training.

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Chapter 2

An intrauterine pressure generator for educational simulation of labor and delivery

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Abstract

Simulation provides a risk free and controllable environment for training of healthcare providers. The limited realism of available simulators and training programs impedes immersive training in obstetric emergencies. In developed countries, intrapartum monitoring in high-risk cases involves continuous evaluation of fetal heart rate and uterine contraction signals. We present an essential component of a high-fidelity simulator for normal and critical situations in labor and delivery, namely an intrauterine pressure generator. The signal model behind the generator consists of a truncated Gaussian curve with the programmable features: amplitude, frequency, duration, and resting tone. Through analysis of 44 hours of physiological data, we demonstrate that the natural variability of these features and of the baseline pressure can be approximated by deterministic trends and stationary stochastic processes. Signal parameters can be controlled by simulation instructors, scripts, or other models to reflect different patients, pathologies, and evolving clinical situations. Twelve 40-minute tracings reflecting three different patients in labor were presented to three clinical experts, who attributed similar realism scores to simulated and to real tracings.

Keywords: medical educational simulation, labor and delivery, uterine activity, signal generator.

Introduction

Labor and delivery is a potentially hazardous process for the fetus, but with improved understanding of potential dangers, combined with regular obstetric emergency training of labor ward teams, perinatal outcomes should continue to improve[1,2]. As in other areas of acute care medicine, simulation of obstetric emergencies provides a risk free and controllable environment for training of healthcare providers[3-5]. However, currently available obstetric simulators and training programs provide limited realism, impeding immersive training in obstetric emergencies[6,7].

Over the last decades, in developed countries, continuous evaluation of fetal heart rate and uterine contractions was incorporated in intrapartum monitoring, resulting in a technology known as electronic fetal monitoring or cardiotocography. This method is used routinely at least in all high-risk cases, and is a valuable tool to assess fetal well-being[8,9]. However, proper use of this tool depends on the knowledge and skills of healthcare providers to interpret fetal heart rate and uterine contraction signals[10,11]. This competency is especially critical in life-threatening situations for mother and/or fetus. Training opportunities in such obstetric emergencies are scarce, due to the rarity of these events and because of their high potential for medical-legal conflict, which usually implies their resolution by the most experienced clinician[12,13].

Adequate monitoring of uterine activity is a prerequisite for the proper interpretation of electronic fetal monitoring tracings[14-17]. Excessive uterine activity can predispose the fetus to hypoxia, due to reduced uterine blood perfusion during contractions and the possible occurrence of umbilical cord compression. In this paper, we focus on the more accurate uterine contraction signal: the intrauterine pressure.

The goal of this paper is to present an essential component of a high-fidelity simulator for normal and critical situations in labor and delivery, namely an intrauterine pressure generator. Given the medical educational application, this signal generator should 1) be able to realistically simulate different uterine activity patterns, and 2) allow for manipulation by simulator instructors, so that it can be adapted to the specific needs of a particular training exercise. The latter requirement implies using a signal model with parameters that are related to well understood physiological and pharmacological concepts or to clinically observable aspects of the monitored signal.

Models for the simulation of uterine contraction waveforms have been published in the literature. Andersen et al. and Young explored two mechanisms of intracellular communication that are known to be involved in the modulation of uterine contractions: the action potential propagation[18,19], and the calcium wave propagation[19]. Note that these are only two mechanisms among many others[20,21]. These models are interesting tools to study the selected mechanisms behind uterine contractility, but do not allow for easy manipulation by a simulator instructor. Vauge et al.[22] developed a more empirical model based on three physiologic states of the uterine muscle: quiescent, contracted, and refractory. Also with this model, underlying parameters are not immediately linked to the clinically observable features of the uterine contractions signal. The empirical model presented by Moreau et al.[23], based on a truncated Gaussian curve, does not include any variability in baseline or waveform features.

To our knowledge, signal models included in commercially available products that simulate uterine contractions, such as Fetal Sim (http://www.advmedsim.com), NOELLE™ (http://www.gaumard.com), SIMone™ (http://www.a3bs.com), are not published. From our observation of these products, the generated signals lack realism, mainly due to the absence of natural variability.

In this paper, we present a new empirical uterine contractions signal model that is both realistic and easy to manipulate to suit specific educational needs.

Methods

Several references point out the bell-shape of the uterine contraction waveform[22,24-26]. To reflect this typical attribute, we describe this waveform using a truncated Gaussian function (Figure 2.1).

This parameterization directly reflects the features of the uterine contractions signal evaluated by health care providers: amplitude, frequency, and duration of contractions and the resting tone[27-29]. Clinical studies often report 10-minute averages of these features[15,17,30]. In a first attempt, we used such averages to generate contraction curves. Initial comments by clinical experts pointed out the unnatural and static nature of these curves. This led us to undertake a more formal investigation of the variability aspects.

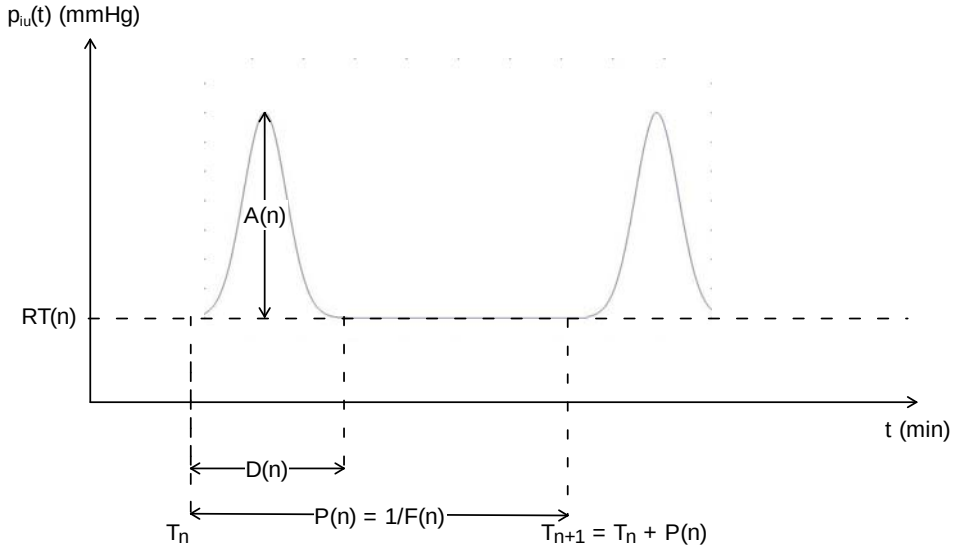

Figure 2.1. Uterine contraction waveform and parameterization. Discrete time n represents the number of contractions; time of onset of uterine contraction n: T_n in min; amplitude: A(n) in mm Hg; duration: D(n) in min; frequency: F(n) in min^{-1} (note that this represents a minor departure from the clinical convention of specifying frequency in the number of contractions per 10-minute period); period: P(n) in min; resting tone: RT(n) in mm Hg; Intrauterine pressure: p_{iu}(t) in mm Hg. Parameters of Gaussian curve: mean = T_n+D(n)/2, standard deviation = D(n)/6.

Six records of intrauterine pressure data with a total duration of 43 hours, 57 minutes, and 17 seconds were obtained to analyze variability of waveform features, measurement noise, and baseline fluctuations. Intrauterine pressure signals were acquired in laboring women at the Máxima Medical Centre, Veldhoven, The Netherlands, with a Hewlett Packard M1350A fetal monitor (Philips Healthcare, Andover, USA) and stored in the "MOSOS <CTG>" healthcare data management system (http://www.bma-mosos.nl). The data did not contain any reference to specific patients or conditions. Sampling frequency was 1 Hz, range 0-130 mmHg, and resolution 1 mmHg.

The computational analysis of each record was carried out independently to take into account potential inter-patient variability. In each 10-minute interval, feature variability around the mean was extracted, taking directed distances to these average values. For none of the features in a particular record, variability depends on the local average and the distribution of directed distances was close to normal. There was no correlation between

deviations from the mean feature value between successive contractions. Waveform features can therefore be modeled by normally distributed white noise in addition to an average value.

Introduction of resting tone variability results in discontinuities in the signal between consecutive contractions. This problem was solved by leveling the onset of the n^{th} contraction with the final value of the previous period: $P_{iu,n-1}$. Equations (2.1) and (2.2) describe the parameterized Gaussian waveform with the discontinuity correction.

$$f(t) = e^{-18\frac{(t-T_n-D(n)/2)^2}{D(n)^2}} \tag{2.1}$$

$$p_{iu}(t) = \begin{cases} \left[RT(n) + A(n) - P_{iu,n-1}\right]\dfrac{f(t) - f(T_n)}{1 - f(T_n)} + P_{iu,n-1} & T_n < t \le T_n + D(n)/2 \\ RT(n) + A(n) f(t) & T_n + D(n)/2 < t \le T_n + 1/F(n) \end{cases} \tag{2.2}$$

f(t) is a Gaussian function with mean T_n+D(n)/2 and standard deviation D(n)/6. With this relationship between duration and standard deviation, about 99.7% of the total surface area of f(t) falls within the range t =[T_n, T_n+D(n)] (see Figure 2.1). Equation (2.2) describes the intrauterine pressure signal for the nth contraction as a piecewise continuous function. Continuity of $p_{iu}(t)$ at $t=T_n$ can easily be verified in Equation (2.2). Due to truncation of the Gaussian curve at T_n there is a small discontinuity in the derivative at this point. At the peak of the contraction, $t=T_n+D(n)/2$, and f(t)=1, resulting in continuity between the two pieces. The left and right derivatives at this point are both zero.

Measurement noise and baseline fluctuations were analyzed by considering directed distances from the resting tone, during resting phases. We are assuming that measurement noise and fluctuations are similar during the resting and contraction phases. We found that variability around the resting tone does not depend on the value of the resting tone, and that distribution of directed distances was close to normal. Autocorrelation plots of directed distances demonstrate that significant correlation exists until up to eight 1-second samples. We further noted inter- and intra-patient differences in measurement noise and baseline fluctuations. These aspects of the intrauterine pressure signal can therefore be represented by additive filtered normally distributed white noise, with filter characteristics corresponding to the autocorrelation plots (autoregressive model). For estimation of the autoregressive model parameters we used the Yule-Walker method, also known as the autocorrelation method[31]. This formulation leads to the Yule-Walker

equations, which are solved by the Levinson-Durbin recursion[32]. Ignoring intra-patient variability (for now), we obtain a set of filter coefficients for each record. Graphical representations of physiologic data records are referred to as real tracings.

Selected real tracings, derived model parameters, and simulation results are presented in the next section. The same twelve 40-minute segments presented in the results section, reflecting three different patients in labor, were presented in random order to three clinical experts who were not involved in development of the model, without identifying the segments as real or simulated. In the introductory text of the questionnaire, two segments were referenced as representing an atypical situation, namely a rise in resting tone. All other segments were denominated "normal". The three clinical experts were asked to attribute realism scores on a scale from 0 ("unrealistic") to 10 ("looks exactly like a real tracing") to all tracings. The results of this questionnaire are presented in the next section.

Results

Figures 2.2, 2.4, and 2.6 show two 40-minute segments of three real intrauterine pressure signal records. Parameters were estimated for the whole record, and are listed in Tables 2.1, 2.2, and 2.3, respectively. Figures 2.3, 2.5, and 2.7 show the corresponding simulated tracings. The average waveform features used in the simulation results are equal to the 10-minute averages of the corresponding real tracings. Linear interpolation was used to plot intrauterine pressure data.

The three real cases are presented with increasing levels of measurement noise. This is confirmed by the estimated standard deviation of the autoregressive models. These results demonstrate the capability of the intrauterine pressure generator to simulate signals with different baseline variability and contraction patterns.

The realism scores attributed to both real and simulated tracings by the three clinical experts are presented in Table 2.4.

The lower realism score attributed by one expert for the real segments displayed in Figure 2.6 were attributed to the high noise levels, which the clinical expert considered unrealistic for intrauterine pressure tracings. Note that one of the corresponding simulated segments has an equally low realism score. For the other simulated segment, the same expert attributed a score that is 2 points higher than the corresponding real tracing. For the

remaining classifications, grades of real and corresponding simulated segments are either equal or differ by only 1 point. The average realism score attributed to simulated tracings (8.8) is equal to the average score attributed to real tracings (8.8). This preliminary evaluation suggests that simulated tracings cannot be distinguished from real ones, so they should be sufficiently realistic for educational simulation.

Discussion

We presented an intrauterine pressure generator, based on literature data and analysis of real intrauterine pressure tracings. Three clinical experts attributed similar realism scores to simulated and real tracings.

The truncated Gaussian function used as the base waveform of uterine contractions fits a typical tracing. Nevertheless, some patterns of uterine contractions may deviate from the bell-shape form. A common deviation consists of "picked fence" contractions, typical in the second stage of labor, where the intensity of the contractions and the excessive movements of both mother and fetus impair a good reading of intrauterine pressure. Provisions for simulating this specific waveform should be included in the envisioned simulator of obstetric emergencies in labor and delivery. Note that we are modeling a 1Hz discrete-time signal, corresponding to a fetal monitoring output standard, but not to the original continuous-time pressure signal. The clinically based decision on the 10-minute window length for variability parameter estimation and for scripted simulation of feature trends produces realistic results. From a mathematical perspective, one or the other could possibly be optimized.

Uterine activity monitoring can be achieved with devices that are placed within the uterine cavity (internal monitoring, giving origin to an intrauterine pressure signal), or with devices that are placed on the maternal abdomen (external monitoring, giving origin to a transabdominal uterine activity signal). The accuracy of internal monitoring is known to be higher than that of external monitoring[33,34], but, because of its more invasive nature, is typically reserved for specific situations such as obese women or the appearance of abnormal uterine contractility. This study focuses on the more accurate internal signal, from which the external signal can easily be derived.

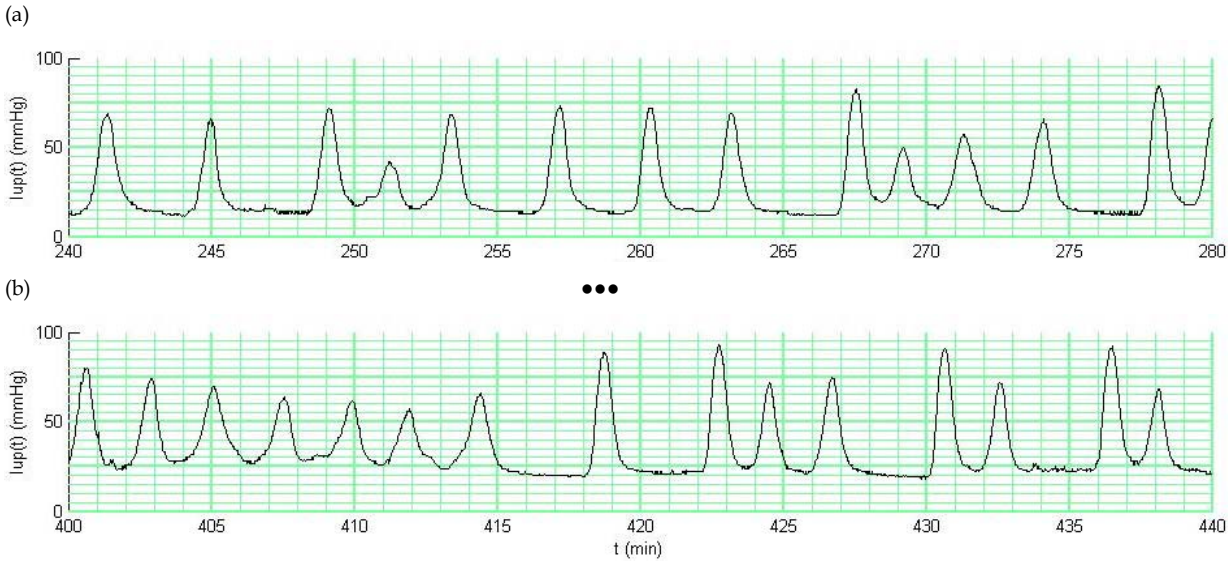

Figure 2.2. Segments of a real intrauterine pressure tracing.

Table 2.1. Model parameters, estimated from the full physiological record corresponding to Figure 2.2

	Standard deviation	**Autoregressive model coefficients (standard deviation)**
Amplitude (mm Hg)	15.0	
Frequency (min^{-1})	0.13	-0.49; 0.04; -0.12; 0.06; 0.003; 0.06; -0.03; 0.07
Duration (min)	0.37	(0.46)
Resting tone (mm Hg)	3.9	

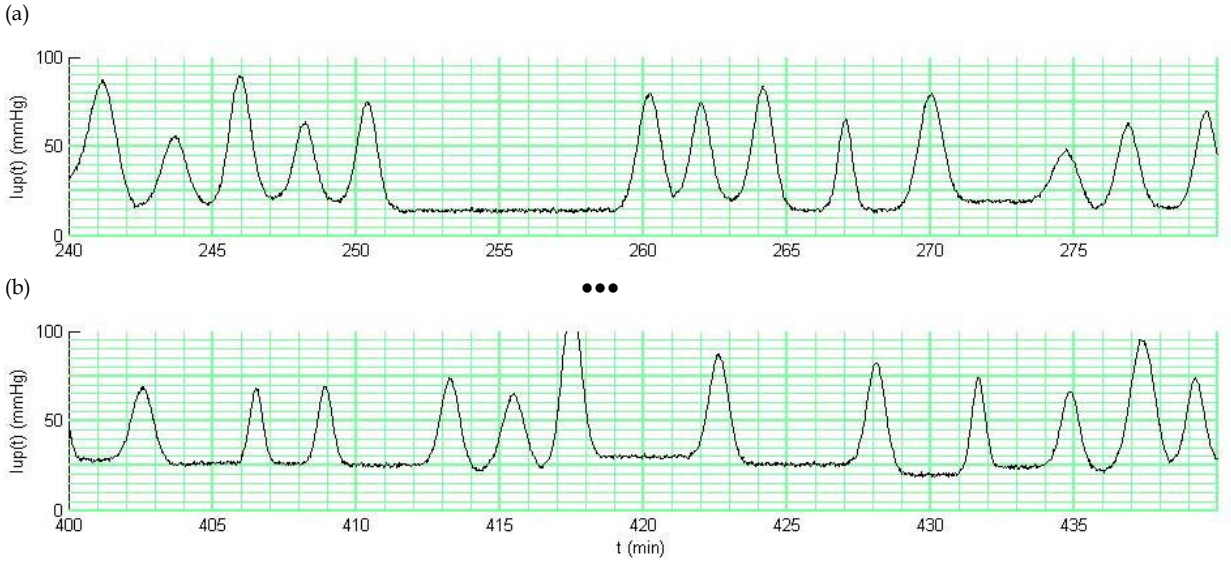

Figure 2.3. Segments of a simulated intrauterine pressure tracing using the parameters of Table 2.1 and 10-min feature averages corresponding to Figure 2.2.

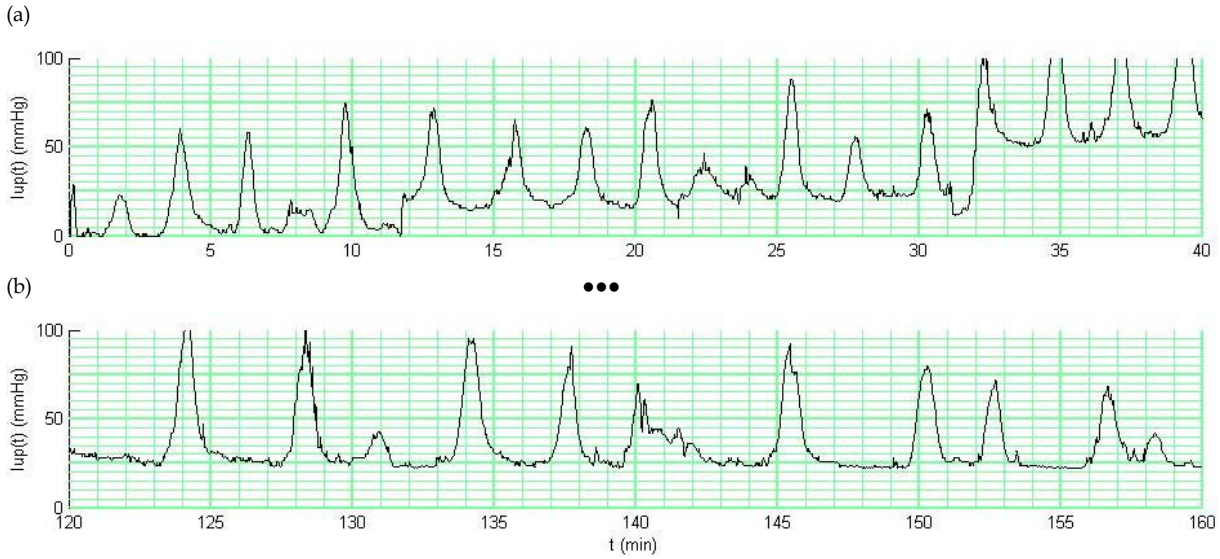

Figure 2.4. Segments of a real intrauterine pressure tracing.

Table 2.2. Model parameters, estimated from the full physiological record corresponding to Figure 2.4

	Standard deviation	**Autoregressive model coefficients (standard deviation)**
Amplitude (mm Hg)	20.3	
Frequency (min^{-1})	0.10	-1.04; 0.14; 0.12; 0.05; -0.06; -0.03; 0.003; 0.02.
Duration (min)	0.47	(0.74)
Resting tone (mm Hg)	5.4	

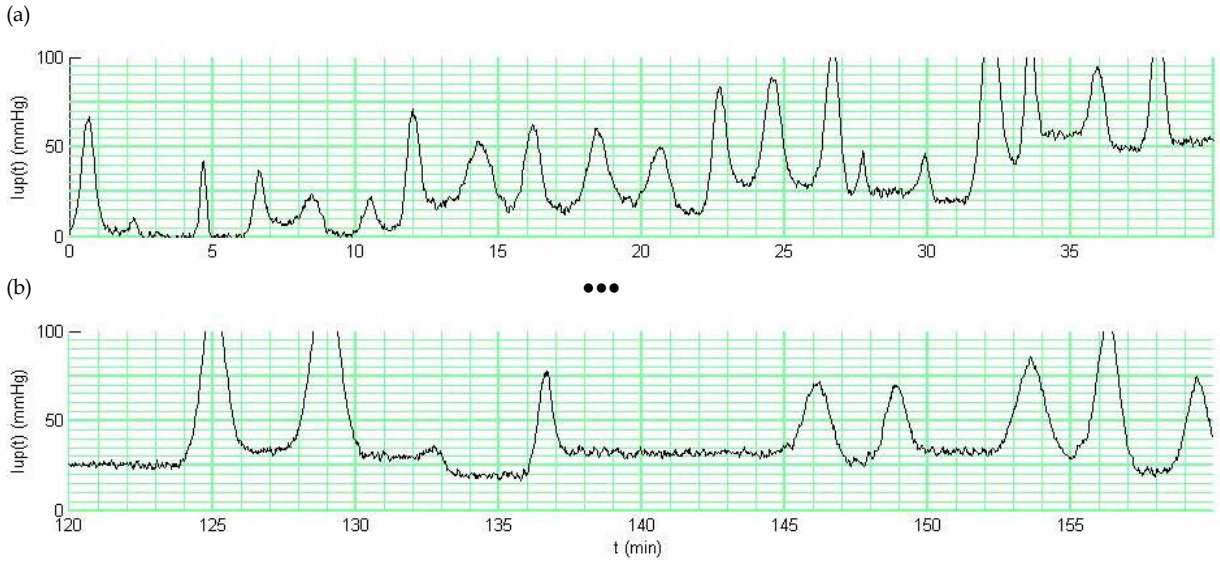

Figure 2.5. Segments of a simulated intrauterine pressure tracing using the parameters of Table 2.2 and 10-min feature averages corresponding to Figure 2.4.

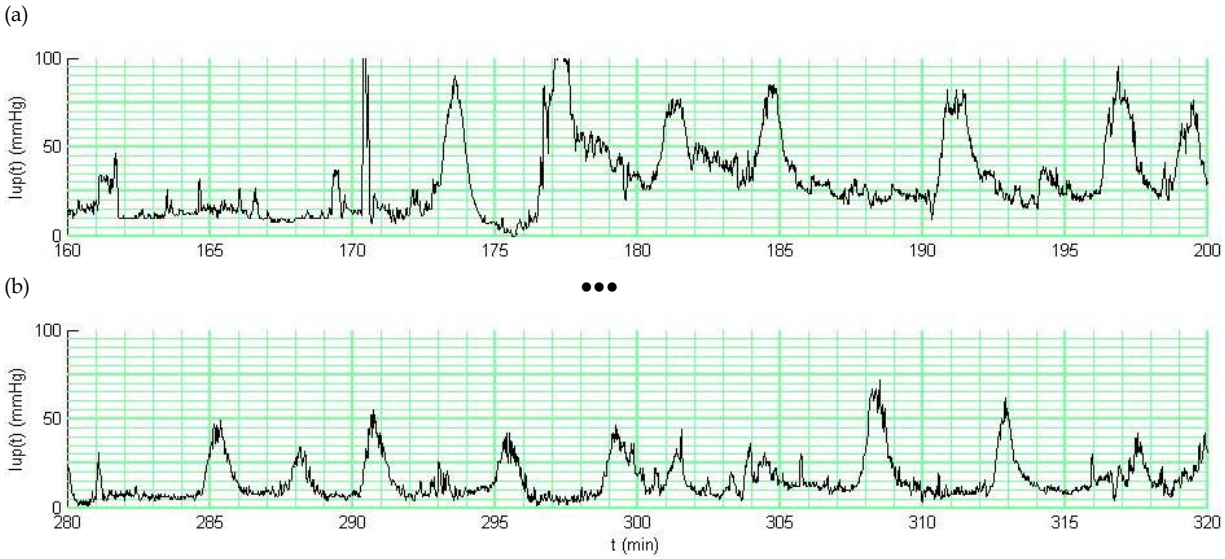

Figure 2.6. Segments of a real intrauterine pressure tracing.

Table 2.3. Model parameters, estimated from the full physiological record corresponding to Figure 2.6

	Standard deviation	**Autoregressive model coefficients (standard deviation)**
Amplitude (mm Hg)	13.6	
Frequency (min^{-1})	0.19	-0.96; 0.14; -0.01; 0.03; -0.03; 0.03; -0.05; 0.02
Duration (min)	0.57	(1.34)
Resting tone (mm Hg)	4.0	

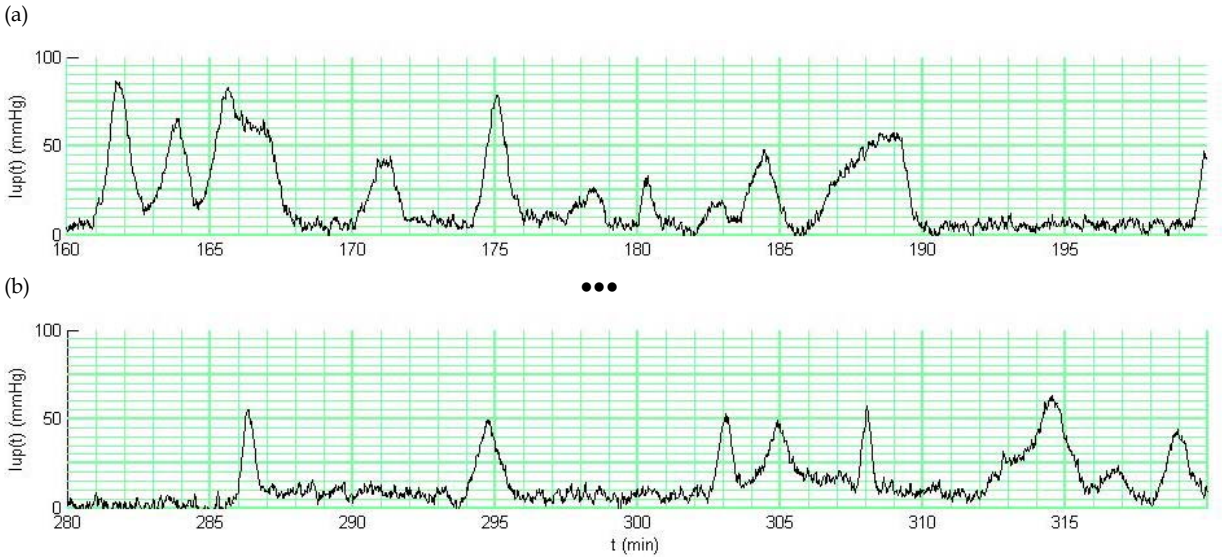

Figure 2.7. Segments of a simulated intrauterine pressure tracing using the parameters of Table 2.3 and 10-min feature averages corresponding to Figure 2.6.

Table 2.4. Expert (I, II, and III) grading of real and simulated tracings. Scale from 0 (unrealistic) to 10 (looks exactly like a real tracing).

Real segment			**Corresponding simulated segment**			**Figures**
I	**II**	**III**	**I**	**II**	**III**	
9	10	10	8	10	9	Fig. 2 a, Fig. 3, a
8	10	10	9	10	9	Fig. 2 b, Fig. 3, b
6	9	10	7	10	10	Fig. 4 a, Fig. 5, a
8	9	10	7	9	9	Fig. 4 b, Fig. 5, b
5	10	10	5	10	10	Fig. 6 a, Fig. 7, a
5	10	10	7	9	10	Fig. 6 b, Fig. 7, b
Averages			**Averages**			
6.8	9.7	10	7.2	9.7	9.5	

The focus of this paper was on signal analysis and model description. The pilot evaluation study provided encouraging results. The presented generator needs further expansion before being incorporated into an educational simulator. At that time, additional validity studies could be carried out before educational use.

In an attempt to mitigate the low realism and limited flexibility of currently available simulation tools, alternative simulation environments are sometimes created using a data base of (fixed) real tracings instead of simulated ones. The approach proposed in this paper provides a more flexible framework for incorporation of clinical scenarios, at similar realism. The model driven approach enhances automaticity during simulation exercises, thereby reducing interventions required by simulation instructors or operators. It also opens up the possibility for true interactivity when combined with, for example, models for the simulation of the effect of drugs on uterine motility.

The model parameters, with intuitive interpretation, facilitate the integration of the intrauterine pressure generator with programmable scripts that can be adapted to specific training needs and scenario requirements for the simulation of spontaneous evolution of uterine contraction signals during labor. The intrauterine pressure generator can be easily manipulated by simulation instructors for this purpose.

We envision the following use in a script-controlled model-driven simulator [35]: to simulate different patients, pathologies, and evolving clinical situations, the uterine contraction waveform features – amplitude, frequency, duration, and resting tone – can be manipulated directly by an instructor/operator or via a pre-programmed time-and-event-based script. Based on the analysis of real data and our experience in mimicking real tracings, we expect that manipulation of parameters of the stochastic processes will add some realism, but a number of pre-set configurations may be sufficient to meet most educational objectives. Expansion with a pharmacokinetic-pharmacodynamic model[36] for drugs that augment or diminish uterine activity will add automaticity, realism, and ease of use.

Several uses of the presented generator in medical educational simulation are envisioned. Combined with a fetal heart rate model, it can form the basis of an interactive screen-based electronic fetal monitoring simulator. Such a program may help healthcare providers develop the necessary skills for identification of critical situations and increase their awareness of the appropriate reactions to them. Integrated in a full-body simulator, it can contribute to a fully immersive simulation environment. Scenarios associated with abnormal uterine activity (e.g. tachysystole, uterine rupture, and placental abruption) can be incorporated, as well as drug interventions. Trainee interfaces for those applications would consist of monitor emulators or real monitors. In both types of simulators, the generated signal could be coupled to models of uterine and placental perfusion and fetal descend.

In conclusion, the presented intrauterine pressure generator was able to simulate different uterine activity patterns in a realistic fashion, and allows for easy manipulation by simulator instructors, adapting responses to specific educational needs.

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Chapter 3

A model for educational simulation of the evolution of uterine contractions during labor

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Abstract

Electronic fetal monitoring remains an important tool in labor ward settings, providing continuous information on fetal heart rate and maternal uterine contractions. A prompt detection of abnormalities in these signals is essential for the timely resolution of situations that may put both mother and fetus at risk. Uterine contraction signals provide information that is important to evaluate the onset and progress of labor, as well as the significance of certain fetal heart rate abnormalities. We present a model for educational simulation of the spontaneous evolution of uterine contractions during labor, which combines a previously published signal generator with literature-based pre-programmed scripts for educationally relevant scenarios. This model is an essential component of a high-fidelity simulator of intrapartum emergencies, aimed to improve the competency of healthcare providers. Real and simulated tracings were presented to three independent clinical experts who judged simulated signals to be indistinguishable or negligibly different from real tracings.

Keywords: medical educational simulation; labor and delivery; uterine activity; script-controlled simulation.

Introduction

Although rare, severe intrapartum complications may put the mother and/or fetus at risk of death or permanent sequela. Prompt detection and time-critical decision making are crucial to avoid an adverse outcome in these cases[1-4]. Because of the rarity of these events, and the ethical and medical-legal issues associated with training on real patients, simulation appears to be the optimal resource for practicing their resolution[5-9].

Electronic fetal monitoring remains one of the most widespread intrapartum assessment tools in industrialized countries. This technology provides continuous information on fetal heart rate (FHR) and uterine contractions (UC) signals[10-13]. Healthcare providers are required to possess the knowledge and skills necessary to recognize the different features and patterns of these signals, leading them to decide on the most appropriate management option.

UC are a crucial part of labor onset and evolution[14-16]. Their features are important to interpret the progress of labor and the significance of certain FHR abnormalities, such as decelerations[17-20]. They are also relevant for the identification of some severe intrapartum complications, such as tachysystole (excessive number of uterine contractions that may lead to reduced fetal oxygenation), uterine rupture, and placental abruption (partial or total separation of the placenta from the uterine bed, potentially causing reduced fetal oxygenation and maternal hemorrhage)[21,17,22-25].

In a previous publication, we presented a UC signal generator for a simulator of normal and critical situations in labor and delivery[26]. To be able to meet educational needs related to the spontaneous evolution of labor, in this study we describe how this generator was combined with pre-programmed scripts to reflect specific scenarios.

Several authors have developed mathematical models for simulation of UC waveforms[27-29]. Andersen et al. and Young explored two mechanisms of intracellular communication that are known to be involved in the modulation of uterine contractions: the action potential propagation[28,29], and the calcium wave propagation[29]. These are only two among many other mechanisms that are known to modulate uterine contractility[30,31]. In spite of their specific interest to study the selected mechanisms, these models do not allow for easy manipulation by a simulation instructor. Vauge et al.[27] developed a more empirical model based on three physiologic states of the uterine muscle: quiescent, contracted, and

refractory. As with the previous models, they do not allow for the manipulation by a simulation instructor, and underlying parameters are not immediately linked to clinically observable features of the UC signal, such as amplitude and frequency. Some commercially available products include a form of simulation of the UC signal. However, the technology behind these products is not disclosed. To our knowledge, no model for the simulation of UC signals for healthcare education and training has previously been published in the scientific literature.

Methods

The signal generator consists of a truncated Gaussian curve with a set of input variables (UC features) that are familiar to healthcare providers in Obstetrics: amplitude, frequency (number of contractions per 10 minutes), duration, and resting tone. The UC signal generator simulates natural variability of these features and of the baseline pressure, using deterministic trends and stationary stochastic processes. These variability components were obtained through the analysis of real intrauterine pressure (IUP) signals. The output variable of this generator is the IUP signal $p_{iu}(t)$. For simulation of spontaneous evolution of uterine activity, we propose to add a script-based engine of the waveform features: amplitude $A(t)$, frequency $F(t)$, duration $D(t)$, and resting tone $RT(t)$ (Figure 3.1).

In the s*pontaneous uterine activity engine*, the evolution of UC signal features $A(t)$, $F(t)$, $D(t)$, and $RT(t)$ is described by linear interpolation between feature values at given points in time, or "knots". These values are set based on data published in the literature and/or in accordance with specific educational scenario requirements. We present three scripts of UC features evolution, associated with three intrapartum scenarios. The description of scripts focuses on those aspects that are essential for the simulation of UC signals.

This model was implemented in Matlab 7.3.0.267 (R2006b), using an Intel® Core™2 CPU,

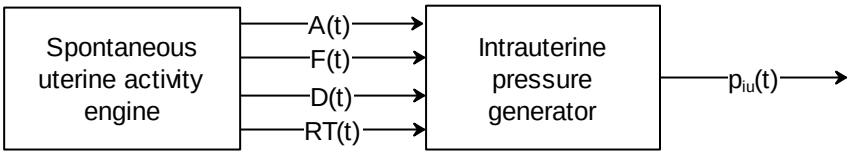

Figure 3.1. Model block diagram.

T7200 @ 2.00 GHz with 2.00 GB of RAM. The program requires approximately 1.7 seconds of running time and 2.5MB of memory.

Normal uterine activity: The vast majority of labors take place without any relevant complication. From the beginning of labor until delivery of the fetus, regular uterine contractions occur with evolving characteristics, accompanied by cervical dilation and fetal decent. During normal labor, healthcare providers evaluate UC characteristics regularly to verify that they are sufficient for the normal progression of labor but not excessive, to avoid putting fetal oxygenation at risk[14,16,32].

Using data from Klavan[14], Parer[16], and Leveno[15], we established the following knots and features values for a normal uterine activity script (Table 3.1). The evolution of UC signal features is given by linear interpolation between those knots. The same method is used for the remaining scripts.

Table 3.1. Knots and features values for *normal uterine activity*[14-16].

Time (min)	**Amplitude (mm Hg)**	**Frequency ((10 min)$^{-1}$)**	**Duration (min)**	**Resting tone (mm Hg)**
≤ 0	0	0.5	0.5	0
120	25	2.0	1.0	8
300	60	3.3	1.3	11
370	65	4.0	1.4	13
≥380	80	5.0	1.5	15

Decline of uterine activity after uterine rupture: In certain clinical situations, uterine activity (whether spontaneous or artificially induced) may decline or even cease unexpectedly, as for example after uterine rupture[21,33]. For this situation we considered a clinical case described by Arulkumaran et al.[21], and Table 3.2 lists the established knots and features values.

In this scenario, health care providers are expected to look for signs of other ensuing complications such as maternal tachycardia, hypotension, and vaginal bleeding, while continuously assessing fetal heart rate.

Table 3.2. Knots and features values for *decline of uterine activity after uterine rupture*[21].

Time (min)	Amplitude (mm Hg)	Frequency ((10 min)$^{-1}$)	Duration (min)	Resting tone (mm Hg)
≤ 14	65	4	1.33	20
16	25	4	1.33	20
≥25	15	4	1.33	20

Uncoordinated uterine hyperactivity during placental abruption: Spontaneous excessive uterine activity may occur during normal labor[34], and has been associated with intrapartum emergencies such as uterine rupture and placental abruption[11,33,35-39]. During placental abruption, two types of UC patterns can be identified[40]. Type one consists of normal or low activity contractions or uncoordinated activity. Type two consists of increased tonus and contraction frequency, possibly combined with uncoordinated activity. For this scenario, we considered a type two uterine activity pattern, and Table 3.3 presents average values of uterine activity features for this situation[40].

In this scenario, health care providers are expected to deliver the baby quickly, while continuously assessing FHR, maternal vital signs, and vaginal hemorrhage, and be aware that oxytocin administration to augment labor will not be effective[40].

The *intrauterine pressure generator* is based on data derived from real tracings, and underwent a preliminary validation, presented in a previous publication[26]. The parameters of the stationary stochastic processes of the signal generator, used for the simulations in the next section, are presented in Table 3.4. Variability of UC features is modeled as Gaussian white noise with the specified standard deviation. Variability of the baseline pressure is modeled with an autoregressive process, using the presented coefficients.

Table 3.3. Knots and features values for *uncoordinated uterine hyperactivity during placental abruption*[40].

Time (min)	Amplitude (mm Hg)	Frequency ((10 min)$^{-1}$)	Duration (min)	Resting tone (mm Hg)
≥ 0	21	10.7	1	38

Table 3.4. Intrauterine pressure generator parameters.

	Standard deviation	Autoregressive model coefficients (standard deviation)
Amplitude	15.0	
Frequency	0.13	-0.49; 0.04; -0.12; 0.06; 0.003; 0.06; -0.03; 0.07
Duration	0.37	(0.46)
Resting tone	3.9	

The scripts described in this manuscript are based on data found in the scientific literature. Probably due to the rarity of the critical incidents reported, independent target data for validation of the simulated tracings could not be found in the scientific literature. Therefore, to evaluate the realism of the tracings and the simulated trends in the integrated model, we asked three independent clinical experts to compare pairs of real and simulated tracings (Figs. 3.2, 3.3 and 3.4). The real tracings for the two critical incidents were taken from the same publications that provided the script parameter data. All experts were specialists in Obstetrics and Gynecology with more than 10 years experience in intrapartum care. They were asked to classify the simulated tracings according to the following scale: 1) The simulated tracing does not represent the real tracing; 2) The simulated tracing is substantially different from the real tracing; 3) The simulated tracing is negligibly different from the real tracing; 4) The simulated tracing cannot be distinguished from the real tracing.

Results

Using the data presented in the tables of the previous section, a script was programmed for each scenario, using linear interpolation between knots for each signal feature. Combining the *spontaneous uterine activity engine* and the *intrauterine pressure generator* (Figure 3.1), we simulated an intrauterine pressure signal for three clinical scenarios: normal uterine activity, decline of uterine activity after uterine rupture, and uncoordinated uterine hyperactivity during placental abruption.

Figures 3.2, 3.3, and 3.4 show real and simulated tracings for these scenarios. Table 3.5 presents the results of the evaluation by three independent clinical experts.

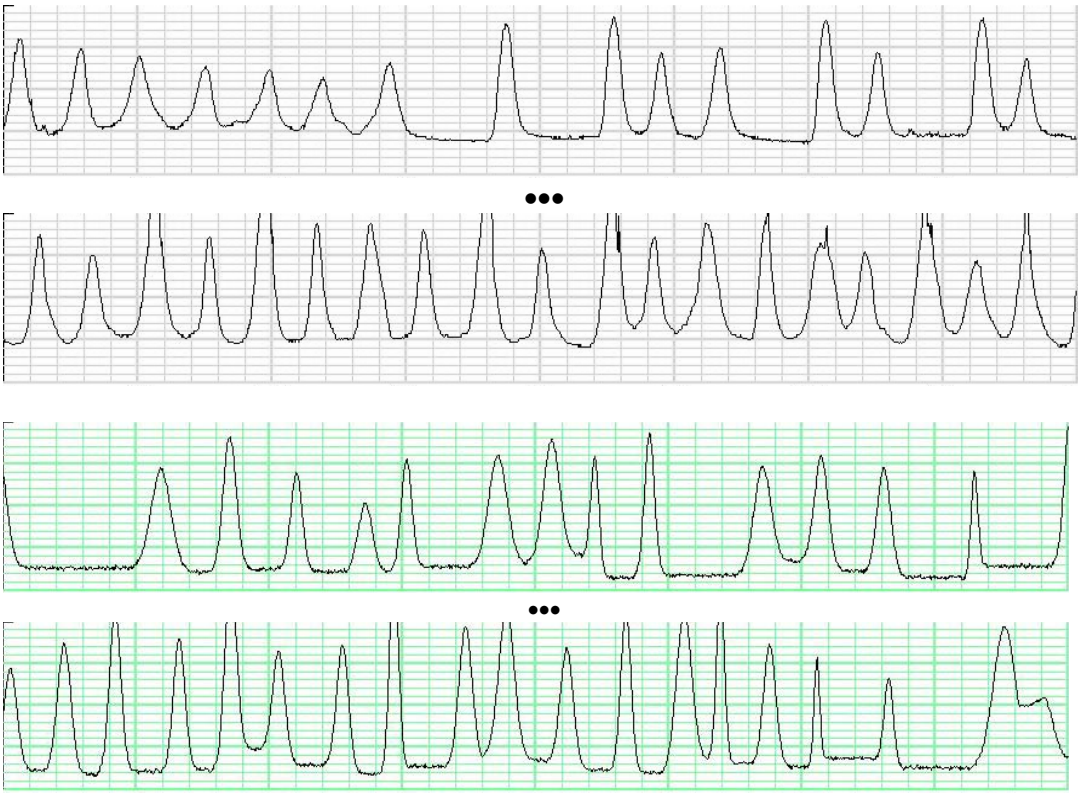

Figure 3.2. Real (top) and simulated (bottom) tracings for normal uterine activity.

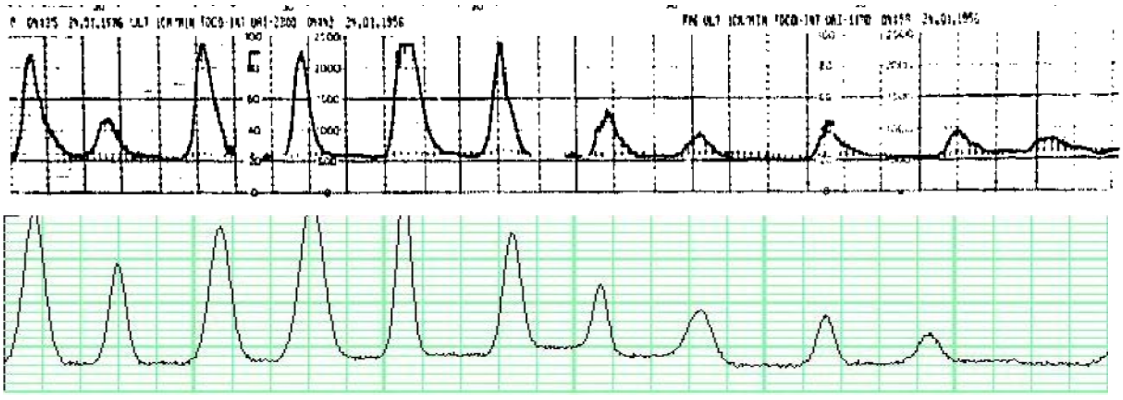

Figure 3.3. Real[21] (top) and simulated (bottom) tracings for decline of uterine activity after uterine rupture.

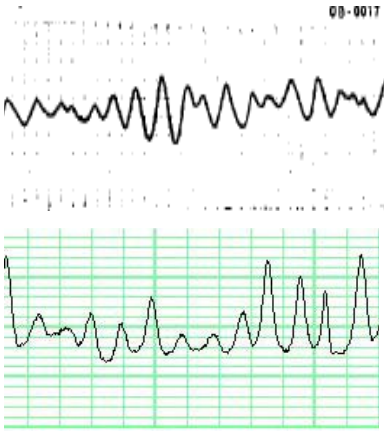

Figure 3.4. Real[4;40] (top) and simulated (bottom) tracings for uncoordinated uterine hyperactivity during placental abruption.

Table 3.5. Expert grading of simulated intrauterine pressure tracings Frequency of scores. (Classification: 1."The simulated tracing does not represent the real tracing", 2."The simulated tracing is substantially different from the real tracing", 3."The simulated tracing is negligibly different from the real tracing", 4."The simulated tracing cannot be distinguished from the real tracing".)

Classification / **Scenario**	**1**	**2**	**3**	**4**
normal uterine activity	0	0	2	1
uterine rupture	0	0	0	3
placental abruption	0	0	3	0
Total	0	0	5	4

All simulated tracings were evaluated as either negligibly different from the corresponding real tracing or cannot be distinguished from the real tracing (Table 3.5). All experts considered the simulated uterine rupture tracing undistinguishable from the real tracing and the simulated placental abruption tracing as being negligibly different from the real tracing.

Discussion

We present a model for educational simulation of the spontaneous evolution of uterine contractions during labor, consisting of the combination of a previously presented intrauterine pressure signal generator[26] and a time-and-event based script. This model is able to simulate different patients, pathologies, and evolving clinical situations, via the manipulation of UC waveform features: amplitude, frequency, duration, and resting tone, using pre-programmed scripts. Data for these scripts, representing three clinically relevant simulation scenarios, were derived from the scientific literature. Three independent clinical experts compared real and simulated tracings and considered the latter to be good or excellent representations of real tracings. This evaluation suggests that the simulated tracings are realistic enough for educational simulation.

The effects of placental abruption on uterine contractions can result in several different patterns of high-frequency activity and hypertonus[11,15,24,36,38,39,40,41]. Also, after uterine rupture, both cessation of contractions and uterine hyperactivity have been described[15,21,22,23,25,33,42]. Because of the different patterns observed in these situations and because of their rarity, which precludes a reliable clinical experience in their identification, it was judged necessary to evaluate the simulated signals via a side-by-side comparison with real tracings, identifying the simulated emergency. Other contraction patterns observed in these situations were not included in this preliminary evaluation of the model. The background lines present in the real tracings displayed in Figures 3.3 and 3.4 made them easily distinguishable from their simulated counterparts, and it was therefore thought unnecessary to withhold information as to the origin of the tracings. The a priori information in this side-by-side comparison and the short length of the real tracings somewhat limits the evaluation. When more data become available, a blind evaluation of real and simulated tracings would provide more robust information on the ability of clinical experts to identify emergencies and to distinguish between real and simulated tracings. An expanded evaluation of the complete model that takes these aspects into account will need to be applied when it is incorporated in a high-fidelity simulator.

UC signals are important for assessing the onset of labor, to interpret labor progress, and to manage dysfunctional labor[32]. Normal uterine contractility is also essential to maintain a stable fetal oxygenation[19]. Assessment of FHR and UC dynamics is an important tool to

predict fetal oxygenation[43]. Combined with a fetal heart rate model, the presented UC model is expected to constitute a strong aid in training the interpretation of electronic fetal monitoring signals.

The adaptability of simulated signals generated by this model provides a flexible framework for incorporation of other patients and clinical scenarios. It also opens up the possibility for further interactivity by incorporating, for example, models of the effect of drugs on uterine motility. The intended use of the presented model is as a generator of monitored signals in screen-based and full-body simulators of obstetric emergencies and less critical labor and delivery situations. Trainee interfaces for those applications consist of monitor emulators or real monitors. In both types of simulators, the generated signal could be coupled to models of uterine and placental perfusion and fetal descend. When integrated into a full-body simulator, this model may contribute to an immersive simulation environment to help healthcare providers develop the necessary skills for identification of critical situations and training of appropriate management.

Acknowledgments

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Chapter 4

A model for educational simulation of the effect of oxytocin on uterine contractions

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Abstract

Exogenous oxytocin is commonly used in labor wards to augment uterine activity, but hyperstimulation may occur as a consequence – a complication which can put fetal oxygenation at risk. We present a model specifically designed for educational simulation that incorporates the pharmacokinetic (PK) and pharmacodynamic (PD) properties of oxytocin, reproducing the effect of this drug on uterine contraction features: amplitude, frequency, and resting tone. The PD model was adapted to take into account underlying spontaneous uterine activity. Based on analysis of the PK model and published data, the number of patient specific parameters was reduced.

This model was used to simulate intrauterine pressure signals from spontaneous and augmented labors. Six 200-minute intrauterine pressure tracings were generated, reflecting the following clinically and educationally relevant situations: spontaneous hypotonic labor, augmented labor, uterine hyperactivity as a consequence of augmented labor, and oxytocin discontinuation after uterine hyperactivity. These tracings were presented to three independent clinical experts. The simulated situations were correctly identified in all 18 tracings. The average realism score was 9.4 on a scale of 0 to 10.

We conclude that the model presented for simulation of the effect of oxytocin on uterine contractions provides sufficiently realistic results to be used in healthcare education. The simulated situations demonstrate that it can easily be adapted to different patients and educational scenarios.

Keywords: healthcare education and training, modeling and simulation, labor and delivery, labor augmentation, uterine activity, oxytocin, pharmacokinetics, pharmacodynamics.

Introduction

Simulation is being increasingly used as an educational tool in acute care medicine. It provides a risk free and controllable environment for training healthcare providers in the technical and nontechnical skills required to handle rare and life-threatening situations[1,2]. Labor and delivery carry with them some risk to the fetus, and educational simulation has been shown to improve outcomes in this area[3-7]. The last decade has seen medical educational simulation thrive[1,8], yet currently available technology and training programs in Obstetrics do not allow for immersive training of emergency situations in this area[4,7,9].

During normal progression of labor, regular uterine contractions provide the forces required for cervical dilatation and fetal descent. Contractions usually increase in frequency and intensity throughout labor and are accompanied by gradual cervical effacement and dilation[10,11]. When labor is slow to progress, uterine activity is frequently stimulated (augmented) by the administration of oxytocin – an endogenous hormone that is also available as a drug for parenteral use[12-15]. In some cases, depending on the infusion rate and on patient sensitivity to the drug, hyperstimulation of uterine activity may occur. Intense and frequent uterine contractions may be associated with decreased blood perfusion of the placental bed, leading to transient decreases in gas exchange across this organ, and a consequent decrease in fetal oxygen supply[12,16]. Healthcare providers aim to reduce the risk of hyperstimulation by following established oxytocin administration protocols, consisting of cautious stepwise increments[14,17,18], and continuous monitoring of the fetus. The latter is usually achieved with the aid of electronic fetal monitoring, also known as cardiotocography. This technology acquires and displays continuous fetal heart rate (FHR) and uterine contraction (UC) signals[11,19].

We previously developed a model for educational simulation of intrauterine pressure signals and spontaneously evolving uterine activity, intended for the use in a full-body model-driven labor and delivery simulator[20]. The main purpose of such model is to provide real-time, automatic, realistic, and consistent evolution of clinical signs and monitored signals, and their response to therapeutic interventions[21]. The aim of this paper is to expand the previous model, by adding an empirical model to simulate the effect of exogenous oxytocin on uterine activity. This effect has been shown to depend on the

underlying spontaneous uterine activity, on infusion rate, and on individual patient sensitivity to oxytocin[22-25].

Specific model requirements include 1) a plausible uterine activity response to different infusion rates of oxytocin; 2) easy manipulation of the patient's sensitivity to the drug; and 3) appropriate interaction with the previously proposed model[20].

To our knowledge, no other mathematical models for simulating the effect of oxytocin on uterine motility have been published in the scientific literature. This may be due to multiple factors, including 1) the simultaneous presence of exogenous and endogenous oxytocin[15,25], 2) the physiologic and pharmacologic changes taking place throughout pregnancy[26-28], and 3) the multiple mechanisms of modulation of uterine activity[29-31].

Methods

Figure 4.1 presents an expanded block diagram, adding models of oxytocin pharmacokinetics (PK) and pharmacodynamics (PD) to the work presented by Bastos et al.[20]. Intrauterine pressure $p_{iu}(t)$ is generated based on the UC waveform features: amplitude A(t), frequency F(t), duration D(t), and resting tone RT(t). Spontaneous evolution of these features is pre-programmed in scripts: $A_s(t)$, $F_s(t)$, $D_s(t)$, and $RT_s(t)$. An oxytocin infusion rate of r(t) will cause the drug concentration c(t) to rise according to the PK model. UC waveform features will reflect both spontaneous uterine activity and concentration of administered oxytocin, combined in the PD model.

Oxytocin PK model

A common approach to modeling the pharmacokinetics of a drug is to represent the

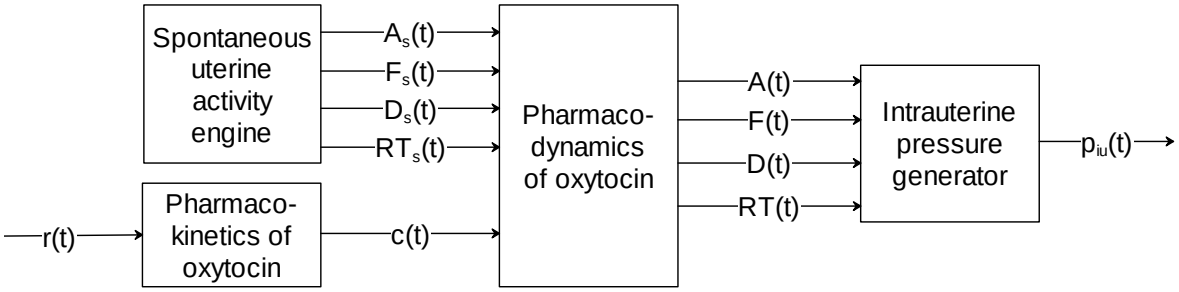

Figure 4.1. Model block diagram.

plasma concentration time profile as a sum of exponentials[32-34]. Typically, these models involve one to three exponentials. Studies of oxytocin pharmacokinetics point to a single exponential model[13,27,35-39]. However, in these studies it is not always clear if multiple-exponential models were explored. Given that oxytocin for labor augmentation is usually administered at constant infusion rates[11,14,17] and post-infusion data are scarce, multiple exponentials are difficult to identify[32,33]. A state-variable formulation of a single exponential plasma kinetics model is described by the set of equations (4.1):

$$\begin{cases} \dot{m}(t) = -\lambda\, m(t) + r(t) \\ c_{pl}(t) = \dfrac{1}{V_1} m(t) \end{cases} \tag{4.1}$$

where the input variable r(t) is the oxytocin infusion rate, the state variable m(t) is drug mass, and the output $c_{pl}(t)$ is the plasma concentration of the drug. Parameters λ and V_1 represent the disposition rate constant and the volume of distribution, respectively. An equilibration equation with a single parameter is often added to the PK model to simulate distribution to the drug effect-site. However, several studies indicate that, during constant infusion administration of oxytocin, the time to reach a steady-state effect is approximately the same as the time to reach steady-state plasma concentration[13,24,28,38,40]. In this study, we therefore ignored the effect of equilibration between plasma and effect-site concentrations on onset and decay.

By normalizing the plasma concentration to the infusion rate, we reduce the number of PK parameters and the output concentration (see Figure 4.1) can be presented in units with a straight forwards clinical interpretation. The steady state response to an infusion rate:

$$r(t) = R\,u(t) \tag{4.2}$$

where u(t) is the unit step function, is:

$$c_{pl_{SS}} = \frac{R}{\lambda V_1} \tag{4.3}$$

By normalizing the plasma concentration as follows:

$$c(t) = \lambda V_1 c_{pl}(t) = \lambda\, m(t) \tag{4.4}$$

we guarantee that:

$$c_{ss} = R \tag{4.5}$$

Equation (4.1) can then be simplified to:

$$\dot{c}(t) = \lambda\left[r(t) - c(t)\right] \tag{4.6}$$

As was demonstrated in more detail for a bolus dose by van Meurs et al.[41], without loss of generality, the PD model (see next section) can be formulated in terms of c(t) and an infusion rate resulting in 50% of the maximum effect, ER_{50}, rather than in terms of $c_{pl}(t)$ and a plasma concentration resulting in the same effect, EC_{50}. The result of this adaptation of the traditional PK-PD model is that we eliminate the parameter V_1, and replace the PD model parameter EC_{50} by the parameter ER_{50}, which has a more direct clinical interpretation.

Oxytocin PD model

The traditional E_{max} model consists of a sigmoidal function describing the concentration-effect relationship[42-44]:

$$E(t) = E_{\min} + (E_{\max} - E_{\min})\frac{c(t)^{\gamma}}{EC_{50}^{\gamma} + c(t)^{\gamma}} \tag{4.7}$$

where c(t) is the drug concentration and E(t) the drug effect. The parameters E_{min} and E_{max} represent the minimum and maximum drug effects, respectively; EC_{50} was introduced in the previous section and is the main sensitivity parameter[34,43]; the parameter γ governs the curve slope.

As presented in Figure 4.1 and based on equation (4.7), the effect of oxytocin is modeled for each UC feature: amplitude, frequency, duration and resting tone – inputs of the intrauterine pressure generator proposed in Bastos et al.[20]. Using equation (4.7) as is would result in a high number of model parameters (4 parameters for each feature; 16 parameters in total), which would make the system difficult to identify. However, analysis of literature data allows for simplifications and a considerable reduction in the number of parameters.

A statistical analysis (t-test, significance at $p < 0.05$) of published data[24] showed that in a dosing range of 0 to 2 mU/min, oxytocin has no significant effect on the duration of uterine contractions. Data consisted of individual mean values of UC duration, before and during administration of 1 and 2 mU/min of oxytocin, in a population of 10 patients. In the absence of further data that could point to an effect of oxytocin on the duration of UC at higher infusion rates, we assume that such effect is not significant.

To reflect the dependency on the underlying spontaneous uterine activity[22,25,45], we substituted the constant minimum effect in equation (4.7) by the scripted spontaneous values of the UC features: $A_s(t)$, $F_s(t)$, and $RT_s(t)$ (see Figure 4.1).

Few studies describing the effect of oxytocin on individual contraction features are available[12,40,45]. Graphs presented in Sica-Blanco and Sala[45] and in Amaya *et al.*[40] demonstrate that UC frequency and amplitude evolve in parallel during oxytocin administration. Based on these observations, we use a single sensitivity parameter for amplitude and frequency, AFR_{50}, and a single γ for those features. The substitution of EC_{50} by ER_{50} was presented in the previous section. Other observations in Sica-Blanco and Sala[45] point to irregular decreases in amplitude and frequency following oxytocin curtail. Given the ambiguous nature of the data and to keep the model as simple as possible, this option is not considered in the present model. Kruse *et al.*[12] point out that the resting tone has a different evolution from amplitude and frequency: "important increases of the resting tone are seen with an already maximal uterine contractility". This can be modeled by a different sensitivity parameter for this feature: $RTR_{50}>AFR_{50}$. For the time being, we assume that the γ for resting tone is identical to the one for amplitude and frequency.

Equations (4.8) to (4.10) describe the resulting oxytocin PD model. The remaining six parameters are the sensitivities AFR_{50} and RTR_{50}, the maximum feature values A_{max}, F_{max}, and RT_{max} and the slope parameter γ.

$$A(t) = A_s(t) + (A_{\max} - A_s(t))\frac{c(t)^\gamma}{AFR_{50}^\gamma + c(t)^\gamma} \tag{4.8}$$

$$F(t) = F_s(t) + (F_{\max} - F_s(t))\frac{c(t)^\gamma}{AFR_{50}^\gamma + c(t)^\gamma} \tag{4.9}$$

$$RT(t) = RT_s(t) + (RT_{\max} - RT_s(t))\frac{c(t)^\gamma}{RTR_{50}^\gamma + c(t)^\gamma} \tag{4.10}$$

Parameter estimation

Model parameters were estimated based on data obtained from the scientific literature[38,40,45,46], from real intrauterine pressure tracings, and from expert opinion.

The disposition rate constant λ, from the PK model (see equation (4.6)), characterizes the time profile of the normalized concentration c(t). It defines the time it will take for the concentration to reach steady-state during a constant infusion, and the time it will take for the drug to be eliminated from the body[32-34]. Oxytocin pharmacokinetic studies indicate that steady-state is reached in approximately 40 minutes[17,35,38,47], which can be achieved by setting λ to 0.0693 min^{-1}. This and other PK-PD model parameter values are listed in Table 4.1.

PD model parameters A_{max}, F_{max}, and RT_{max} reflect the maximum response to oxytocin administration for labor augmentation. RT_{max} and A_{max} were set to the maximum values found in the literature for augmented labor[46]. A clinical expert with experience and routine practice in uterine activity monitoring established the value of F_{max} as the highest frequency of contractions observed in tracings of women with tachysystolic contractions.

PD model parameters AFR_{50} and γ were estimated using published graphical data[40]. Data consisted of UC frequency values in steady-state for different infusion rates (0, 2, 4, and 8 mU/min) in a population of 10 women during the early stages of labor. The Matlab (Mathworks, Inc.) function *lsqnonlin* was used to find the optimal fit of simulated to real data for each patient. A population average pharmacokinetics, described by equation (4.6), was assumed for all patients. The function *lsqnonlin* solves nonlinear least square optimization problems[48], using a large-scale trust region reflective Newton algorithm[49,50]. Sica-Blanco and Sala[45] show that uterine activity of women during the early stages of labor returns to its initial value after oxytocin curtail. This suggests that, at this early stage, spontaneous uterine activity does not evolve significantly. Therefore, the PD model input variable $F_s(t)$ (spontaneous frequency) was assumed constant and equal to the baseline frequency. The distribution of the estimated AFR_{50} was 7.88 (2.49-23.14) mU/min (median(range)) and of the estimated γ 1.11 (0.53-2.73). The wide ranges are consistent with clinically observed inter-patient variability in sensitivity to oxytocin.

Independent clinical experts and statements in the scientific literature[12,45,46] concur in the opinion that oxytocin affects resting tone. Yet, unambiguous numerical data for such effect could not be found. For this reason, RTR_{50} was estimated based on:

- A quantitative statement: "Infusion rates of 4 mU/min or less do not usually produce a significant increase in tonus, despite marked stimulation of uterine contractions."[45], and

- A graph of the resting tone in steady-state, during constant oxytocin infusion in one patient[45].

Sica-Blanco and Sala[45] studied the uterine activity response to several infusion rates of oxytocin (1, 2, 4, 8 and 16 mU/min, and occasionally higher infusion rates) in sixty women during the early stages of labor. In this study, recorded intrauterine pressure signals were analyzed in terms of the evolution of uterine activity and UC features during onset, maintenance, and decay of oxytocin effect. The pre-existing level of uterine activity was recorded during two or more hours before oxytocin administration. The Matlab routine described above, *lsqnonlin*, was used to fit simulated to real data to estimate RTR_{50} (see equation (4.10)). As for frequency and amplitude, the spontaneous resting tone $RT_s(t)$ was considered constant, using the spontaneous value observed before oxytocin administration was started[45].

Table 4.1. Oxytocin pharmacokinetic and pharmacodynamic model parameters.

Model	Parameter	Value	Units
PK	λ	0.0693	min^{-1}
PD	A_{max}	80	mm Hg
	F_{max}	0.7	min^{-1}
	RT_{max}	20	mm Hg
	AFR_{50}	7.9	mU/min
	RTR_{50}	33.0	mU/min
	γ	1.11	–

Model evaluation

Literature data on pharmacokinetics and pharmacodynamics of oxytocin is very limited, which precludes a formal validation including a comparison of the PK-PD model results with independent target data. As an alternative, a questionnaire was designed to assess the realism of intrauterine pressure tracings generated by the model to simulate the evolution of uterine activity during oxytocin augmentation. Six tracings were presented to three independent clinical experts, all with more than five years experience as a specialist

in Obstetrics and Gynecology. Each simulated tracing represented one of the following educationally relevant clinical situations:

A. Spontaneous hypotonic labor.
B. Spontaneous hypotonic labor treated with successive increments of oxytocin infusion rates until adequate uterine activity is achieved.
C. Spontaneous hypotonic labor treated with successive increments of oxytocin infusion rates, evolving unexpectedly into uterine hyperactivity.
D. Spontaneous hypotonic labor treated with successive increments of oxytocin infusion rates, evolving unexpectedly into uterine hyperactivity, followed by oxytocin curtail to relieve the latter.

The simulated oxytocin administration protocol followed the guidelines adopted at the institution where the clinicians worked. These contain successive increments in oxytocin intravenous infusion rates. The infusion rate starts at 2.5 mU/min for 40 minutes, and increments of 2.5 mU/min are applied every 20 minutes thereafter, until adequate uterine activity is achieved or a maximum rate of 25 mU/min is reached.

Different uterine activity baselines and different levels of sensitivity to oxytocin were combined to simulate different patients and clinical situations. The maximum infusion rate administered depends on the combination of these factors.

Two scripts were designed for the *Spontaneous Uterine Activity Engine* (see Figure 4.1) to create the uterine activity baseline in the absence of exogenous oxytocin. One of these scripts represents a stable spontaneous *hypotonic labor* and consists of low, fixed contraction feature values. The other script represents a *prolonged labor*, i.e., labor starts with a long latent phase, but eventually evolves spontaneously to the active phase (Figure 4.2). Feature and baseline variability are incorporated in the *intrauterine pressure generator* (see Figure 4.1), via stationary stochastic processes[51]. Parameters of these processes were kept constant for all simulations (Table 4.2).

Two different levels of sensitivity to oxytocin were used for the simulations, by adjusting the values of AFR_{50} and RTR_{50}. One of the sensitivity levels corresponds to the parameter values in Table 4.1: AFR_{50} = 7.9 mU/min and RTR_{50} = 33.0 mU/min. The other corresponds to a patient with a higher sensitivity to oxytocin: AFR_{50} = 4.2 mU/min and RTR_{50} = 16 mU/min. For later reference to these sensitivity levels, we will use the terms “average” and “high”, respectively.

For each tracing, clinicians were asked to 1) identify the simulated clinical situation among the four listed cases, including "I don't know" as a possible fifth answer; and 2) attribute a realism score on a scale of 0 ("The tracing is a weak representation of the clinical situation") to 10 ("The tracing is an excellent representation of the clinical situation").

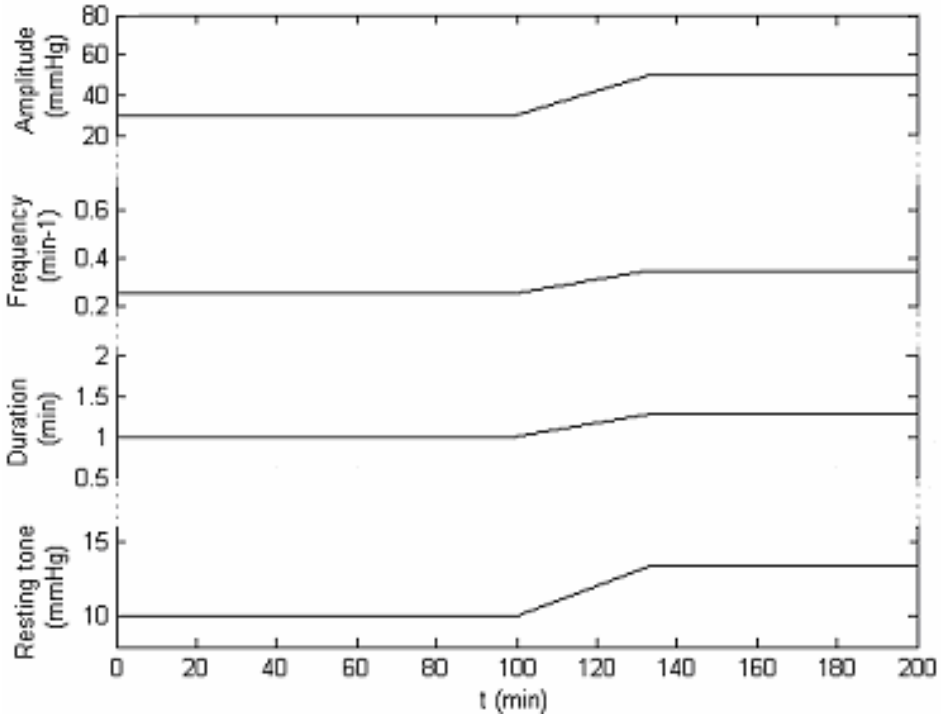

Figure 4.2. Simulated spontaneous uterine contractions features (amplitude $A_s(t)$, frequency $F_s(t)$, duration $D_s(t)$, and resting tone $RT_s(t)$) of the script *prolonged labor*.

Table 4.2. *Intrauterine pressure generator* variability parameters.

	Standard deviation	**Autoregressive model coefficients (standard deviation)**
Amplitude	15.0	
Frequency	0.13	-0.49; 0.04; -0.12; 0.06; 0.003; 0.06; -0.03; 0.07
Duration	0.37	(0.46)
Resting tone	3.9	

Data underlying the six tracings included in the evaluation questionnaire are presented in Table 4.3. A detailed description of three of the six simulations is presented in the results section.

Results

Figures 4.3, 4.4, and 4.6 present three 200-minute simulated intrauterine pressure tracings, corresponding to cases B, C, and D, respectively. To illustrate how the model integrates spontaneous evolution of uterine activity and its response to exogenous oxytocin, Figure 4.5 presents the evolution of UC features used to generate the intrauterine pressure signal in Figure 4.4.

The realism scores attributed by the clinical experts to the six simulated tracings are presented in Table 4.4. All clinical situations were correctly identified by the three clinicians. Realism scores of 9 or 10 were assigned in 17 out of the 18 evaluations. The remaining classification was 8. The average realism score of the 18 evaluations was of 9.4 on a scale of 0 to 10. Thus, this preliminary evaluation suggests that these situations are represented realistically by the described model, and can easily be identified by expert clinicians.

Table 4.3. Input variables and model parameter settings used for simulation of the different patients and clinical situations presented in the evaluation questionnaire. (n.a.: not applicable)

Tracing No	Case	Spontaneous uterine activity script	Drug sensitivity	Maximum Infusion rate (mU/min)
1	C	Prolonged labor	Average	10
2	D	Prolonged labor	Average	10
3	A	Hypotonic labor	n.a.	n.a
4	B	Hypotonic labor	Average	7.5
5	D	Hypotonic labor	High	7.5
6	B	Hypotonic labor	High	5

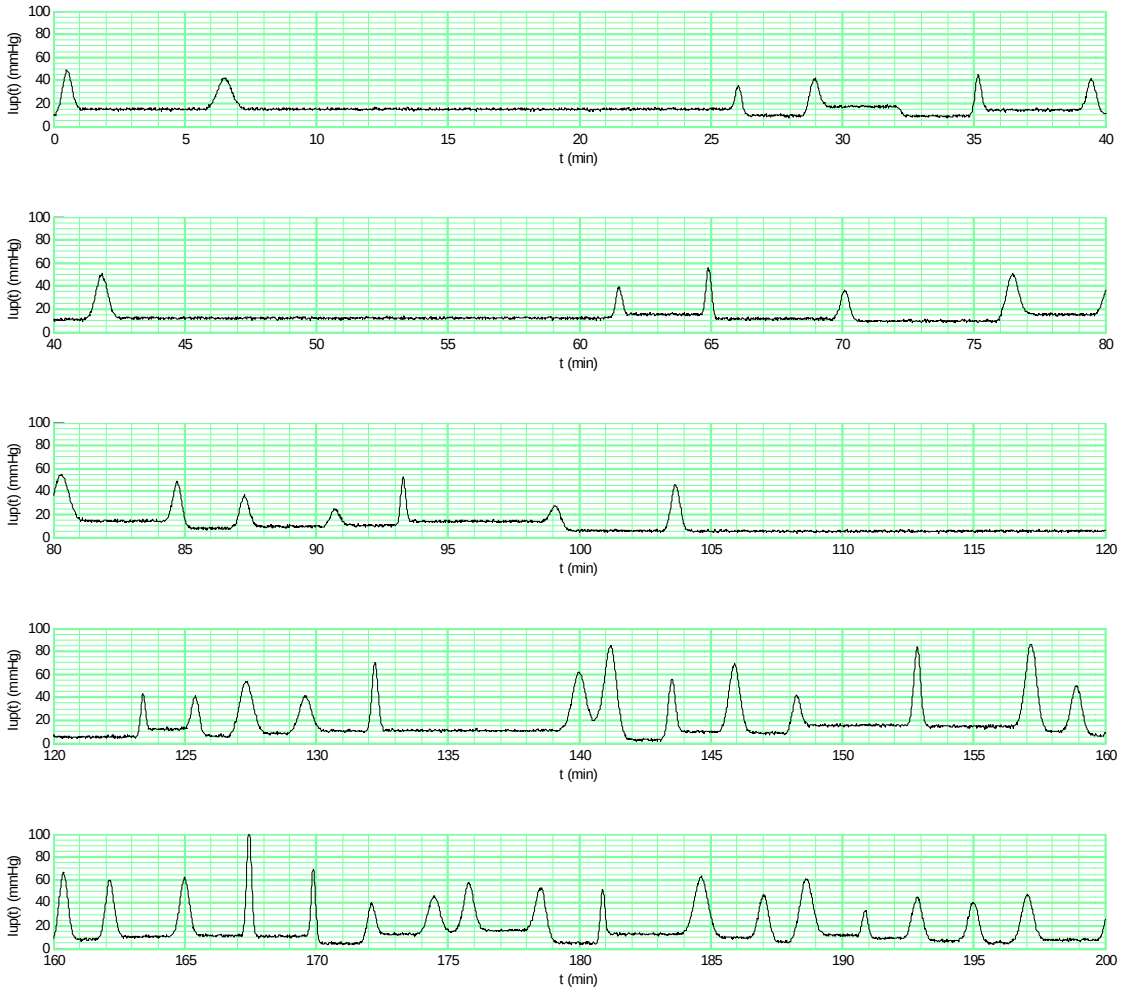

Figure 4.3. Simulated intrauterine pressure signal of a patient with hypotonic labor and average sensitivity to oxytocin, treated with successive increments of oxytocin until adequate uterine activity is achieved (case B).

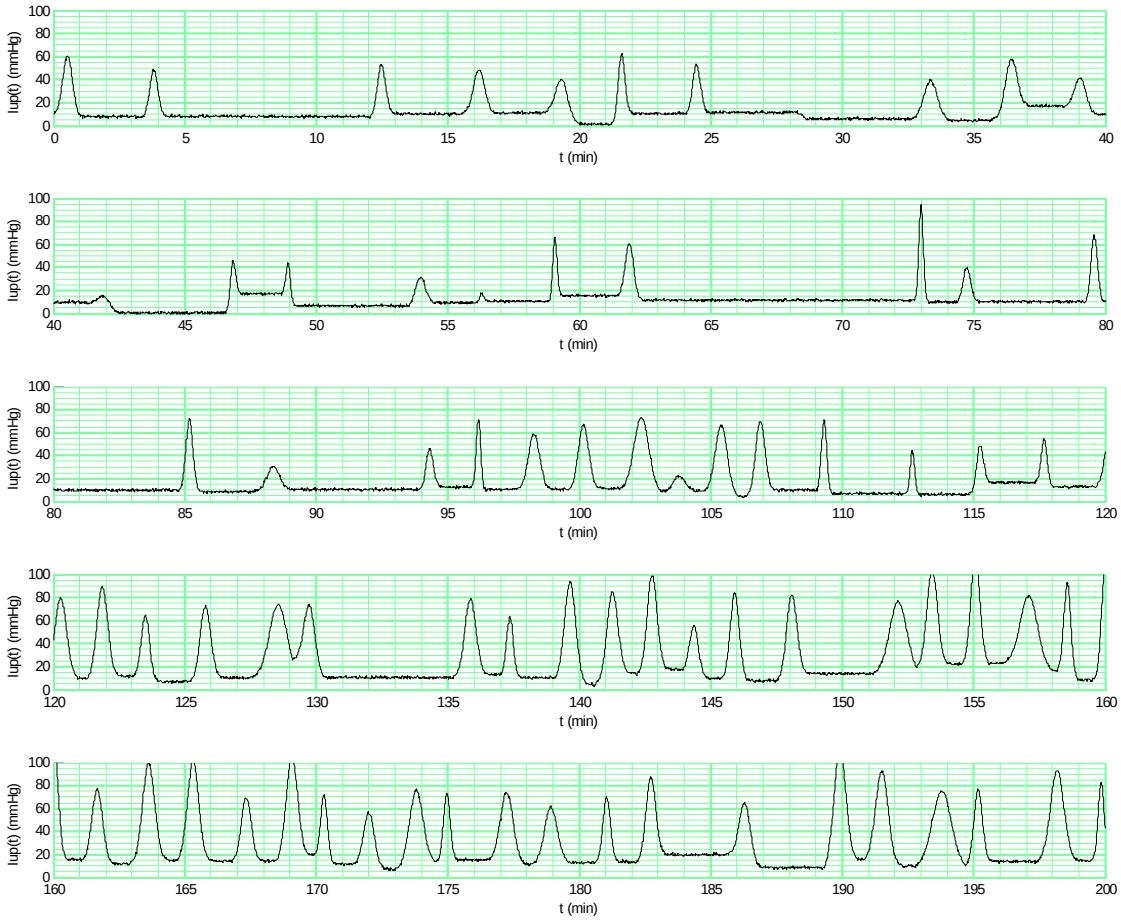

Figure 4.4. Simulated intrauterine pressure signal of a patient with hypotonic labor and average sensitivity to oxytocin, treated with successive increments of oxytocin, evolving unexpectedly into uterine hyperactivity due to combination of the oxytocin effect and spontaneous evolution of uterine activity (case C).

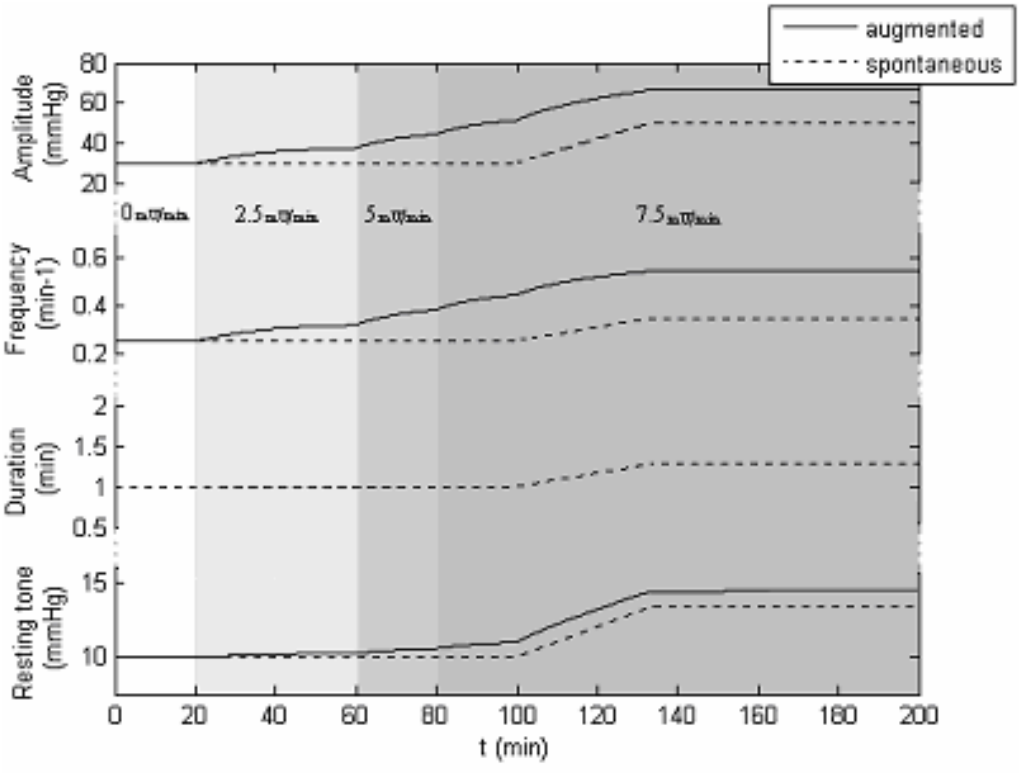

Figure 4.5. Simulated uterine contraction features used to generate the intrauterine pressure signal in Figure 4.4: (- -) piece-wise linear script of the underlying spontaneous evolution: $A_s(t)$, $F_s(t)$, $D_s(t)$, $RT_s(t)$; and (––) combination of spontaneous evolution and uterine activity response to oxytocin: A(t), F(t), D(t), RT(t) (see Figure 4.1). Different shades of grey represent successive oxytocin increments (see description of administration protocol in the methods section).

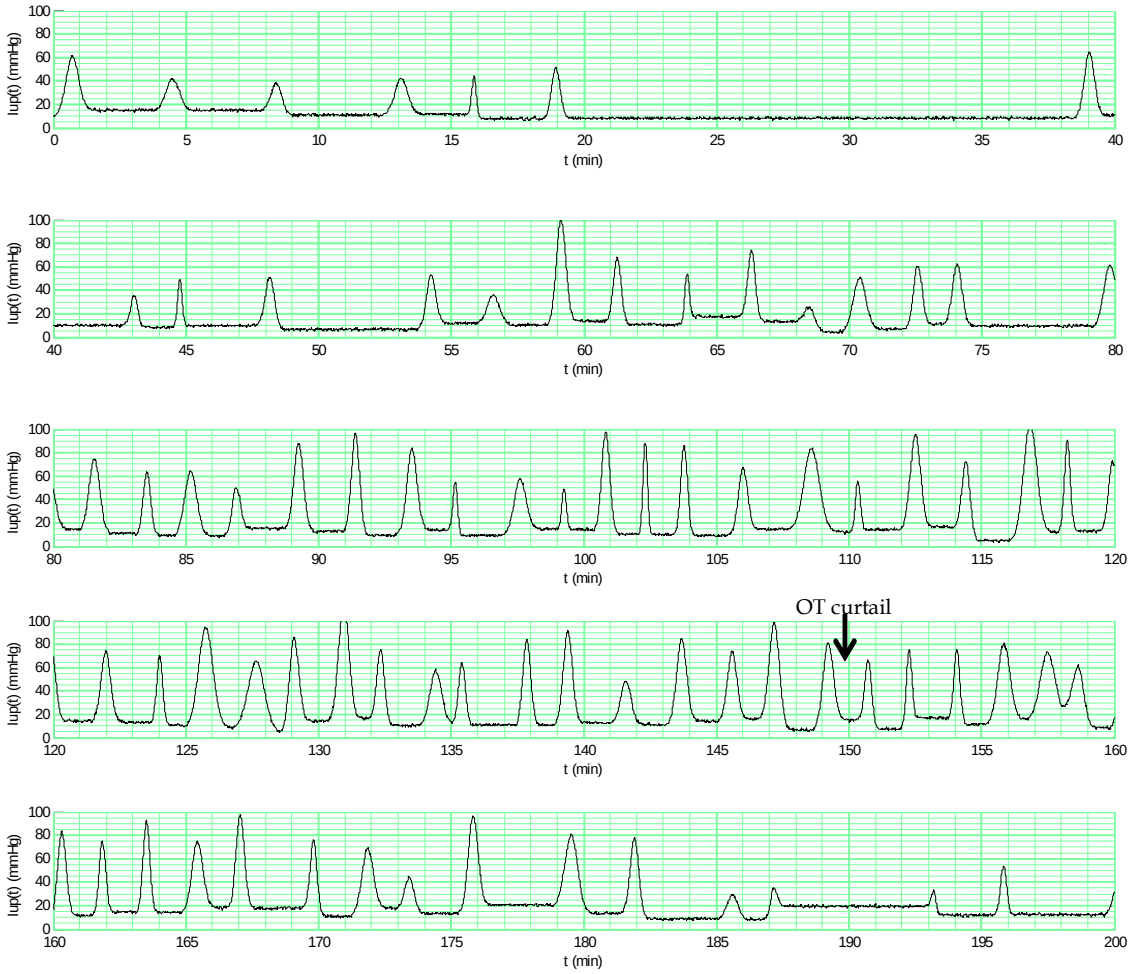

Figure 4.6. Simulated intrauterine pressure signal of the response to oxytocin curtail (arrow) in a patient with uterine hyperactivity due to high sensitivity to oxytocin (case D).

Table 4.4. Identification of simulated clinical situations and realism scores attributed by clinical experts (I, II and III).

Tracing No	Case	Proportion of correctly identified cases	Realism of case representation (0 to 10)			Average realism score
			I	II	III	
1 (Fig. 4.4)	C	3/3	10	9	10	9.67
2	D	3/3	8	9	10	9
3	A	3/3	10	9	9	9.3
4 (Fig. 4.3)	B	3/3	9	9	10	9.3
5 (Fig. 4.6)	D	3/3	10	9	10	9.67
6	B	3/3	9	9	10	9.3

Discussion

In this paper we expanded a previously developed model[20], incorporating the pharmacokinetic properties of oxytocin and its effect on uterine contraction waveform features. Independent clinical experts were able to correctly identify clinically and educationally relevant clinical situations underlying simulated tracings. They also considered them to be "good" or "excellent" representations of those situations.

The PK model consists of a single differential equation for a drug concentration normalized to infusion rate. The concentration time profile depends on a single parameter: the disposition rate constant λ. Because there is considerable inter-patient variability in the half time of oxytocin ($t_{½} = \ln(2)/\lambda$)[13,24,28,38,40], λ needs to be adjusted if simulation of different patients is required. Adapting this parameter would influence, for example, the time to reach normal uterine activity after oxytocin curtail due to hyperstimulation. This could influence the decision on use and timing of tocolysis.

The PD model consists of an original adaptation of the traditional E_{max} model. It takes simulated spontaneously evolving contraction waveform features as a starting point, adding the effect of exogenous oxytocin. The main sensitivity parameters are formulated

in terms of steady state responses to the oxytocin administration rate. To facilitate programming different patients, we carefully simplified the model, eliminating selected PD parameters.

Literature data on pharmacokinetics and pharmacodynamics of oxytocin are scarce. This may be due in part to the fundamental problem that changes in uterine activity cannot be attributed with certainty to spontaneously evolving uterine activity or to exogenous oxytocin. The frequent combination of several uterine contraction features into global uterine activity descriptors further complicates the use of published data. We used all available data for model parameter estimation, thereby ruling out the possibility of model validation with independent target data. As an alternative, recognition of simulated situations by clinical experts, and their opinion on the realism of simulated tracings was chosen. Keeping in mind the intended educational use of the model, we consider such evaluation to be appropriate and sufficient.

The high inter-patient variability in underlying spontaneous activity and sensitivity to oxytocin is a major concern in labor augmentation, particularly in the presence of a scarred uterus. Moreover, oxytocin administration protocols frequently differ among countries and sometimes even among institutions within the same country. In the described model, spontaneous evolution of uterine contraction features can be scripted[20] and the sensitivity of the patient to oxytocin can be adjusted via the parameters AFR_{50} and RTR_{50}. A simulator incorporating this model would thus allow users to train the recognition and appropriate response to uterine hyperactivity. The possibility of simulating patients with different sensitivities to oxytocin has, to our knowledge, not been incorporated in commercially available simulators.

Several other uses of the presented model can be envisioned for healthcare education and training. Combined with a fetal heart rate model, it can form the basis of an interactive screen-based electronic fetal monitoring simulator. Such a program would allow healthcare providers to practice the identification of critical situations and to select appropriate therapeutic interventions, thus increasing their situation awareness and decision making skills. Integrated into a full-body simulator, it can contribute to an immersive simulation environment where many aspects of obstetric management can be safely trained. The trainee interface for this application would consist of a monitor emulator or a real monitor, and patient mannequins for the mother and fetus. In both

types of simulators, the generated intrauterine pressure signal could be coupled to models of uterine and placental perfusion, as well as of fetal descent, further increasing simulation automaticity and realism.

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Chapter 5

A model for educational simulation of the effect of salbutamol on uterine contractions

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Abstract

The use of simulation as a tool for teaching diagnostic and therapeutic skills in acute care medicine has been increasing over the last few years. It provides a risk free and controllable environment for training healthcare providers in rare but life-threatening situations. Labor and delivery is a potentially hazardous process for both mother and fetus, and it can benefit from educational simulation to reduce the risks and improve outcomes. However, available obstetric simulators and training programs provide limited realism and capabilities, which hinders immersive training of obstetric emergencies.

When uterine hyperactivity occurs, associated with compromised fetal oxygenation, the rapid administration of drugs that inhibit contractility (tocolytic drugs) is the best approach to rapidly reverse this situation. By reducing uterine contractility, these drugs allow the normalization of placental bed perfusion and thus increased fetal oxygenation during contraction intervals.

In developed countries, fetal surveillance during labor, at least in high-risk cases, is achieved with the aid of electronic fetal monitoring, also known as cardiotocography. This technology involves the continuous monitoring of fetal heart rate and uterine contractions.

Mathematical models have been previously developed by our team to simulate the more accurate uterine contractions signal – the intrauterine pressure – during spontaneous and augmented labors. In this paper we expand these models with a mathematical model for the simulation of the effect of the tocolytic drug salbutamol on uterine activity. Model simulation results were validated with published literature data. The combination of these models is important for the educational simulation of situations where acute fetal hypoxia is caused by increased uterine contractility, of exogenous or endogenous nature, and where the rapid administration of a tocolytic drug normalizes fetal oxygenation.

The combined models are intended for use in a full-body simulator allowing the immersive training of healthcare providers in response to obstetric emergency situations.

Keywords: healthcare education and training, modeling and simulation, labor and delivery, tocolysis, uterine activity, salbutamol, pharmacokinetics, pharmacodynamics.

Introduction

The use of simulation as a tool for teaching diagnostic and therapeutic skills in acute care medicine has been increasing over the last few years. It provides a risk free and controllable environment for training healthcare providers in rare but life-threatening situations[1-5]. Labor and delivery is a potentially hazardous process for both mother and fetus, and it can benefit from educational simulation to reduce the risks and improve outcomes[6]. However, available obstetric simulators and training programs provide limited realism and capabilities, which hinders immersive training of obstetric emergencies[3,5,7].

Obstetric emergencies are rare but acute situations that put the life of the mother and/or the fetus at risk. For example, acute fetal hypoxia due to increased uterine contractility puts the fetus at high risk of perinatal mortality or long-term neurological sequelae. The rapid administration of drugs that inhibit contractility (tocolytic drugs) is the best approach to rapidly reverse this situation[8-12]. By reducing uterine contractility, these drugs allow the normalization of placental bed perfusion and thus increased fetal oxygenation during contraction intervals[9,13].

In developed countries, fetal surveillance during labor, at least in high-risk cases, is achieved with the aid of electronic fetal monitoring, also known as cardiotocography (CTG). This technology involves the continuous monitoring of fetal heart rate (FHR) and uterine contractions (UC)[13,14].

Mathematical models have been previously developed by our team to simulate the more accurate uterine contractions signal – the intrauterine pressure – during labor[15], the spontaneous evolution of uterine activity during labor[16], and the effect of oxytocin, a drug that stimulates uterine activity[17]. In this paper we expand these models with a model for the simulation of the effect of the tocolytic drug salbutamol on uterine activity. With this integration, the combined models are able to simulate intrauterine pressure signals in spontaneous or augmented labor (artificially stimulated with oxytocin), as well as the effect of administering a tocolytic drug.

The model is intended for use in a full-body simulator allowing the immersive training of healthcare providers in response to obstetric emergency situations. For this purpose, it needs to respond realistically to the intravenous administration of salbutamol, both in the suppression of uterine activity and in the recovery of normal uterine activity after

cessation of drug administration. No mathematical models of the effect of salbutamol on uterine contractility were found in the literature. The next section presents the developed model and the method used for its validation.

Methods

Figure 5.1 presents the block diagram of the combined models. Each model is described briefly below:

- The *intrauterine pressure generator* simulates intrauterine pressure tracings $p_{iu}(t)$ based on a set of input variables representing clinically observable uterine contraction features: amplitude A(t), frequency F(t), and duration D(t), and the resting tone RT(t)[15];
- The *spontaneous uterine activity engine* provides pre-programmed scripts for simulation of spontaneous evolution of the uterine contraction features $A_s(t)$, $F_s(t)$, $D_s(t)$, and $RT_s(t)$[16];
- The *pharmacokinetics of oxytocin*[17] and *pharmacokinetics of salbutamol* describe the drug concentration profiles, $c_{ot}(t)$ and $c_{st}(t)$, given the infusion rates $r_{ot}(t)$ and $r_{st}(t)$, respectively.
- The *pharmacodynamics of oxytocin and salbutamol* represents the – possibly combined - effect of the plasma concentrations to augment (oxytocin)[17] or reduce (salbutamol) uterine activity, taking the spontaneously evolving uterine activity as a baseline.

The new salbutamol pharmacokinetics (PK) model, and the pharmacodynamics (PD) model expanded with salbutamol effects, are described in detail below.

Pharmacokinetic model

To our knowledge, no complete salbutamol PK model has been published in the scientific literature. A common approach to modeling the pharmacokinetics of a drug is to represent the plasma concentration time profile as a sum of one to three exponentials[18-20]. We assume, for now, that a single exponential model can describe the pharmacokinetics of salbutamol. We will come back to this assumption in the discussion section. A single exponential plasma kinetics model is given by the set of equations (5.1)[19], where the input

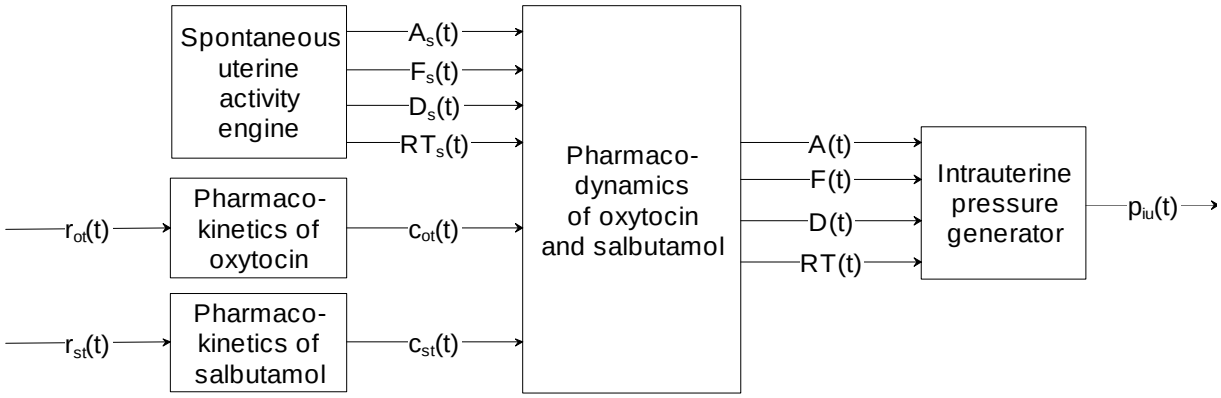

Figure 5.1. Model block diagram.

variable $r_{st}(t)$ is the salbutamol infusion rate, the state variable m(t) is the drug mass, and the output $c_{pl,st}(t)$ is the plasma concentration. Parameters λ and V_1 represent the disposition rate constant, and the volume of distribution, respectively.

$$\begin{cases} \dot{m}(t) = -\lambda m(t) + r_{st}(t) \\ c_{pl,st}(t) = \dfrac{1}{V_1} m(t) \end{cases} \tag{5.1}$$

An equilibration equation with a single parameter is often added to a PK model to simulate distribution to the drug effect-site. However, the delay in equilibration between plasma and effect site is not observable in the available drug effect data, which is restricted to 10-minute averages of uterine contraction features. Therefore, we ignore effect-site equilibration.

By normalizing the plasma concentration on infusion rate, the number of PK parameters is reduced by one, and the output concentration is presented in units that are easier to interpret. Assume an infusion rate:

$$r_{st}(t) = Ru(t) \tag{5.2}$$

where u(t) is the unit step function and R is a constant. Then the steady state plasma concentration can easily be derived from equation (5.1):

$$c_{pl,st_{ss}} = \frac{R}{\lambda V_1} \tag{5.3}$$

By normalizing the plasma concentration as follows:

$$c_{st}(t) = \lambda V_1 c_{pl,st}(t) = \lambda m(t) \tag{5.4}$$

we guarantee that:

$$c_{st_{ss}} = R \tag{5.5}$$

Equation (5.1) can then be written as:

$$\dot{c}_{st}(t) = \lambda[r_{st}(t) - c_{st}(t)] \tag{5.6}$$

As was demonstrated in more detail for a bolus dose by van Meurs et al.[21], without loss of generality the PD model (see next section) can be formulated in terms of $c_{st}(t)$ and an infusion rate resulting in 50% of the maximum effect, ER_{50}, rather than in terms of $c_{pl,st}(t)$ and a plasma concentration resulting in the same effect, EC_{50}. The result of this adaptation of the traditional PK-PD model is that we eliminate the parameter V_1, and replace the PD model parameter EC_{50} by the parameter ER_{50}, which has a more direct clinical interpretation.

Pharmacodynamic model

Equation (5.7) presents the model for the effect of oxytocin on UC amplitude as presented by Lobo et al.[17]. Equivalent models were used for frequency and resting tone.

$$A_{s,ot}(t) = A_s(t) + [A_{\max} - A_s(t)]\frac{c_{ot}^{\gamma_{ot}}(t)}{AR_{50,ot}^{\gamma_{ot}} + c_{ot}^{\gamma_{ot}}(t)} \tag{5.7}$$

The independent variables are $A_s(t)$, representing UC amplitude due to spontaneous uterine activity, and $c_{ot}(t)$, the oxytocin concentration normalized to infusion rate. The dependent variable $A_{s,ot}(t)$ represents the resulting UC amplitude. This relationship contains the parameters A_{max}, the maximum amplitude that can be achieve during labor augmentation with oxytocin, $AR_{50,ot}$, the oxytocin infusion rate resulting in 50% of the maximum effect in steady state, and γ_{ot}, governing the slope of the relationship. Following a similar PD modeling approach, we propose to represent the effect of the salbutamol concentration via the inhibitory model of equation (5.8).

$$I_{st}(t) = \frac{IR_{50,st}^{\gamma_{st}}}{IR_{50,st}^{\gamma_{st}} + c_{st}^{\gamma_{st}}(t)} \tag{5.8}$$

The independent variable of this relationship is $c_{st}(t)$, introduced in the previous section. The dependent variable $I_{st}(t)$ represents the inhibition of UC amplitude with a value going from 1 in absence of salbutamol ($c_{st}(t) = 0$) to 0 for very high salbutamol concentrations

($c_{st}(t) \rightarrow \infty$). This relationship contains the parameters $IR_{50,st}$, the salbutamol infusion rate resulting in 50% inhibition, and γ_{st}, governing the slope of the relationship. The UC amplitude $A_{s,ot,st}(t)$ under the combined influences of spontaneous evolution, oxytocin, and salbutamol is computed as follows:

$$A_{s,ot,st}(t) = I_{st}(t) A_{s,ot}(t) \tag{5.9}$$

corresponding to the variable A(t) in Figure 5.1. Since no indication was found in support of distinct inhibitory effects of salbutamol on amplitude and frequency, we assume a single inhibitory model for these features. Two studies by Lipshitz et al. indicate that duration and resting tone are not affected by salbutamol[22,23].

Parameter estimation

Because no simultaneous PK-PD data for salbutamol could be found in the literature, we used dose-response data from Lipshitz and Baillie[22] to estimate the parameters λ, $IR_{50,st}$ and γ_{st} of equations (5.6) and (5.8). In this study, patients had elective inductions of labor. Oxytocin infusion rate was increased until adequate, stable uterine contractions occurred, and was maintained for the remainder of the experiment. Subsequently, salbutamol was administered intravenously at an infusion rate of 10 μg/min during a 20-minute period. Intrauterine pressure was recorded during the whole study. Ten-minute averages of amplitude and frequency were reported for the 10 minutes before salbutamol infusion, the first 10 minutes during infusion, the subsequent 10 minutes during infusion, and for the first 10 minutes after infusion was discontinued. Reported values are population averages. The authors also report that uterine activity took approximately 43 minutes to return to its initial level. A non-linear least squares method implemented via the Matlab function *lsqnonlin* was used to find the best fit for our salbutamol PK-PD model to published values of amplitude and frequency, taking pre-salbutamol infusion conditions as a baseline (Table 5.1). Table 5.2 presents estimated salbutamol PK-PD parameters.

Model verification and validation

In the next section, we present simulation results demonstrating that data from Lipshitz and Baillie[22], used for parameter estimation, are correctly reproduced by the model. The salbutamol PK-PD model was subsequently validated with data from an independent

study by the same group[23], and these results are also presented in the next section. Parameters governing variability of UC features and intrauterine pressure baseline were as specified in Table 2.1 from Bastos et al.[15].

Results

Data used for parameter estimation, and model simulation results are presented in Table 5.3.

Figure 5.2 presents a real intrauterine pressure tracing from Lipshitz and Baillie[22] and a simulated tracing, using the same salbutamol administration protocol.

Data used for parameter estimation were judged to be satisfactorily reproduced by the developed model (Table 5.3).

Table 5.1. Baseline reflecting the Lipshitz and Baillie study[22].

	Value	**Units**
Spontaneous amplitude, $A_{s,ot}(t)$	43.8	mm Hg
Spontaneous frequency, $F_{s,ot}(t)$	4.25	$(10\ min)^{-1}$
Spontaneous duration, $D_{s,ot}(t)$	0.7	min
Spontaneous resting tone, $RT_{s,ot}(t)$	12	mm Hg

Table 5.2. Estimated salbutamol parameters.

PK parameter	**Value**	**Unit**
λ	0.3	min^{-1}
PD parameter	**Value**	**Unit**
$IR_{50,st}$	8.8	$\mu g/min$
γ_{st}	0.7	-

In a second study from Lipshitz et al.[23], salbutamol was administered as an intravenous bolus of 200 µg to seven patients in labor induced with oxytocin. During this study, oxytocin administration was maintained at a constant rate. Table 5.4 lists the baseline for this study. Table 5.5 shows data from Lipshitz et al.[23] and simulation results using the parameters estimated based on Lipshitz and Baillie[22].

Figure 5.3 presents a real intrauterine pressure tracing from Lipshitz et al.[23] and a simulated tracing, using the same salbutamol administration protocol.

All simulation results in Table 5.5 fall within one standard deviation of the target data.

Table 5.3. Published data[22] (mean ± standard deviation) and simulation results in response to a 20-min infusion of 10 µg/min of salbutamol. ((10 min)$^{-1}$: number of uterine contractions per 10 minutes.)

	Lipshitz & Baillie	**Simulation results**
Effect on intensity of contractions		
Initial intensity (mm Hg)	43.82 ± 8.24	43.82
1st 10 minutes period(mm Hg)	26.70 ± 6.37	23.91
2nd 10 minutes period(mm Hg)	20.47 ± 9.22	21.06
10 minutes period after end of infusion(mm Hg)	30.59 ± 7.13	29.47
Effect on frequency of contractions		
Initial frequency ((10 min)$^{-1}$)	4.25	4.25
1st 10 minutes period ((10 min)$^{-1}$)	2.05	2.32
2nd 10 minutes period ((10 min)$^{-1}$)	2.1	2.04
10 minutes period after end of infusion ((10 min)$^{-1}$)	2.75	2.86
Time to initial uterine activity after infusion (min)	42.60 ± 11.60	44

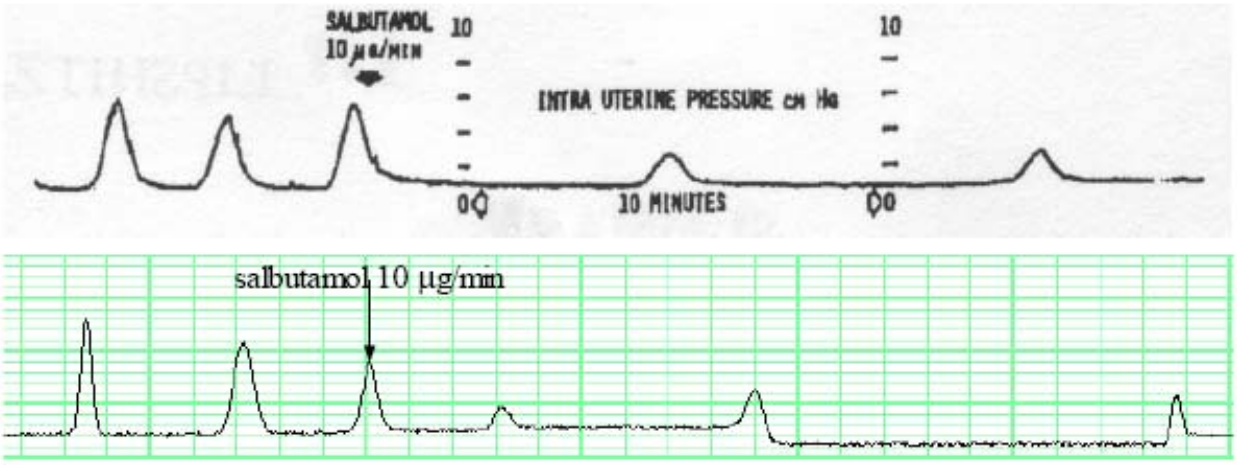

Figure 5.2. Real[22] (top) and simulated (bottom) intrauterine pressure tracings showing the effect of an intravenous administration of 10 µg/min of salbutamol on uterine contractions.

Table 5.4. Baseline reflecting the Lipshitz et al. study[23].

	Value	Units
Spontaneous amplitude, $A_{s,ot}(t)$	60	mm Hg
Spontaneous frequency, $F_{s,ot}(t)$	6.1	$(10\ min)^{-1}$
Spontaneous duration, $D_{s,ot}(t)$	1.5	Min
Spontaneous resting tone, $RT_{s,ot}(t)$	12.5	mm Hg

Table 5.5. Published data[23] (mean ± standard deviation) and simulation results in response to a bolus injection of 200 µg of salbutamol (area of contractions is computed over a 10-min period).

	Lipshitz et al.	**Simulation results**
Before drug administration		
Area of contractions (mm Hg min)	226.75 ± 35.75	222.89
Area below baseline (mm Hg min)	125 ± 28.75	129.5
After drug administration		
Area for 1st 10 minutes (mm Hg min)	137.5 ± 33	167.87
Time to 1st contraction of >30 mm Hg (min)	10.29 ± 5.51	6.45
Time to initial uterine activity (min)	38.43 ± 17.12	50

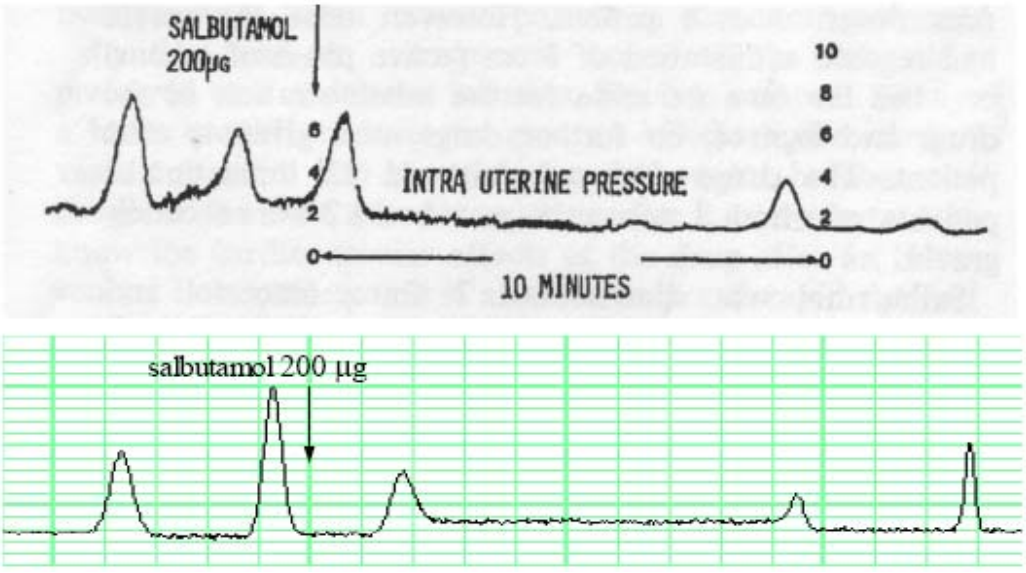

Figure 5.3. Real[23] (top) and simulated (bottom) intrauterine pressure tracings showing the effect of an intravenous bolus of 200 µg of salbutamol on uterine contractions.

Discussion

This paper presents an extension of a previously developed model[15-17], incorporating the pharmacokinetic and pharmacodynamic properties of salbutamol, administered

intravenously to reduce uterine contractility during labor. Simulation results were validated with published literature data.

The PK model consists of a single differential equation for a drug concentration normalized to infusion rate. The concentration time profile depends on a single parameter: the disposition rate constant λ. The few PK studies on intravenously administered salbutamol encountered in the literature[24,25] do not provide enough data for the identification of the optimal order for a PK model. The single-exponential model that was used was easy to identify and provides satisfactory results.

Due to the lack of simultaneous PK-PD studies, and the limited available literature data on salbutamol PK and PD, model parameters were estimated with dose-response data.

The PD model consists of an original adaptation of the traditional Imax model[26]. It takes simulated spontaneously evolving and augmented contraction waveform features as a starting point, adding the effect of salbutamol. To reduce the complexity of the model, the salbutamol PD model was simplified, eliminating selected parameters. The resulting model combines the spontaneous evolution of labor, the effect of labor augmentation with oxytocin, and the administration of the tocolytic drug salbutamol.

The combination of these three features is important for the educational simulation of situations where acute fetal hypoxia is caused by increased uterine contractility, of exogenous or endogenous nature, and where the rapid administration of a tocolytic drug normalizes fetal oxygenation.

Available literature data suggest that salbutamol does not affect resting tone. However, further experimental studies would be useful to evaluate the effect of higher dosages or that of normal dosages in rare situations, such as hypertonic contractions. Pharmacodynamic studies of drug effects on uterine activity have the inherent inconvenience of reporting discrete data. To improve the accuracy of PD parameter estimation, it would be useful to measure uterine contraction characteristics at each contraction before, during and after drug administration, instead of using the common 10 to 15 minutes windows.

Different countries, and even different institutions within the same country, use different salbutamol administration protocols. The described model will simulate the response to any administration protocol. A simulator incorporating this model would allow trainees to recognize increased uterine contractility, administer their institution's salbutamol

protocol, and observe the effect of this drug on uterine contractility. To our knowledge, the simulation of the effect of a specific tocolytic agent using a customized administration protocol has not been previously published or incorporated in commercially available simulators.

Other tocolytic agents are used throughout the world to decrease uterine contractility in acute intrapartum situations, including ritodrine, terbutaline, atosiban, nitroglycerine and magnesium sulfate, and these could all be included in the presented model.

Envisioned applications of the presented model - in combination with the other characteristics of the intrauterine pressure simulator and a fetal heart rate simulator – include: (1) an interactive screen-based electronic fetal monitoring simulator for education and training of the identification of critical situations and selection of appropriate therapeutic interventions; and (2) a full-body simulator for immersive simulation of obstetric emergencies. The trainee interface for the latter application would consist of a monitor emulator or a real monitor, and patient mannequins for the mother and fetus. In both types of simulators, the intrauterine pressure model could be coupled to models of uterine and placental perfusion, as well as to those controlling fetal descent, further increasing automaticity and realism.

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Chapter 6

Conclusions and perspectives

This chapter presents concluding remarks, including the achievements of this thesis, what we consider to be the innovations of the presented modeling work, its envisioned use, and suggestions for further developments. In the last section we take a broader perspective and review some of the challenges in modeling and simulation for healthcare education and training.

Mathematical models for educational simulation of uterine contractions during labor

After introducing modeling and simulation for healthcare education and training, a brief analysis of simulation in Obstetrics, and a short description of monitoring in labor and delivery, we presented the requirements of a model for the educational simulation of intrauterine pressure during labor. We then derived and integrated a set of original mathematical models for this purpose. The specific conclusions concerning this work involve the individual models, their integrated use, and contributions to modeling methodology in educational simulation, and these are described below.

Individual models

The intrauterine pressure generator for educational simulation of labor and delivery simulates uterine contraction signals. Due to the close relationship between model parameters and signal features, the generator can be easily manipulated by simulation instructors to adapt it to specific training needs. It incorporates intrinsic variability of uterine contraction features and of the signal baseline. Clinical experts attributed similar realism scores to real and simulated tracings, suggesting that these two signals could not be distinguished.

The model for spontaneous evolution of uterine contractions during labor combines the intrauterine pressure signal generator and a time-and-event based script. Different patients, pathologies, and evolving clinical situations can be represented using this model, via manipulation of the UC waveform features: amplitude, frequency, duration, and resting tone, using pre-programmed scripts. With simple linear interpolation of real data, the model simulates a smooth spontaneous evolution of uterine contraction features throughout labor. Experts considered that the simulated tracings were either negligibly different, or could not be distinguished from real tracings.

The model for educational simulation of the effect of oxytocin on uterine contractions provides the possibility to simulate patients with different drug sensitivities. When incorporated in a labor and delivery simulator, this model will allow users to practice the

recognition and appropriate response to uterine hyperactivity. Clinical experts were able to identify correctly all presented clinical situations, and considered the simulated signals to be "good" or "excellent" representations of real signals.

The model for educational simulation of the effect of salbutamol on uterine contractions allows for the simulation of intravenous administration of this tocolytic during labor. Model simulation results were validated with independent data published in the scientific literature.

Use of integrated models

The integrated models allow for the simulation of spontaneous evolution of uterine activity, labor augmentation with oxytocin, and tocolysis with salbutamol. The combination of these three features is important for the educational simulation of situations where acute fetal hypoxia is caused by increased uterine contractility, of exogenous or endogenous nature, and where rapid administration of a tocolytic drug may normalize fetal oxygenation.

Programmable model features allowing for the simulation of different types of waveforms and tracings, reflecting different patients and clinical situations, include intrauterine pressure signal variability, scripted spontaneous evolution, and drug kinetics and sensitivities.

Contributions to modeling methodology

In our opinion, the presented combination of a deterministic-stochastic signal generator, piece-wise linear scripts for evolving signal features, and continuous-time models of pharmacokinetics and pharmacodynamics of two interacting drugs represents an original, and potentially more generally applicable technique in modeling for medical educational simulation.

Model validation procedures were selected based on their applicability to simulated situations and adapted to available data and human resources. In addition to model validation with independent target data, several methods for the evaluation of simulated

clinical signals were applied, using expert opinion. Realism of simulated signals was evaluated via "blind" and side-by-side comparisons of real and simulated signals. Correct identification of underlying situations was also employed. In our opinion, the presented evaluation methods have a more general applicability in the validation of models for medical educational simulation.

In summary, the developed integrated model realistically simulates intrauterine pressure signals during labor, for different patients, pathologies, and evolving clinical situations. It can easily be adapted to accommodate additional training needs. It was developed and evaluated using an original combination of methods.

Use of developed models in medical educational simulators

As mentioned in previous sections, the developed models need to be combined with a fetal-heart-rate model before their incorporation in an educational simulator. Furthermore, to augment the fidelity of the simulator, they can be coupled to models of cervical dilation and fetal decent. Such a simulator could be a screen-based simulator that allows for training the identification of critical situations and clinical decision making. The model would allow for real or accelerated time simulation of the consequences of these decisions. The model can also be incorporated in a full-body, model-driven simulator, to contribute to an immersive simulation environment for healthcare providers to practice the technical and non-technical skills required for the management of obstetric emergencies.

Suggestions for further development

In addition to the coupling of other models for the simulation of labor and delivery scenarios, further design and evaluation issues can be considered. First, the bell-shaped waveform could be adapted to simulate the pattern that arises during the second stage of labor, when maternal pushing is added to uterine contractions in order to aid the delivery of the fetus. This can be modeled by a deterministic deformation of the base waveform

and/or by a stochastic process. For this purpose, an analysis of intrauterine pressure signals near delivery needs to be performed. Another characteristic that could be added to the current model is the simulation of the externally measured transabdominal uterine activity signal. As mentioned in the first chapter, this signal can most likely be modeled based on the more accurate intrauterine pressure signal. Ideally, such a model should be established after analysis of simultaneously measured intrauterine pressure tracings and transabdominal uterine activity signals[1-3].

To assist in programming patients with different sensitivities to oxytocin, a physiologically plausible range of parameter values could be established, based on the scientific literature or on expert opinion.

Since different tocolytic agents are used throughout the world, it would be valuable to develop models for the simulation of the effect of other agents. This could be achieved by incorporating independent pharmacokinetic models and by adapting the pharmacodynamic model, as described by Minto et al[4].

In this thesis we validated simulation results separately, adding one individual model at a time (see Fig. 5.1). The validity of the models would be expanded by considering additional patients and clinical situations, and by involving more clinical experts.

Challenges in modeling and simulation for healthcare education and training

Researchers have been looking at the related questions of the need for, and the efficacy of, simulation-based training in healthcare. There is a growing confidence in the usefulness of simulation in healthcare[5-8], and there are two international societies dedicated to this area: (1) the Society in Europe for Simulation Applied to Medicine (SESAM), created in 1994; and (2) the Society for Simulation in Healthcare (SSH), created in 2004, as well as several national societies. Their missions are to encourage and support the use of simulation in Medicine for the purpose of training and research, and to facilitate healthcare education, practice, and research through simulation modalities. These societies have joined research communities from the four corners of the globe to discuss questions and ideas that arise from the understanding that, although simulation has now gained recognition as a

valuable technique, further development and validation is needed to improve its effectiveness and efficiency. The amount of research is growing and spanning more and more areas of expertise, now also including, for example, hospital management, and industrial development. In the remaining part of this section we will discuss several of what we consider the current challenges for modeling and simulation in healthcare education and training. These challenges include educational, clinical, economical, and technical issues, alone or in combination.

Integration of simulation-based training in standard curricula

One of the challenges in healthcare education is the integration of simulation-based training in the official undergraduate and post-graduate curricula. One of the greatest difficulties in this context has been to demonstrate that this educational approach results in better clinical care[9,10]. With increasing evidence of improved clinical care after implementation of simulation-based training programs[11,12], awareness of the need to implement such programs has been steadily growing.

Assessment and evaluation of educational effectiveness

Assessment tools that objectively measure trainee performance are important for providing feedback to the trainee, and for evaluating trainee and training[13,14]. Some virtual reality simulators for training selected surgical skills already contain such tools, based on, for example, the time to complete an intervention, or proximity to an expert trajectory[6,15-17], but most assessment tools in other areas of healthcare simulation, such as video-aided debriefing[6,17], keep an important subjective component. Several training evaluation techniques were explored over the last few years[16,18-28]. However, the amount of required data and the complexity of the involved processes still limit their use and impact. The effect of cultural, social, and organizational factors on the effectiveness of simulation-based training programs only became apparent in multinational studies involving multiple variables (e.g. healthcare specialties and trained skills)[8,29] and simulation centers[6,7,13,30-32]. These results underline the importance of worldwide scientific collaboration in the study and improvement of educational effectiveness.

Proficiency-based training and accreditation

Patients and the healthcare system share an awareness of the need for proficiency-based training throughout a professional career[14,33]. In addition to the challenges associated with implementation of simulation-based training in official undergraduate and post-graduate curricula, further difficulties arise when moving towards multi-professional proficiency-based training. Both individual and team training would greatly benefit from the availability of objective assessment tools[13,14]. Demonstration of improvement after training would be an important argument in favor of proficiency-based training. Until now, few educational programs and associated assessment tools were accepted as a valid environment for proficiency-based training[20,23].

Evolution of medical procedures, equipment and healthcare simulation

The complexity and constant evolution of medical procedures and equipment pose considerable challenges for healthcare education and training[34]. Prompt adaptation of training programs and training media are required. This translates into challenges for the healthcare system and the medical simulation industry. This rapid evolution, in combination with the rather long process of validation, may reflect a natural tension between design and evaluation[16]. Some recent advice concerning improved research to attenuate this tension includes[23,33,35-37]:

- Fewer resources to try to demonstrate that simulation-based training is a superior educational tool.
- Comparison of simulation engines to evaluate how different design and development approaches should be used (alone or in combination).
- Economic analysis of different teaching and training media and of transferring training technology to industry.
- Curricular development for evaluation of the need to incorporate simulation technology.

- Evaluation of the same simulation technology used in different learning environments and with different target audiences.

Combining resources from healthcare organizations and industry could possibly improve the current situation.

Complexity, fidelity and cost of simulation technology

Increased simulator fidelity may result in increased cost of development, acquisition, and operation, and increased complexity of use and maintenance. Increased simulator complexity, fidelity, and cost have to be considered in the light of potential educational gains[9,37,38]. Costs considerations should also include the availability of the real system for education and training, the safety of training in the real system, and the opportunity to train rare acute events[39]. Challenges in this area involve optimization of training cost-effectiveness, involving several layers of education and training that span from undergraduate studies to continuing training of healthcare professionals. Fox-Robichaud and Nimmo explore adapting training media to different levels of training, for example, knowledge acquisition, training of basic technical skills, training of basic non-technical skills, training of complex technical skills, and training of complex non-technical skills, as a cost-saving factor, alongside costs associated with human resources, space, and learning time[9].

Integrated approach to simulation design and evaluation

The use of simulators in education and training has - at least partially - been a technology-pushed process. This means that training programs were adapted to the available training media, rather than the other way around[9,10]. There seems to be an agreement in the healthcare community that an integrated approach to the design and evaluation of simulators, simulation environments, scenarios, and curricula is needed[10,11]. One strategy, derived from simulation-based training in the military, and adopted in part by the medical education community, includes the phases[33,38]: Training Needs Analysis (TNA)[18], Training Program Design (TPD)[9], and Training Media Specification (TMS)[39]. Additional phases of the strategy for design and evaluation of simulation based training include Training

Implementation (TI)[40] and Training Evaluation (TE)[18,31,40]. The quality of training programs depends on multiple interacting factors[31]. Therefore, training evaluation studies often involve long term analysis, or are presented as partial evaluations only.

Model requirements are set as part of TMS. After development, model validation again refers to these requirements. Even though the use of unvalidated models in training simulators is not recommended[6,16,23,41], formal design and evaluation procedures have yet to be established[33]. When setting model requirements, a delicate balance between needs and effectiveness has to be established[37]. Model complexity and validation have associated costs, and validation has a necessarily limited range. For example, if it is envisioned that a model-driven simulator will be used for healthcare education and training worldwide, a broad variety of experiences, protocols, equipments, and procedures in different clinical environments may have to be considered as part of the validation procedure. An exhaustive validation may be unfeasible, yet a validation with too many restrictions may not show the effectiveness of the model for the intended purpose. Given the number of variables in the application environment, the ideal method may involve several iterations. But the major challenge in defining a formal design and evaluation procedure may be that development of models requires combining expertise from applied sciences such as education, clinical medicine, and engineering, and from basic sciences including physiology, pharmacology, physics, and mathematics. Furthermore, development of model-driven simulators may require collaboration between academic institutions and industry. Therefore, progress in design and evaluation methods will have to rely on carefully coordinated multidisciplinary collaborative efforts[33,38].

Besides its practical implications, the work presented in this thesis also contributes to meeting several of these more global challenges. It results from international and multidisciplinary scientific collaboration, which is essential in meeting most of these challenges. More specifically, such collaboration in models design and evaluation makes it easier to substantiate realism claims concerning the educational technology. Model-driven simulators may also contribute to realistic environments and objective performance assessment tools[15,42]. Moreover, model validation is an integral part of simulator and simulation evaluation. By considering various pharmacological interventions and uterine

contraction monitoring modalities, we also illustrate how simulation can be adapted to evolving medical procedures and technology.

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