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Integration of Drug Dosing Data with Physiological Data Streams using a Cloud Computing Paradigm

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Abstract— **Many drugs are used during the provision of intensive care for the preterm newborn infant. Recommendations for drug dosing in newborns depend upon data from population based pharmacokinetic research. There is a need to be able to modify drug dosing in response to the preterm infant's response to the standard dosing recommendations. The real-time integration of physiological data with drug dosing data would facilitate individualised drug dosing for these immature infants. This paper proposes the use of a novel computational framework that employs real-time, temporal data analysis for this task. Deployment of the framework within the cloud computing paradigm will enable widespread distribution of individualized drug dosing for newborn infants.**

I. Introduction

Preterm newborn infants are admitted to the neonatal intensive care unit (NICU) to support treatment for various conditions that are either present at birth, such as respiratory distress and early onset neonatal sepsis, or are complications of prematurity, such as apnoea of prematurity, intraventricular haemorrhage, necrotising enterocolitis, late onset neonatal sepsis, bronchopulmonary dysplasia, and retinopathy of prematurity. Fluids and electrolytes are administered to maintain fluid balance; protein, carbohydrate, fat, vitamins and trace elements are provided to promote optimal postnatal growth. Antimicrobial drugs are administered to treat infection; analgesia and sedation are provided to keep the infant comfortable and free of pain. Infants who require surgery will also be anaesthetised.

Ampicillin, caffeine, cefotaxime, diazepam, dobutamine, dopamine, epinephrine, fentanyl, gentamicin, heparin, midazolam, morphine, paracetamol, pavulon, vancomycin, vasopressin, and vecuronium are some of the many drugs commonly used in the NICU. Drugs and fluids are administrated based on evidence-based standards that take into account the infant's maturity and size as dosage parameters. However, drug dosing in the newborn is complex, with a delayed absorption of gastric emptying; renal and liver activity at only 35% of an adult; a body composition of 80-90% of water; the relative number of drug receptors or the influence of age in enzyme function [1].

Drug exposure in the preterm infant over prolonged periods may cause side effects and irreversible damage that have not been reported in the literature for lack of prospectively collected data. Physiological data correlation with drug exposure has the potential to provide extensive knowledge within this domain. Knowledge that the infant is exposed to different drug concentrations in time, correlated with physiological data, has the potential to provide a tool to evaluate the actual condition of the preterm infant [2]. The goal of this study is to describe an approach for the integration of pharmacokinetic/pharmacodynamics processes in the newborn infant and the biological effect of the drug. A platform that provides high fidelity, temporal physiological data will enable the estimation of the kinetics of the drug dose and effect-site characterization of the drug in the premature population.

Advanced computational methods can facilitate this task. Artemis is a framework for concurrent multi-patient, multi-diagnosis and multi-stream temporal analysis currently in use at The Hospital for Sick Children, Toronto [3]. The Artemis framework has the potential to be deployed within the NICU for the identification of condition onset predictors for the common complications of prematurity. This technology allied with infusion data may enable the delivery of more advanced clinical decision support for clinicians in the NICU. Moreover, if the available information through the platform is leveraged using the cloud computing paradigm, the translation of a data into information can go beyond the expectations given dynamic to decision and knowledge.

Cloud computing, which has evolved from services computing, enables the use of computing resources external to the health care facility. An application of cloud computing for the provision of a service of critical care supporting both real-time patient monitoring and retrospective clinical research is presented in [4]. However that research does not present the integration of data relating to drug and other infusions. This paper presents a method to integrate drug and fluid administration data with physiological data for more integrated and advanced clinical decision support. This research recognises the need for drug and fluid administration data to be used by the clinical decision support system integrated with the physiological data together with the provision of slower frequency data within the electronic health record for traditional charting.

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II. BACKGROUND

Nelson, in 1961 presented a review about drugs and substances "foreign to the body" and the pharmacological activity-time relationships. It was the first time the term pharmacokinetic was used in the English language after Dost published in German in 1953 [5].

Starr, in 1937 studied 85 subjects analysing the action of epinephrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitressin, quinidine, morphine and strychnine on the cardiac output. The study demonstrated variations in the cardiac output in dosages during the stimulation of the heart [6]. This was one of the first studies, in the last century, correlating physiological variables and drug dose in different dosage systems. The author pointed out two problems that are still recurrent now a days: "Since no two patients are identical, the question might be raised whether it was proper to draw conclusions from an average of the studies obtained" and "In the future when series of more similar conditions and dosages are available, more accurate conclusions can be drawn concerning the action of drugs under special circumstances."

The statements make reference to the pharmacogenomics; a science developed during the 1950's to study how variations of the human genome affect the response to drugs. Beyond Starr [6] assumptions, the variations in pharmacogenetic can occur among subpopulations that differ by race. Meyer [7] enumerates three pharmacogenetic mechanisms that influence pharmacotherapy being genetic polymorphisms of the genes; genetic variants producing unexpected drug effects; and genetic variations in the drug target, modifying effect, response and side effects.

In a recent study, Silverman [8] reaffirms that network medicine is the new field in development to better understand complex diseases and pharmacology systems interactions. The drug network may help to better phenotype patients with complex diseases by merging with clinical information and physiological variables to personalize drug development and place pharmacology into the realm of medical cyber physical systems.

Recent research has demonstrated the potential to monitor and analyze physiological data from critical care patients at very high frequency for earlier onset detection late onset neonatal sepsis [9, 10]. HeRO® can identify transient decelerations and reduced baseline variability in heart rate in the neonatal population predicting sepsis [11]. Drugs may change heart rate variability. Wanga has shown that morphine induces proinflammatory cytokines [12]. Belderbosa has shown that the polarizing effect of TLR4 increases the susceptibility to infection leading to the assumption that morphine doses may increase chances of sepsis in premature population [13].

In [14] the impact of drug dosage on the use of heart rate variability analysis as a positive early onset detector for late onset neonatal sepsis was introduced. The incorporation of drug and fluid dosage data in real-time from the newborn infant, especially the incorporation of high frequency rather than hourly charted data, together with high frequency physiological data has the potential to generate fewer false positive diagnoses when physiological data is used for the earlier onset detection of various conditions based on changes in physiological behaviors.

Almost a century after the pioneering studies correlating physiological variables, drug dose and the subject's condition, there is still a deficit in clinical practice regarding to information systems and decision support technology. Liu developed a proportional-integral-derivative controller for closed-loop co-administration of propofol and remifentanil deployed in the Infusion Toolbox 95. The closed-loop application controls infusion pumps and generates reports about the anesthetic procedure; however there is no additional clinical information such as laboratory test results, images, or the response to previous interventions to elevate the informatics tool to a decision support system for drug dosing [15].

These data stress the need for a an architecture integrating the data stream in the bed side from patient's monitor, smart infusion pumps, laboratories test, image information as well as clinical information. The Artemis platform with the deployment of a cloud for smart infusion pumps may be enable personalized drug dosing in neonatal clinical practice. This study aims to explore the opportunities and viability of such research field correlating drug data (PKPD information) and physiological variables sharing this information through cloud computing.

III. METHODS

Artemis is a framework that acquires real-time data from several monitors within the NICU such as electrocardiogram (ECG), heart rate (HR), blood oxygen saturation (SpO_2), and respiratory rate (RR), to discern critical events that could influence patient outcome [16]. The platform incorporates IBM's InfoSphere Streams, a middleware software application, to record and process the patient data. A pilot of Artemis has been operational at The Hospital for Sick Children, Toronto, since August 2009 supporting a clinical research study for earlier onset detection of late onset neonatal sepsis (LONS) [10]. A cloud implementation of Artemis known as Artemis Cloud has been operational since April 2010 supporting a companion clinical research study relating to neonatal instability [17].

An extended diagram of the Artemis platform is shown in Figure 1. As detailed in [16] real-time synchronous medical device data and asynchronous Clinical Information Management System (CIMS) data is provided to the Artemis platform via the data acquisition component. The real-time Online Analysis component employs IBM's InfoSphere Streams, a novel streaming middleware system that processes data in real-time and then enables data storage within the Data Persistency component. It has been demonstrated to be capable of processing and then storing the raw and temporally abstracted data from multiple infants at the rate they are generated [3]. Clinical rules are encoded in the Online Analysis component using the Streams Processing Language (SPL), which is the programming language for IBM's InfoSphere Streams middleware. For the Knowledge Extraction component, Artemis utilizes a newly proposed temporal data mining approach [3]. This component

supports the discovery of condition onset behaviours in physiological data streams and associated clinical data. New knowledge, once tested through rigorous clinical research techniques, is deployed within the Online Analysis through the Redeployment component that translates the relevant temporal abstraction based behaviours to SPL.

The Artemis framework has the potential to be deployed within the NICU for the identification of condition onset predictors for pneumothorax and the complications of prematurity including, but not limited to, intraventricular haemorrhage, apnoea of prematurity [18], periventricular leukomalacia, and retinopathy of prematurity [19]. Here we propose the implementation of a drug delivery module to enable improved control/assessment by the physician of drugs and fluids in critically ill newborns and pediatric patients.

The acquisition of drug dose information for inclusion within the Pharmacokinetic/Pharmacodynamic (PKPD) model together with physiological data streams as currently extracted and processed by Artemis in real-time will elucidate the drug interactions, synergies and consequences of drug titration in neonates. Therefore, Artemis a multi-patient, multi-diagnoses and multi-stream temporal analysis will also provide estimated drug concentration and predict drug side effects of therapies before its use. The inclusion of a PKPD model into the Artemis platform will support a highly dynamic and evolving clinical state as is found in neonatal population. The infusion drug data record in specific post-gestational age, under particular conditions could compose a historical clinical protocol to guide health providers in undeveloped countries, where the physician access is constrained, through the Artemis Cloud.

The Artemis diagram in Figure 1 is extended to include the PKPD web service to enable analyses of drug data and physiological changes. Given the dynamic movement of Smart Infusion Pumps (SIP) within intensive care, the most practical connectivity to extract data is wireless. As this data could be used to periodically populate the electronic medical record in addition to support real-time monitoring, consideration must be given to the dual needs for the data when determining connectivity for real-time monitoring. The Artemis Cloud platform from [16] is further extended in figure 1 to include an Infusion Web Service which can either receive data from the (SIP) directly or via a SIP server as indicated by the yellow lines within Figure 1. This data would then be available to any real-time clinical support algorithms running for that patient.

The infusion drug data streamed to Artemis platform includes: bolus delivery rate, bolus dose, drug concentration, continuous dose, limit drug dose, loading dose, dosing regime and an encrypted patient identifier. Real-time drug infusion data represents a big data problem due to its volume, velocity and variability. The drug data captured from the SIP contains 66 different fields including institution data, patient data, log error, pharmacological data, infusion data, alerts, device alarm, start/stop times, programming codes and libraries. The SIP provides data into its buffer every 10s including headings sizing 1230kb. Given that the average length of stay in the NICU for a preterm infant is 30 days, one SIP will generate 4.4MB/hour, 106MB/day and 3GB monthly. However, it is important to note that a preterm infant can have up to 13 SIP resulting in 39GB of drug infusion data from a single patient per month. While, the data volume represents a concern for storage and for the display of meaningful data, this data has no relevance for clinical decision support if the time of its analysis is not taken into account. Midazolam, a drug usually titrated for sedation in the NICU, has its peak effect time between 3 and 5 minutes. The drug data captured and transmitted must be

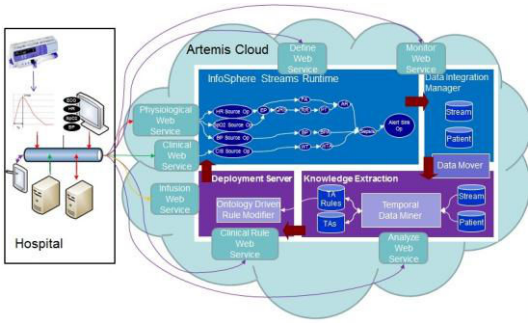

Figure 1 - Artemis Cloud with Smart Infusion Pump Drug Information

analysed in less than 5 minutes to provide valid and relevant information to physicians and nurses, avoiding overdose or any unexpected side effect. Considering the big data characterisation of the drug data, the cloud computing approach provides unlimited resources on demand to capture and distribute meaningful information to advanced clinical decision support systems.

IV. Discussion

In a recent NIH White Paper, Sorger stressed the relevance of a drug-development network. A network sharing drug research information may translate preclinical discoveries into research medical progress as well as improving the knowledge about patient-to-patient variability in therapeutics [20]. The physician's decision about drug treatment is based exclusively on the inter-individual variability and subject health condition. The acquisition and introduction of the infusion drug data into a platform to diagnose multi-stream temporal analysis in real-time, could represent the missing step to correlate data stream and drug dose in the neonatal population. Beyond improving the drug titration development, the cloud will enable remote regions access drug data information, pharmacological parameters and new titration practice.

Capturing infusion drug data from specific clinical cases and procedures could construct a world database for premature infants. The infusion drug data record in specific post-gestational age, under particular conditions could compose a historical clinical protocol to guide health providers in undeveloped countries where the physician access is inexistent.

With an international database accessible by Artemis Cloud, drug concentrations, maximum drug dose and any other pharmacological parameter could be reviewed and updated for this critical population, constrains and limits, becoming a powerful tool allowing the physician a wider

range of devices when titrating neonates. Intelligent alarms were developed over the last decades and implemented in advisory tools to assist physicians, also improving the diagnosis of critical situations prior to their occurrence. The alerts generated by Artemis with infusion drug data will represent another powerful clinical decision support application for use in the NICU.

The integration of infusion drug data in intelligent alarms will open a new research at neonatal intensive care in the development of novel algorithms to improve clinical practice and health care. The way the drug is administered or the dosing regime of the SIP itself is relevant information considering the immaturity of neonatal organism and its functions: distribution, metabolism and excretion. These new information will allow for example the deployment of algorithms to determine the life cycle of the drug in the preterm infant and with this knowledge in the immature organism and its effect with data stream evidences, it may be possible to determine if conditions such as intraventricular haemorrhage or late onset neonatal sepsis are influenced by prior drug exposure.

Another benefit of Artemis Cloud for SIP would be the management of drug libraries used for premature infants and a device errors database for SIP. Trbovich stated: "To determine if a response to a limit alert message was clinically appropriate, smart pumps must be integrated with other IT system. Incorporating these technologies into the IV medication administration process means that smart pump data could be linked to patient data."[20]. With the inclusion of SIP in Artemis Cloud, the cloud will enables the use of drug libraries in the format of Platform-as-a-Service providing an information technology to developers or in this case, healthcare providers, the ability to create, change and deploy into the SIP application. Adding, changing new/routine drugs as well as programming the multi-channels pumps by the clinical web service would be simpler and easier. The cloud enables to connect with the SIP and to a specific patient avoiding errors, increasing reliability and maximizing the use of the infusion drug data collectively through the cloud for the NICU under the supervision of physicians and manufactures.

The SIP in a cloud will be the next step for smart infusion pump devices and a step forward in individualized drug dose titration for newborn infants.

V. CONCLUSION

This paper has presented a framework for concurrent multi-patient, multi-diagnosis and multi-stream temporal analysis that incorporates data from the electronic health record, patient monitoring devices, patient care devices such as incubators and ventilators as well as drug infusion pumps. We are currently progressing research using the Knowledge Extraction component for earlier onset detection of apnoea of prematurity, late onset neonatal sepsis and retinopathy of prematurity to determine clinically validated earlier condition onset detection using all these data sources. We will then demonstrate the translation of this to rules for use in the Online Analysis component and validate these rules within the real-time care setting ultimately through clinical studies.

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