Infusion Profiler: Automatic Generation of Intravenous Infusions Profiles

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Abstract: Infusions intravenous are among the most common hospital procedures and use different industrial, medical devices. But these medical devices, so far, have a high volume of adverse events in their operation. Considering this situation, this paper presents the Infusion Profiler, a novel software/hardware approach that allows an agile, automatic generation of operational profiles of gravitational and electromechanical intravenous drug delivery, avoiding the high time demanded by actual infusions measurements. The Infusion Profiler uses a mixture of measured data from industrial infusion pumps and mathematical modeling to allow the generation of different intravenous infusion profiles. The Pearson Linear Correlation coefficient analysis demonstrates the equivalence between the generated profiles and the measured ones. This is the first architecture able to generate gravitational and electromechanical intravenous infusions profiles to the best of the author's knowledge. A case study using data from real industrial devices indicated promising results for the Infusion Profiler Architecture, encouraging study and research efforts.

Keywords: Biomedical Instrumentation, Gravitational Intravenous Infusion, Electromechanical Intravenous Infusion, Automated Infusion Profile Generation

1. INTRODUCTION

Modern industrial medical devices aim to qualify the management of health professionals' tasks and often exploit autonomous operations in the different procedures performed by offering intelligent and proactive health services Dey et al. (2018). The intravenous systems are used in the most routine clinical procedures in hospitals, and about 80% of hospitalized patients require these therapeutic resources Cheng et al. (2016).

Regarding the risks associated with the use of health technologies, the Emergency Care Research Institute (ECRI) ECRI (2017), which annually ranks the top 10 hazards in a hospital environment, identified that the infusion errors were the first in this rank in 2017 and this is still an important hazard nowadays.

The use of infusion therapy devices is usually required in situations that need different decisions of health professionals, which may have multiple impacts on the treatment of a patient Chambers (2019).

Drug administration is a physical process that is characterized by variations in time. For example, drug concentration at different points of the bloodstream varies drastically, driven by complex blood flow and drug diffusion dynamics. In most drug delivery systems, keeping a flow rate of less than one drop per minute is complex. Thus, it is a significant technological challenge to the medical industry to develop high precision devices, considering that their composition aggregates multiple components, from different manufacturers IEC 60601-2-24 (2012); ECRI (2017); Stradolini et al. (2018). The main manufactured products medical device that influences intravenous applications are: (i) infusion tubes; (ii) drug reservoir; (iii) infusion pumps Chambers (2019).

Intravenous infusions are generally monitored by persons and thus subjected to follow-up flaws, even though the most popular and usual clinical activity in hospitals worldwide. Negligence in these intravenous procedures has a high potential risk to the life of the patient receiving the infusion therapy. Furthermore, associated adverse events may also stress the patients themselves, their families, and the health professionals Zhang and Wu (2011); Malagutti (2014); Fink et al. (2018).

The automated drug administrations have been the subject of intense research for decades due to the potential benefits regarding cost savings and improvements in patient's clinical treatments Malagutti (2014). This paper considered a literature review to appraise empirical evidence relating to automated drug intravenous administrations. The scientific repositories were searched with the association of the terms "delivery", "drugs", "flow", "intravenous", "simulation" and "model", in the following repositories: ACM, IEEE, IET, Science, Springer, Pubmed, Cochrane, and Scielo.

Selection inclusion and exclusion criteria were applied to identify eligible publications through title analysis followed

by abstract and then full-text examination. The reference lists of included articles were searched using an online tool, Parsifal, designed to support researchers Parsifal Ltd. (2018). This mapping has resulted in two research fronts, which are discussed below.

The first one explores the patient's vital data analysis as a method to make the feedback of the infusion devices and permit it to turn autonomous. The obtainment of a treatment diagnosis allows to input and verify the flow control and dosage of drugs in the bloodstream. Related to these research themes, the following methods of evaluating the patient's vital data are stood out: (i) the use of electroencephalography signals with a feedback source for automating drug infusions Petersen et al. (2014); (ii) employment of blood pressure reading with the control signal of infusion therapy Malagutti (2014); Fan (2010); (iii) interpretation of the patient's bispectral index signals as a closed-loop control variable in intravenous infusions Moore et al. (2009).

The second research area explores the pharmacokinetic and pharmacodynamic models of drugs to control intravenous infusion dosages. In this line of research, we highlight the following related works that employ the models of drug absorption by intravenous routes: (i) development of a treatment-controlled infusion system model, which according to its target, explore concepts of mathematically manipulated pharmacokinetics able to consider the particular characteristics of patients resulting in specific parameters Bressan et al. (2009); (ii) analyzing the pharmacokinetic employed to study the time dependence of the administered medicines in the definition of the absorption, distribution, metabolism, and excretion of a given drug, thus allowing the configuration modeling of infusion pump operations Trzaska (2014); (iii) enabling predictability in a wide range of possible situations involving many variables and dependencies, which provides the healthcare professional with an accurate prediction of dosing errors and interactive delay times for many scenarios Konings et al. (2017)

Although there are several works in the literature on these two fronts of research, there are studies that report many factors which may compromise these automation methods. For example, the patient's physiological and pathological characteristics and pharmacological drug factors may negatively influence the control and monitoring actions of infusion system operations Eusuf and Thomas (2019).

The method explored in this paper does not analyze the drug effects and the patient's clinical reactions, and reach the goals through the intravenous operational profiles, allowing the inference about the infusion therapy behavior Rosen et al. (2016). In this case, a typical operational profile can be compared with a measured profile to define if the infusion is correctly happening.

This paper presents the Infusion Profiler, a novel software/hardware approach which allows an agile generation of gravitational and electromechanical intravenous drug delivery methods, avoiding the high time demanded by actual infusions measurements. The Infusion Profiler uses a mixture of measured data from industrial infusion pumps and mathematical modeling to allow the generation of different intravenous infusion profiles.

The Infusion Profiler modeled the gravitational and electromechanical intravenous infusions through mathematical equations and, with real measures, which were done through a hardware and firmware platform specifically designed to collect real infusion data. The Infusion Profiler conception considered the main characteristics of industrial medical devices Beaudoin et al. (2016).

Then, this paper presents three main contributions:

- The first one is the developing a novel model for intravenous therapy procedures, considering drug delivery by gravitational and electromechanical infusions.
- The support future works in this field since the Software Infusion Profiler is freely available for download NEITZKE F. (2019) and it can generate expressive data-sets that characterize different infusion profiles along infusion procedure time.
- The support of a future development of a system able to automatically verify the behavior of the infusion profiles.

The remaining text is organized in the following sections. Section 2 discusses the measurement platform: Hardware/Software Aspects. Section 3 describes the conception of the architecture of the Infusion Profile. Section 4 analyzes the validation of generated. Section 5 discusses results and the directions for future research.

2. MEASUREMENT PLATFORM: HARDWARE/SOFTWARE ASPECTS

The Infusion Profiler was modeled using, as a basis, a Strain Gauges sensor. The Strain Gauges outputs are voltage values related to the drug reservoir's weight force, and the difference of the voltage outputs was used to define the drug flow profile.

2.1 Mechanical Aspects

A physical system using a Strain Gauges sensor was built and was used to measure real infusions in both scenarios: gravitational and electromechanical infusions. This information was used as one of the Infusion Profiler inputs to allow the generation of all possible infusion profiles, as discussed in the next section.

The conception of the measurement platform was made considering the normative requirements, which specify sets of rules of functional behaviors for the physical characteristics regarding the intravenous infusions IEC 60601-2-24 (2012)

This platform is an instrumentation system that allows the acquisition of intravenous infusion profile data based on the acquisition of the infused liquid quantity. The acquisition was performed by introducing a sensing method in the infusion line. Figure 1 shows the designed system to measure gravitational and electromechanical infusions, including the infusion line (formed by the tube and the drug reservoir), the sensor, the developed hardware, and firmware, and the infusion pump.

The measurement platform showed in Figure 1 was developed in three steps: (i) the construction of a mechanical system capable of support the continuous measurement;

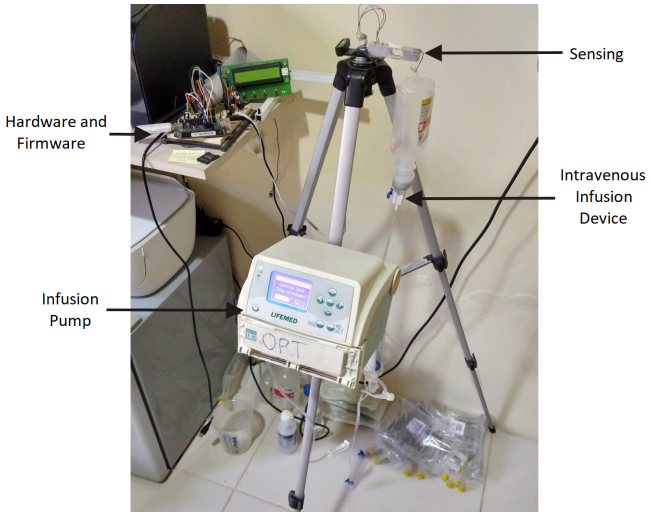

Figure 1. Infusion Profiler: Measurement Platform.

(ii) the development of an appropriate electronic system for the data acquisition, electrical signal preprocessing, and data recording; (iii) the programming of firmware to create a supervisory management system and to store the sampled values.

2.2 Electronic Aspects

The measurement system uses a load cell (part number CZL635) to measure the weight force at the anchor point from which all other data are inferred Measuring Technology Co Ltd. (2011). The load cell changes its electrical resistance from the submitted weight. Thus, it is possible to read the electrical signals that, adequately characterized, may be processed to infer the infusion flow. The electrical connection of the load cell used a Wheatstone bridge to allow an accurate reading even with low amplitude electrical signals.

The electronic measurement system of Infusion Profiler was subdivided into two components: (i) use of a commercial microprocessor board to allow you to embed an open-source Linux operating system, (ii) the design of a specific electronic circuit with the functions of preprocessing the electrical signals obtained by the load cell. The microprocessor board is the Beaglebone Black Rev-C board from Texas Instruments, since this board has the necessary resources to implement the system.

In Figure 2 a), the microprocessor system used in the prototype is shown, while in the 2 b) the electric circuit blocks are shown, which is divided into: (i) connection circuit of the weight force sensor, Strain Gauge; (ii) differential amplification of the electrical signal with a signal gain of $A = 560$, obtained by the Equation (1); (iii) preprocessing stage, low pass filter with cut-off frequency $FC = 6\ Hz$, which is determined by the Equation (2). Lastly, the 2 c) shows the Strain Gauges sensor image and the alphanumeric display interface.

$$A = \frac{R1}{SG} \tag{1}$$

$$FC = \frac{1}{2.\pi.R3.C2} \tag{2}$$

The Equations variables (1) and (2) are defined by: A amplification factor, $R1$ resistor resistance value 1, SG Strain Gauges resistance value (GZL635), FC cut-off frequency in the low-pass circuit configuration, π numerical constant, $R3$ resistor resistance value 3 and $C2$ capacitor's capacitance value 2.

2.3 Firmware Aspects

The firmware of the measurement system was developed in Python under BeagleBone Linux. The main functions of this firmware are: (i) configure the hardware; (ii) manage the data storage; and (iii) synchronize the events over time.

The electromechanical infusions used an infusion pump from Lifemed Brazilian manufacture Lifemed Industry (2019) (model is LF SMART). This infusion pump is presented in Figure 1, and it is widely used in Brazilian hospitals.

The acquisition of real infusion operational profiles with the designed platform was made through configurations with the potential to represent intravenous drug delivery by gravitational and electromechanical infusions. A total of 74 different flow rates were measured, using two types of drug reservoirs, four nominal variations of the infusion liquid volume, ten gravitational infusion sets, 100 infusion pump flow sets, five different types of needle gauges of intravenous access, and one infusion pump Lifemed Industry (2019).

A total of 440 hours of measurements were done for gravitational and electromechanical infusions, considering various infusions scenarios. The measured infusions profiles were used as one of the Infusion Profiler inputs to allow the most precise modeling of the infusion procedures. These results were also used to validate the operational profiles generated with the software. These discussions will be detailed in the following sections.

3. INFUSION PROFILER MODELING

The research method used to model the infusion profiles was based on actual data from industrial intravenous devices together with mathematical modeling.

The infusion profiles were modeled based on: (i) transport phenomenon equations to obtain the flow rate speed of liquids; (ii) the load cell equations, to model the electric behavior of the Strain Gauges sensor Measuring Technology Co Ltd. (2011); and (iii) the measured information, to adjust the results considering other physical characteristics that are not fully modeled by the equations.

The international standardized definitions of intravenous infusions were also used to model the system. In this case: (i) the drug reservoir height was defined as $h = 1m$; (ii) the infusion liquid density was defined as $\rho = 0.998\ g/mL$; (iii) the accuracy of the delivered liquid was defined with a maximum error of 5 %; (iv) each $1mL$ of the drug infusion was defined as 20 *drops*; and (v) the tube validity was defined as 24 *hours* IEC 60601-2-24 (2012). Finally, the

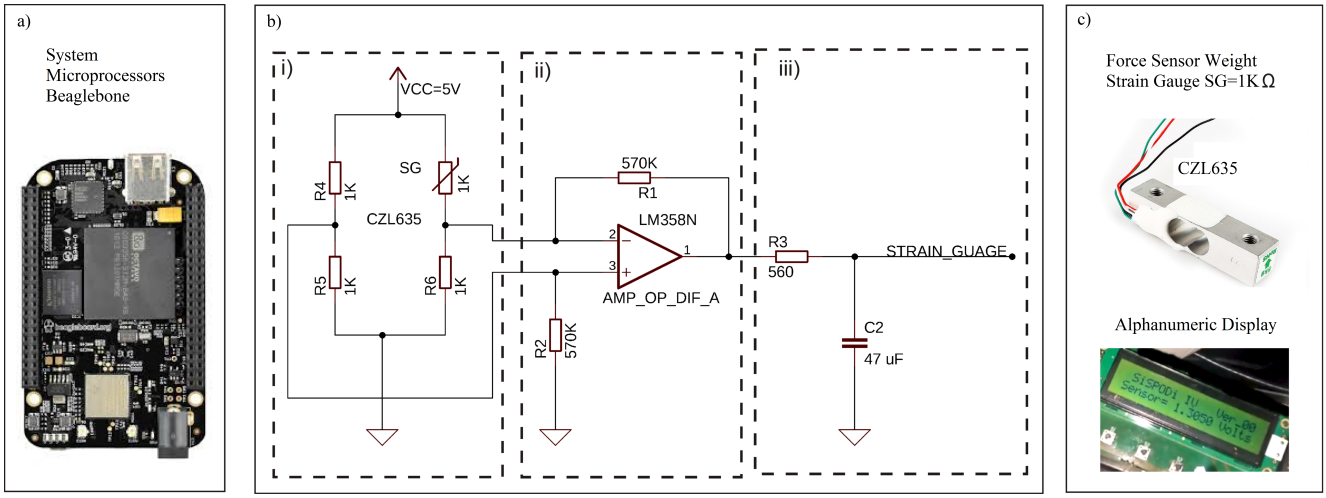

Figure 2. Infusion Profiler: Hardware Measurement System.

supervisory agencies' definitions were used to define the reservoir vial dimensions and weights.

The transport phenomenon equations used to define the delivered volume behavior are presented in (3) to (5), were: (i) v is the flow rate of the gravitational infusion; (ii) g is the gravity acceleration; (iii) $\Delta.h$ is the height difference of reservoir liquid (hydrostatic pressure); (iv) Q is the flow rate; (v) a_{tube} is the tube inner opening area, adjusted by the roller clamp (gravitational infusion liquid); (vi) $V_{delivered}$ is the quantity of the delivered volume; (vii) i is the current sample of delivered volume quantity; (viii) n is the number of samples; and (ix) t is the time.

3.1 Equations Used to Model the Infusion Profiles

In electromechanical infusions (using infusion pumps), the drug delivery has a constant flow throughout the infusion IEC 60601-2-24 (2012). Therefore, for the infusion pump flow profiles generation, the Equation (4) is changed by a constant value defined by the programmed flow rate.

$$v = \sqrt{2.g.\Delta h} \tag{3}$$

$$Q = a_{tube}.v \tag{4}$$

$$V_{delivered} = \sum_{i=1}^{n} [Q_i.(t_{i-1} - t_i)] \tag{5}$$

The load cell equations that represent the electric signal behavior of the Strain Gauge sensor are described in (6) and (7) Measuring Technology Co Ltd. (2011), where: (i) V_{out} is the sensor output voltage; (ii) Vcc is the electrical supply voltage; (iii) C is the Strain Gauge nominal sensitivity; (iv) F_{weight} is the applied force on the sensor; (v) $F_{nominal}$ is the nominal reading force defined by the sensor manufacturer; and (vi) ρ is the drug liquid density.

$$F_{weight} = V_{delivered}.\rho \tag{6}$$

$$V_{out} = Vcc.C.\frac{F_{weight}}{F_{nominal}} \tag{7}$$

The data generation explores the load cell sensor equation presented in (7). This equation provides an electrical voltage from which it is possible to deduce the weight strength of the drug reservoir. Since this tension is proportional to the weight, it is possible to infer the flow profile behavior of intravenous infusions using this information. This approach has been widely accepted in the scientific community that exploits weight fluctuation to infer the delivered volume Bhavasaar et al. (2016); Cheng et al. (2016); Thongpance and Roongprasert (2014).

Finally, the measured information of gravitational and electromechanical infusions was used to model the captured physical characteristics.

Some authors argue that it is impractical to obtain a system of equations capable of the model all the physical characteristics of infusion therapy Piper et al. (2018); Banerjee et al. (2011); Trzaska (2014), because of the physical tolerances among different tubes and reservoir manufactures and hydrodynamic behavior.

Then the infusion was modeled using measured information and mathematical formulation to transpose the limitations of the system complexity. The metric information was used to determine an adjustment factor, thus establishing a numerical scale of the difference between the data measured by the sensor and those calculated by the equations that represent the flow. The aspect is unique and was obtained with the analysis of all interactions of the physical measurements.

In the stage of acquisition of the real values through the projected platform, it was chosen configurations that have the potential to represent intravenous drug delivery. Remembering that in total they were explored, seventy seven different flow rates were tested, using two types of drug reservoirs, four nominal capacities variations of the infusion liquid volume, ten gravitational infusion sets, and five different types of needle gauges of intravenous access.

3.2 Infusion Profiler Implementation

The Infusion Profiler was developed in Python programming language, in which the mathematical models were

coded. The interface for the Infusion Profiler is presented in Figure 3.

The Infusion Profiler input interface is presented in Figure 3 (a), where the user must inform: (i) the flow rate ($60mL/h$ in this example) and (ii) the infusion volume ($100ml$ in this example). The software will generate the required intravenous infusion profile for both gravitational and electromechanical infusions with this information.

Infusion Profiler output interface is presented in Figure 3 (b), where a gravitational and an electromechanical infusion profiles are presented considering Figure 3 (a) inputs. The output profiles consider a sampling rate of one sample per second. The graphically presented information is also delivered in an output (.csv) file with one line for each sample.

Figure 4 represents the flowchart of the Infusion Profiler main routine, which is considered in any repetition produced by the different input data parameters.

The main functions of Infusion Profiler are detailed above:

(1) The software receives, as input, the flow rate and the amount of liquid that will be infused, as presented in Figure 3 (a). The software receives, as input, the rate flow parameters mL/h and the amount of liquid that will be infused mL.
(2) Then the initialization routines define the liquid height inside the drug reservoir to determine the weight of this reservoir and, for gravitational infusion, the internal opening area of the tube is also set, characterizing the crushing of the roller clamp for the desired flow.
(3) The next operation, for the booth, gravitational and electromechanical infusions, is the update of the amount of liquid emptying rate in the drug reservoir according to the input flow behavior and infusion device type.
(4) Then, the software generates the electrical signals of the load cell sensor. To consider a more realistic scenario, the electrical signal is added to an Additive White Gaussian Noise (AWGN) with power spectral density (PSD) and amplitude with probability density function (PDF).
(5) The next step is the tolerance definitions, as follows: (i) changes in the average flow rate; (ii) variation in delivered volume; (iii) weight of the set of disposable components of the infusion line; (iv) strain gauge accepted error (up to 0.05%) Measuring Technology Co Ltd. (2011). The tolerance definitions are done with a pseudo-random process, allowing data generation with characteristics more similar to real physical systems. All applicable limits are following regulatory agency specifications.
(6) Then, the software evaluates the accuracy of the flow rate, and volume delivered values within the selected tolerances. If the results are accepted, the next step is applied. Otherwise, the software will return to the initialization routines (item 2), and a new infusion profile will be generated.
(7) Finally, the valid infusion profile is showed as a graph (Figure 3 (b)) and stored in a file adequately labeled according to the types of tests, and the program finishes its execution.

The current normative requirements were used as validation parameters. These requirements define acceptable tolerances for the behavior of intravenous flows IEC 60601-2-24 (2012). The tolerance value insertion has considered the full range of the established limits. The choice of tolerance values applied was individual for each assay. The selection process was pseudo-randomly generated to allow the generation of operational profiles with the potential to sweep all existing limits on the physical tolerances of industrial manufacturing processes.

4. INFUSION PROFILER EVALUATION

The validation of the intravenous operational profiles generated with the Infusion Profiler was performed, comparing the measured profiles with the profiles generated by the software. This comparison was done based on Pearson correlation coefficient analyses, using the metrics adopted in similar works in literature Seifermann et al. (2019); Flavio Abrantes, Gabriel Luche, Luciano Loder, Odair Noskoski (2015); Min et al. (2010); Law (2008).

In Table 1, the flow rates exploited, the physical quantity of the infused volume, the intravenous access characteristic, and the types of medical devices.

The influences of variations in needle types and drug reservoirs are only perceived in gravitational infusions, which have the force of gravity as a source displacement of the flow Chambers (2019). In electromechanical infusions (Infusion Pumps), because there is an extra pumping mechanical force over the liquid, these influences are not perceived Baxter International Inc. (2019). Therefore, these setup type characteristics, needle and drug reservoirs, are only identified in Table 1 for the gravitational device.

The validation of the intravenous operational profiles generated with the Infusion Profiler was performed, comparing the measured profiles with the profiles generated (predicted) by the software.

A graphical analysis of the actual and the generated data sets was evaluated exploring the dispersion curves, which used the Cartesian coordinates to display the value set of the two data sets to be analyzed Zhu et al. (2019).

Therefore, in Figure 5, we can observe the scattering curves of the two types of medical devices, representative of the flow rate employed in drug delivery. These samples allow us to analyze the output data of the Infusion Profiler architecture against the data measured by the measuring platform of Figure 1.

The graphical evaluation has the result shown as follows: For gravitational infusions, Figure 5 a), the flow rate 68.8 mL/h presented the largest variation in relation to the actual and predicted data. For electromechanical infusions, Figure 5 b), the flow rate 41.6 mL/h was the one that had the worst result.

Therefore, analysis of the dispersion curves of the two types of devices, Figure 5 a) and b), we can observe a tendency for a straight line, thus characterizing an equivalence between the data generated by the Infusion Profiler architecture and the real data measured by the physical system, for both types of intravenous infusion devices Zhu et al. (2019).

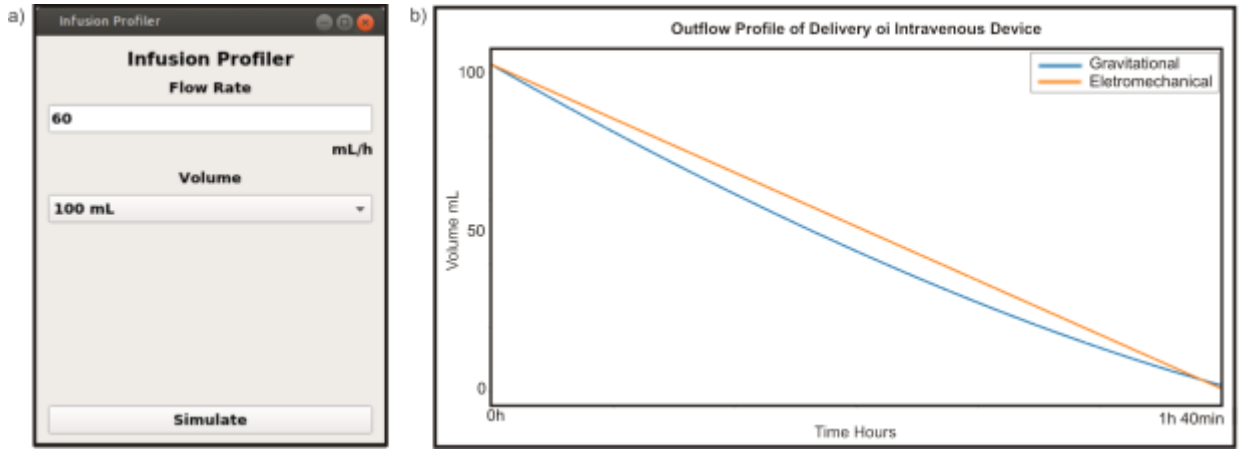

Figure 3. Infusion Profiler: input and output interfaces.

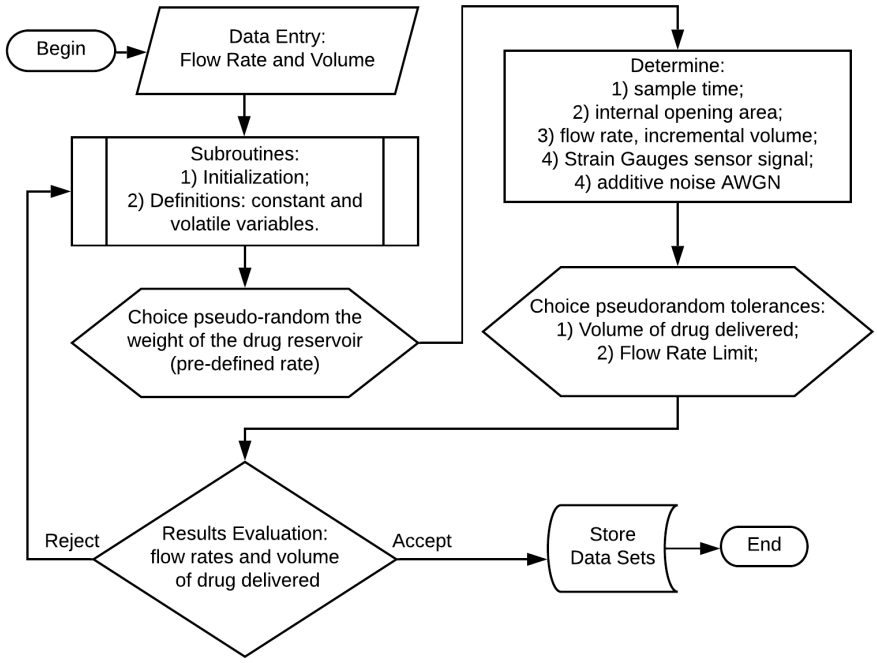

Figure 4. Infusion Profiler Flowchart.

Table 2 shows the results of Pearson's correlation coefficient analysis for both types of devices. To determine the correlation coefficient, Python statistical libraries were used.

The lowest correlation coefficient obtained was for the gravitational infusion with the flow rate of 92.8 mL/h. The other infusions presented correlation indices closer to one and without variations.

The results presented in Table 2 show the high correlation level of the profiles generated by the Infusion Profiler with the measured profiles. The typical variations presented In Table 2 and Figure 5, are within the practical limits for the identification of intravenous drug flow rates IEC 60601-2-24 (2012).

These results allow the conclusion that the operational profiles for gravitational and electromechanical infusions generated with the Infusion Profiler are similar to the measured ones and then, these values were considered validated.

5. CONCLUSIONS

This paper presented the Infusion Profiler, a software/hardware approach conceived to generate operational profiles of gravitational and electromechanical intravenous infusions. The main contributions of this work are (a) the definition of a novel model for intravenous infusions, (b) the support for future works in this field, since the Infusion Profiler is freely available for download, and (c) the support of a future development of a system able to automatically verify the behavior of the infusion profiles.

This paper also presented a measurement platform, that allow the automated acquisition of real operational profiles

Table 1. Real Infusion Data Set Characteristics

Device Medical	Drug Delivered	Flow Rate / Needles / Drug Reservoirs							
Gravitational	125 mL	22.0 mL/h 18G Flexible	30.4 mL/h 24G Flexible	60.4 mL/h 18G Flexible	68.8 mL/h 21G Flexible	74.2 mL/h 22G Flexible	153 mL/h 21G Flexible	170.2 mL/h 21G Flexible	197.3 mL/h 24G Flexible
	250 mL	9.3 mL/h 21G Flexible	72 mL/h 21G Flexible	72.4 mL/h 26G Flexible	163 mL/h 21G Flexible	187.5 mL/h 26G Flexible	192.2 mL/h 26G Flexible	194.8 mL/h 26G Flexible	220.3 mL/h 18G Flexible
	500 mL	13.8 mL/h 22G Flexible	14.6 mL/h 22G Flexible	33.8 mL/h 26G Flexible	49.3 mL/h 21G Hard	52.2 mL/h 21G Hard	66.3 mL/h 18G Hard	92.8 mL/h 18G Hard	95.5 mL/h 18G Hard
		147 mL/h 22G Hard	163.8 mL/h 22G Flexible	167.6 mL/h 18G Hard	178.5 mL/h 21G Flexible	181.8 mL/h 21G Hard	185.2 mL/h 21G Hard	239.9 mL/h 18G Hard	288.3 mL/h 21G Flexible
		306 mL/h 21G Hard	336.9 mL/h 18G Hard	352.8 mL/h 21G Flexible	370 mL/h 18G Hard	—	—	—	—
	1000 mL	64 mL/h 18G Flexible	235.1 mL/h 18G Flexible	240 mL/h 24G Flexible	297 mL/h 18G Flexible	666.6 mL/h 18G Flexible	—	—	—
Infusion Pump	125 mL	10.4 mL/h	20.8 mL/h	22.0 mL/h	30.4 mL/h	31.2 mL/h	41.6 mL/h	74.2 mL/h	125 mL/h
		153 mL/h	170 mL/h	200 mL/h	—	—	—	—	—
	250 mL	10.3 mL/h	14.0 mL/h	15.6 mL/h	31.1 mL/h	50.0 mL/h	72.0 mL/h	125.1 mL/h	163 mL/h
		187.5 mL/h	194.8 mL/h	250 mL/h	—	—	—	—	—
	500 mL	25.0 mL/h	39.6 mL/h	49.3 mL/h	52.2 mL/h	53.6 mL/h	95.5 mL/h	147 mL/h	181.8 mL/h
		185.2 mL/h	300 mL/h	339.6 mL/h	370 mL/h	500 mL/h	584.6 mL/h	—	—

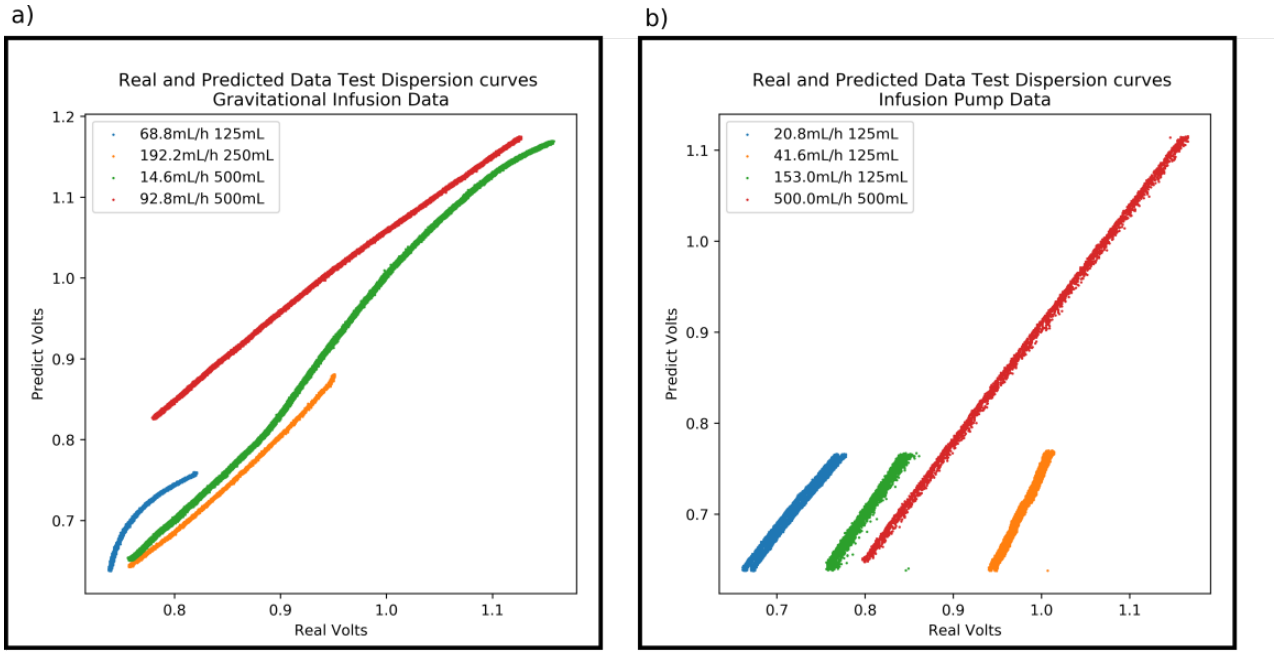

Figure 5. Real and Predicted Infusion Dispersion Curves.

Table 2. Correlation Analysis.

Types Devices Medical					
Gravitational			Electromechanical Infusion Pump		
Flow mL/h	Volume mL	Correlation Coefficient	Flow mL/h	Volume mL	Correlation Coefficient
14.6	500	0.997167	20.8	125	0.98885
68.8	125	0.955391	41.6	125	0.98689
92.8	500	0.803863	153	125	0.98492
192.2	250	0.994726	500	500	0.99954

for a large variety of infusions procedures. These measured operational profiles were used to improve the infusion model of the Infusion Profiler, and, also to validate the generated results. The reached results showed that there is a high correlation between the measured profiles and the profiles generated with the Infusion Profiling, allowing the conclusion that both results are similar and then, that the Infusion Profiler is validated.

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