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# Impact of Physical Parameters on Dosing Errors due to a Syringe Exchange in Multi-Infusion Therapy

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## Abstract

**Introduction:** Infusion therapy is challenging and dosing errors may occur due to physical phenomena related to the infusion hardware, despite the use of accurate syringe pumps. These errors typically occur after interventions, such as the exchange of a syringe. We aimed to characterize and quantify dosing errors due to a syringe exchange in relation to physical properties of infusion hardware.

**Methods:** An analytical simulation model was used to investigate dosing errors due to two different syringe exchange protocols (variations). Each protocol involved a fast syringe pump, containing a non-critical medication, and a slow syringe pump, containing a critical drug. The protocols were also reproduced in *in vitro* experiments to verify the simulation results. In addition, impact of syringe size, infusion set compliance, catheter diameter and the duration of the syringe exchange procedure on the quantity of the dosing errors was investigated.

**Results:** The syringe exchange of the slow pump resulted in an additional delay of up to 3536 seconds due to backflow. Syringe exchange of the fast pump resulted in an undiluted volume of critical drug (0.17 ml) accumulated in the infusion system, which may result in a dosing error rate of 2400 %. The quantity of the dosing errors are related to the syringe exchange duration; however, impact of infusion hardware properties is generally

larger. Smaller syringes, catheters with larger diameters and less compliant infusion systems in general give rise to smaller dosing errors during a syringe exchange. If both lines are clamped, additional dosing errors can be prevented.

**Conclusion:** Infusion hardware has a substantial impact on the dosing errors during a syringe exchange. Clamping or blocking the infusion lines using, e. g. stopcocks, on all infusion lines during a syringe exchange is essential.

**Keywords:** syringe exchange, drug administration, modeling, dosing error, physical effects, multi-infusion

## Introduction

In critical care, almost all critically ill patients require intravenous (IV) infusion therapy. However, infusion therapy is challenging and constitutes a high potential for adverse effects in critically ill patients [1–6]. There are several reasons for this. Many patients in critical care suffer from conditions that require the administration of critical drugs, such as, vasoactive drugs, sedatives, analgesia etc. For example, patients on the ICU are frequently diagnosed with hypotension and require the immediate administration of vasopressors. Because these drugs often have short half-lives, continuous administration is required. Moreover, these potent short- and rapid-acting vasoactive drugs have to be administered accurately as well as precisely. In order to meet these demands, syringe pumps are used. Another important difficulty is limited vascular access, the challenging nature of inserting a vascular access device [7] and the high risks of infection such as catheter-related sepsis [8, 9]. To reduce the vascular access points to a minimum, multiple pumps are used to deliver their drugs to one central infusion set and catheter lumen. This principle is called multi-infusion [10] and is associated with significant flow rate variability and dosing errors, despite the use of syringe pumps [10–12]. Even small dosing errors in vasoactive drugs may cause hemodynamic instability. This is especially true during clinical

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interventions [13]. An important example of an intervention is a syringe exchange (also called syringe change-over), i. e. the renewal of an old, empty syringe with a full new one. Syringe exchanges are frequently conducted due to the limited capacity of syringes, which is typically 10 to 50 ml. From clinical practice and laboratory investigations it is known that a syringe exchange produces relatively large dosing errors and several techniques aiming to reduce these errors have been investigated [14–17]. However, to date the improvement achieved by technical innovations are limited. A recurring conclusion is that awareness and understanding of the physical mechanisms related to drug delivery by infusion may reduce errors [5, 18, 19]. Argaud et al. [20] argued that operators may lack knowledge about syringe exchange mechanisms and therefore resort to poorly established empirical procedures. In a before and after intervention study they found that standardization of a syringe exchange procedure resulted in significantly less incidents [20].

Although laboratory studies have produced ample evidence that physical properties of the infusion hardware are related to dosing errors [21], the exact relationship between the syringe exchange duration, the infusion hardware and drug dosing errors remains elusive. Moreover, laboratory investigations are essentially limited to static infusion configurations, i. e. the properties of the hardware and therefore the physical parameters are either fixed or the variation is limited. Simulation studies may be able to establish this relationship better, which could help to provide a well-substantiated advice for hospital personnel.

Our objective is two-fold. First, to investigate the impact of physical parameters on dosing errors as a result of a syringe exchange in multi-infusion therapy using a realistic multi-infusion setup. Second, to investigate the impact on the dosing error of hypothetical situations due to a syringe exchange, in which the physical parameters of the infusion hardware, as well as syringe exchange duration time, are varied.

## Theoretical simulation model

An analytical theoretical simulation model has been described previously [22]. The model incorporates the most important [21] physical parameters necessary to simulate a low-flow multi-infusion system. The physical parameters used in this study are:

- (1) **Mechanical compliance (C)** [volume per pressure]: which occurs due to the elasticity of components, especially the syringe.

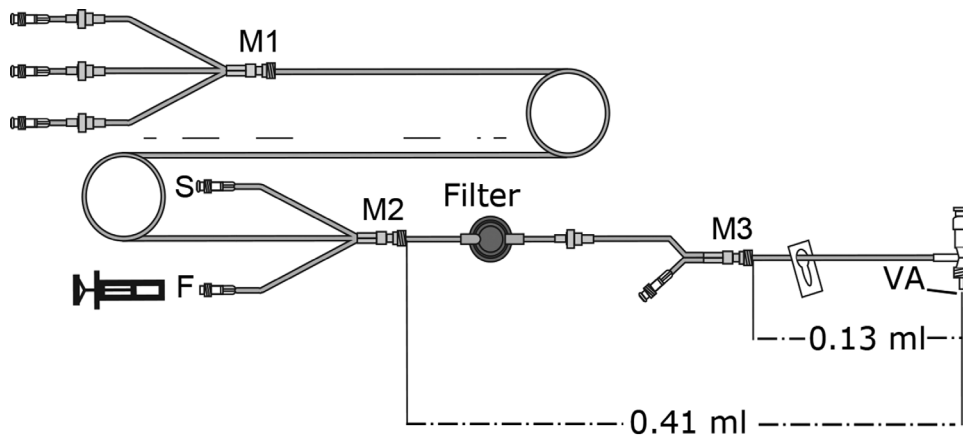
- (2) **Flow resistance (R)** (pressure per flow rate): which is due to the small diameters of some components, most notably the catheter.

## Materials and methods

### A typical clinical case

To start with, a typical NICU-case (Neonatal Intensive Care Unit) based on a patient treated on the NICU at the Wilhemina Children's Hospital, Utrecht, the Netherlands (WKZ) is described. This case was investigated in order to acquire typical parameters of a challenging case of infusion therapy. Accordingly, the infusion hardware properties and flow rates used in this case are defined as the “typical clinical case” and used for the *in vitro* experiments and simulation explained later. Because the patient suffered from hypotension, IV-treatment with dopamine was started with a flow rate of 0.5 ml/h, defined as the “slow pump” (S) containing the “critical drug”. Multiple medications are typically co-administered with dopamine. For simplicity we defined one second pump containing the “non-critical drug” total parenteral nutrition (TPN) as the “fast pump” (F) with a flow rate of 12 ml/h. The pumps used were two Perfusor Bbraun syringe pumps (B.Braun, Melsungen, Germany) which were equipped with 50 ml-syringes B.Braun Omnifix (B.Braun, Melsungen, Germany). In our NICU, dopamine and TPN are typically administered through one lumen of a double lumen catheter. This leaves the other lumen open for drugs that are more compatible with temporary flow rate changes. This allows clinicians, for example, to administer a bolus. The co-administration of dopamine and TPN was achieved using a custom 173 cm central infusion set disposable (Impromediform GmbH, Lüdenscheld, Germany) (Figure 1). Both pumps were connected to the mixing point M2. Subsequently, the central infusion set was connected to the distal lumen of a 4 Fr double lumen catheter (Vygon, Ecouen, France). The catheter entered the patient through the umbilical route.

Next, two protocols (A–B) are defined, each describing a different procedure of syringe exchange. These two situations are selected on the basis that they illustrate two main types of procedures that may occur in clinical practice and may produce dosing errors. In protocol A, syringe S is exchanged without clamping or stopping syringe F. In protocol B, syringe F is exchanged without clamping the infusion line S. See Figure 2 for a graphical representation of the protocols.



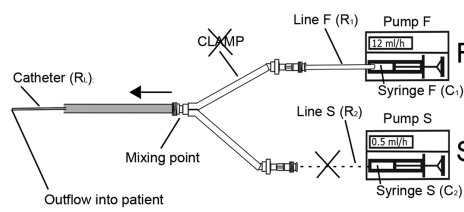
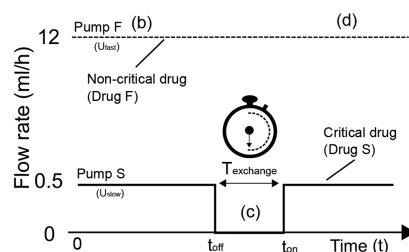
**Figure 1:** Neonatal central infusion set disposable (173 cm), going upstream from mixing points M1 to M3.

The Luerlock connector at M1 may be used for non-critical medication, not considered in this study. M2 is used for the pumps containing the non-critical and critical medication, which are co-administered through one line, respectively indicated as F and S. M3 is used for lipids, not considered in this study. VA indicates the outflow and the location where a vascular access device, e. g. the catheter, is typically connected.

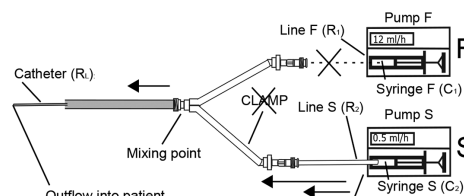
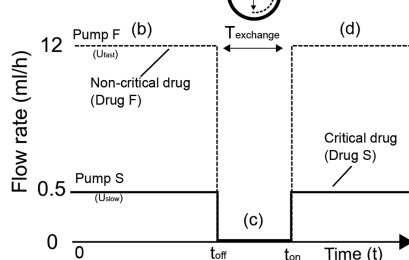
The duration of a syringe exchange procedure varied. The protocol for syringe replacement, if it exists at all, may differ per hospital. A variation of methodologies was observed to conduct the changeover. For example, if the infusion lines were also renewed, the exchange process

took longer compared to the situation in which only the syringes were exchanged. From our own time measurements on the NICU it was found that a syringe exchange procedure, performed by an experienced nurse, takes approximately 30–120 seconds.

## Protocol A



## Protocol B



**Figure 2:** Schematic of a graph representing the set-point flow rates of two pumps F and S as a function of time, for protocols A–B (left). The Flow rates of the fast pump F and slow pump S are 12 and 0.5 ml/h, respectively (b). The syringe exchange is performed between  $t_{\text{off}}$  and  $t_{\text{on}}$  for a period of  $T_{\text{exchange}}$  (0–120 seconds), according to the description of protocol A, in which the slow pump S is exchanged, and protocol B, in which the fast pump F is exchanged (c). Next, the delivery was continued, in this period dosing errors and delays in drug delivery were observed (d). The corresponding condition of the infusion setup is represented schematically (right). Compliances  $C_1$  and  $C_2$  resp. of the syringes F and S and resistances (impedances) resp. of the infusion lines F ( $R_1$ ) and S ( $R_2$ ) are indicated. Resistance of the catheter  $R_L$  is indicated as well.

## Mathematical modeling of a syringe change: Multiple causes and multiple effects

### Input

The dosing errors are dependent on several physical parameters, which in turn are based on the physical properties of the infusion hardware. These physical parameters are used as input parameters for the model. In the following, each input parameter will be explained.

The flow rates were chosen according to the case described earlier. Next, the syringe exchange was simulated for the pumps S and/or F, according to the protocols A–B. In principle, a syringe exchange results in a temporary and abrupt decrease in flow rate from the set point to 0 ml/h (Figure 2). The syringe exchange duration ( $T_{\text{exchange}}$ ) was varied according to the clinical case described earlier as well, it was decided to add an extra margin in order to observe possible theoretical effects. For the simulation,  $T_{\text{exchange}}$  was varied between 0–240 seconds. Appendix I explains the eqs (1) and (2) that were used for the evaluation of protocols A and B, respectively.

### Varying hardware parameters within realistic boundaries

In order to investigate the influence of the physical parameters, low and high extremes for each parameter within realistic boundaries in critical care were explored. The quantities of the physical parameters were either acquired from literature, measured or calculated for this study. Table 1 lists all the physical parameters related to infusion hardware. See appendix II for the methodologies used to acquire the hardware parameters.

- Mechanical compliance (C):

**Table 1:** Infusion hardware input parameters, compliance and resistance, respectively related to syringe and filter compliance and catheter resistance. See Appendix II for values that were measured.

Compliance (ml/Pa)	Resistance (Pa per ml/h)
10-ml syringe	1 Fr Catheter
$0.159 \times 10^{-5}$	1949
50-ml syringe	4 Fr Catheter and flowmeter*
$1.5 \times 10^{-5}$ [25]	23.68
50-ml syringe (non-rigid, filter)*	7 Fr Catheter†
$2.1 \times 10^{-5}$ [25]	0.058
	<i>in vitro</i> situation (4 Fr catheter + flowmeter)*
	$23.68 + 1121 = 1145$

\*Value used in the *in vitro* simulation based on the generic clinical case with a neonatal infusion set including a filter. Value calculated using the Poiseuille law.

Compliance is mostly related to syringes. Some syringes are more rigid, additionally, smaller syringes are known to be less compliant [21, 23]. However, some of the compliance is also caused by filters, the infusion line and the pump itself [24, 25]. We previously found 2.1 ml/bar ( $2.1 \times 10^{-5}$  ml /pa) for a relatively compliant setup including a filter and a 50-ml B.Braun syringe (B.Braun, Melsungen, Germany), which approximately corresponds to the compliance of the typical clinical case and *in vitro* setup (explained later). The filter was estimated to have a compliance of about 0.5 ml/bar ( $0.5 \times 10^{-5}$  ml/pa) [24]. For a more rigid setup with a 50-ml syringe, 1.0–1.5 ml/bar ( $1.0\text{--}1.5 \times 10^{-5}$  ml /pa) was found [24]; as an intermediate value 1.5 ml/bar was therefore used. A very small compliance of 0.159 ml/bar ( $0.159 \times 10^{-5}$  ml/pa) was measured for a 10-ml Plastipak syringe (Becton Dickinson, NJ, USA) syringe (Appendix II).

- Flow resistance (R):

Resistance was mostly related to the catheters. To acquire a full range of resistive quantities, the resistances of three catheters were acquired. The catheters were a Vygon Premicath 1-Fr (Ecouen, France), Vygon double lumen (proximal lumen used) umbilical catheter 4-Fr (Ecouen, France) and 7-Fr catheters Argon Careflow Single Lumen (Plano, TX, USA). The resistances were calculated and measured by producing a flow, with the use of a non-compliant syringe and syringe pump, Chemyx Nexus 3000 (Stafford, TX, USA) and an in-line pressure gauge SensorTechnics CTE8002AY4N and CTE8005AY4N (Berlin, Germany) (appendix II). See Table 1 for an overview of the compliance and resistance values.

### Output

Several end point were investigated following the syringe exchange after  $t_{\text{on}}$  (Figure 2) as a function of the input parameters, defined in the previous section. In **protocol A** the quantity  $T_{\text{no medication}}$  was acquired. This is the time that the patient does not receive the critical medication due the syringe exchange, in addition to the unavoidable, potentially substantial  $T_{\text{deadvolume}}$  (caused by the dead volume, see discussion) [22] and  $T_{\text{exchange}}$ . In **protocol B** the quantity  $V_{\text{undiluted}}$  was acquired. This is the amount of drug solution unintendedly not diluted by the faster pump F. The simulation results based on the multi-infusion system used in the *in vitro* experiments (explained later) are defined as “*in vitro*”.



The end point quantities of the simulation model and their dependent parameters are summarized as follows:

- (1) **Protocol A:  $T_{\text{no medication}}(R, C)$  [s]:** The duration in seconds, in addition to  $T_{\text{deadvolume}}$  and  $T_{\text{exchange}}$ , in which the patient does not receive the critical medication presented in seconds as a function of resistance ( $R$ ) and compliance ( $C$ ).
- (2) **Protocol B:  $V_{\text{undiluted}}(R, C, T_{\text{exchange}})$  [ml]:** The volume in milliliters of critical undiluted medication administered to the patient as a function of resistance ( $R$ ), compliance ( $C$ ) and the duration of the exchange procedure ( $T_{\text{exchange}}$ ).

The equations that were used, were evaluated in Mathematica 10.3 Wolfram (Champaign, IL, USA).

## In vitro experiments

In order to validate the simulation results experimentally, the syringe exchange procedures were mimicked *in vitro* in a laboratory according to the two protocols A–B (Figure 2). Two different *in vitro* experiments were performed to acquire  $T_{\text{no medication}}$  and  $V_{\text{undiluted}}$  experimentally for protocols A and B, respectively. Hardware properties and flow rates of the typical clinical case were used.

### Protocol A

In order to measure  $T_{\text{no medication}}$ , the cumulative flow from pumps S and F at the catheter tip was measured using a Coriolis flowmeter M12P (Bronkhorst, Ruurlo, The Netherlands). The cumulative flow rate was 12.5 ml/h in steady state prior to the syringe exchange, i. e.  $U_{\text{total}}(t) = U_{\text{fast}}(t) + U_{\text{slow}}(t)$  [ml/h], where  $U_{\text{total}}$ ,  $U_{\text{slow}}$ ,  $U_{\text{fast}}$  and  $t$  are the total flow rate, the flow rates of pumps S and F, and time, respectively. After the syringe exchange, when the syringe S is reattached, the flow rate  $U_{\text{fast}}$  of pump F (12 ml/h) remains unaltered. Consequently, any flow registered by the flow meter lower than 12 ml/h necessarily flows towards the newly attached syringe S. The time from the point where the flow rate is lower than 12 ml/h, after syringe S is reattached, until the flow rate of 12 ml/h is reached again is defined as  $T_{\text{to syringe}}$ . The total volume produced during  $T_{\text{to syringe}}$  (while the total flow rate was lower than 12 ml/h) was defined as backflow ( $V_{\text{backflow}}$ ) [ml]. Once the measured flow rate is larger than 12 ml/h again, pump S (with a set point of 0.5 ml/h), thus produces a flow rate larger than 0 ml/h and therefore pushed the volume  $V_{\text{backflow}}$  of the non-critical medication (drug

F), still inside line S, beyond the mixing point. From this tipping point, pump S produces a flow rate of 0–0.5 ml/h. Assuming that  $U_{\text{fast}}$  retains a flow rate of 12 ml the whole time,  $U_{\text{slow}}$  is obtained as:  $U_{\text{slow}}(t) = U_{\text{total}}(t) - U_{\text{fast}}(t)$ . The time required by  $U_{\text{slow}}$  to push  $V_{\text{backflow}}$  beyond the mixing point after the tipping point is defined as  $T_{\text{to patient}}$ . Adding  $T_{\text{to syringe}}$  and  $T_{\text{to patient}}$  together results in  $T_{\text{no medication}}$ . Figure 3(a) illustrates this measurement principle.

Similar to the simulation model output, the results are presented as  $T_{\text{no medication}}$  in seconds.

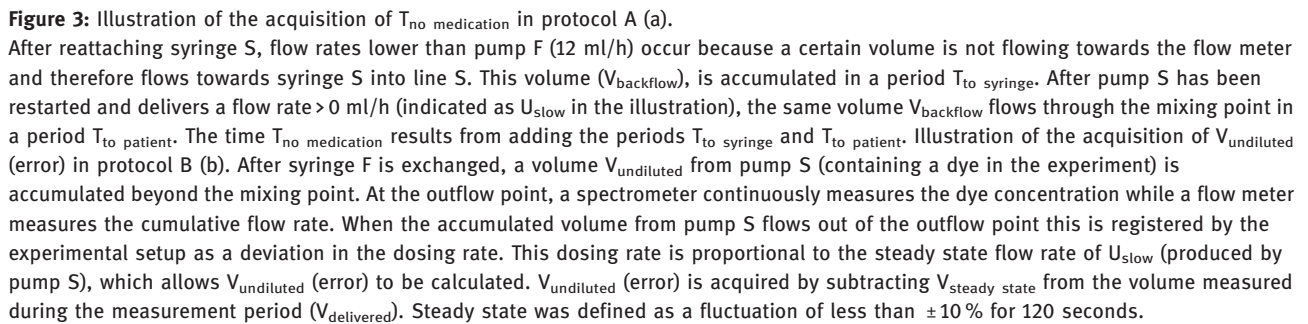
### Protocol B

Instead of a critical and non-critical medication for pumps S and F, e.g. TPN or NaCl and Dopamine or Norepinephrine, we respectively used the dyes Indigo Carmine (20 mg/l) and Tartrazine (20 mg/l). The relevant physical properties of the dye solutions were assumed not to differ significantly from the actual drug solutions. To measure the dye concentration at the catheter tip, absorption spectrophotometry was used. This method was demonstrated before [11]. The dye concentrations at the catheter tip were measured using a QE65000 spectrometer (Ocean Optics, Dunedin, FL, USA) within the visible light spectrum (250–2500 nm) at wavelengths of 610 nm and 425 nm for Indigo Carmine and Tartrazine, respectively. The cumulative flow rate was again measured using the Bronkhorst M12P flowmeter. Because both concentration and flow rate were measured, it was possible to acquire the value of  $V_{\text{undiluted}}$  (error), which is defined as follows:

$$V_{\text{undiluted}}(\text{error}) = V_{\text{delivered}} - V_{\text{steady state}}$$

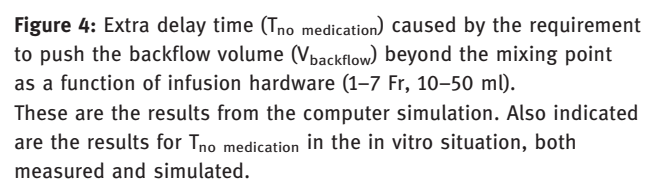
Where  $V_{\text{delivered}}$  is the volume of drug S, delivered after the initiation of the syringe exchange procedure until steady state was reached again.  $V_{\text{steady state}}$  is the volume delivered in the nominal situation by pump S, i. e. without dosing errors. In this case, steady state was determined as a period of 120 seconds, after the syringe exchange, in which the dosing rate fluctuated less than  $\pm 10\%$ .  $V_{\text{undiluted}}(\text{error})$  was used to remove systematic errors and obtain only the dosing error relative to steady state. See Figure 3(b). The results of the simulation model were corrected accordingly:  $V_{\text{undiluted}}(\text{error}) = V_{\text{undiluted}} - (U_{\text{slow}} \times T_{\text{exchange}}) = V_{\text{undiluted}} - (0.5 \text{ ml/h} \times T_{\text{exchange}})$

In this experiment,  $V_{\text{undiluted}}(\text{error})$  in milliliters, is presented as a function of the duration of the syringe exchange procedure ( $T_{\text{exchange}}$ ). The experiment was performed with a  $T_{\text{exchange}}$  of 30, 60 and 120 seconds.



The measurements were analyzed with Matlab 2014a (Mathworks, Natick, MA USA). All measurement results are presented as **mean  $\pm$  SD**.

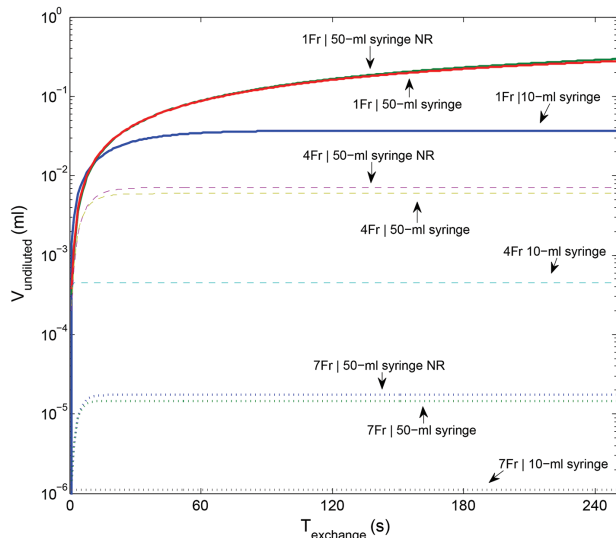
Figure 4 shows an overview of the simulated results of  $T_{\text{no medication}}$ .  $T_{\text{no medication}}$  was between 0.008 and 3536



seconds according to the simulation model. It can be seen that  $T_{\text{no medication}}$  is virtually zero for the 7-Fr catheter for all of the syringes and almost one hour for the 1-Fr catheter and the 50-ml syringe with the non-rigid setup. Moreover, if smaller catheters were used, the relative impact of the syringe size/infusion set compliance, on  $T_{\text{no medication}}$  increased. The typical clinical case that was reproduced in the *in vitro* experiment resulted in a  $T_{\text{no medication}}$  of  $1623 \pm 122$  seconds.

## Protocol B: Syringe exchange of the fast pump

Figure 5 shows all the results for  $V_{\text{undiluted}}$  for each of the listed catheters and syringes/infusion sets.  $V_{\text{undiluted}}$  was between  $1.1 \times 10^{-6}$  and 0.17 ml after a syringe exchange duration ( $T_{\text{exchange}}$ ) of 120 seconds.

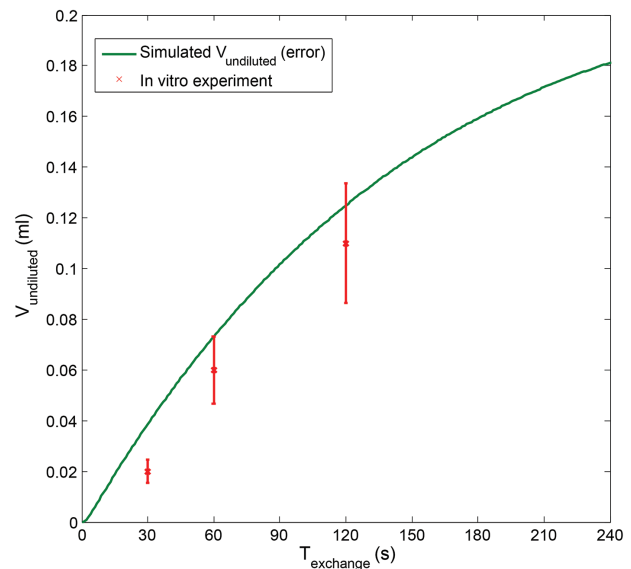


**Figure 5:** Results of the computer simulation model for  $V_{\text{undiluted}}$ , the excess volume accumulated beyond the mixing point as a function of  $T_{\text{exchange}}$ , the duration of the syringe exchange. Note the logarithmic scale for the Y-axis. NR = non-rigid.

The results of the *in vitro* experiment, which reproduced the typical clinical case, are shown in Figure 6. The simulation results, using input parameters corresponding to the *in vitro* experiment are also illustrated in Figure 6.

## Discussion

The results show that each mechanism results in counter-intuitive dosing errors, which are strongly related to the mechanical and physical properties of the infusion



**Figure 6:** Comparison of  $V_{\text{undiluted}}$  (error) acquired from the *in vitro* experiment and the simulation model results according to the input parameters based on the *in vitro* experiment.

hardware used. It was shown that if the slow pump (S) is exchanged, a significant additional delay of up to almost one hour may occur until the desired delivery of the critical medication has been reestablished. Next, it was shown that if the fast pump (F) is exchanged, a significant amount of undiluted critical drug was administered, which causes an overdose. If both infusion lines are clamped, none of the physical mechanisms described in this study will produce dosing errors or delays during a syringe exchange. The results therefore reinforce the importance of clamping or otherwise blocking of all infusion lines during a syringe exchange. The results also show that smaller syringes and catheters with larger diameters reduce the quantity of dosing errors. Catheter diameter, however, is limited by the size of the vasculature. For example, in preterm neonates these may be very small. Smaller syringes, also have disadvantages. First of all, smaller syringe deplete faster than larger syringes and are therefore required to be replaced more often. Second, smaller syringes produce much more pressure when a similar force is introduced at the plunger in comparison to larger syringes. Among other reasons, this may pose a serious danger in case a vascular access device is inserted erroneously, such as an accidental subcutaneous position.

It is known that a syringe exchange causes errors in drugs administration. Backflow has also been studied extensively [10, 13, 26]. The impact of compliance on backflow was investigated in a simulation study before [27]. In that study, backflow was caused by an occlusion

in the infusion set, beyond the mixing point. Due to the compliance, a volume of fluid was allowed to accumulate. This volume which was bigger for a 50-ml syringe compared to a 10 ml-syringe. These results are thus in agreement with our study [27].

In our study a set of realistic clinical situations were assessed and simulated for a range of infusion components. We have provided a generalized overview of all the important factors that impact dosing errors during a syringe exchange. These findings can be used by hospital personnel to substantiate the decisions for a syringe exchange protocol as well as the decisions for using certain infusion hardware.

## Physical interpretation and clinical considerations

Refer to Appendix I for a comprehensive explanation of the physical effects involved in the simulated mechanisms.

**Protocol (A)** Whereas clinicians and nurses will be aware of the effects of  $T_{\text{exchange}}$ , and hence will try to minimize the duration of the syringe exchange procedure in order to minimize  $T_{\text{exchange}}$  and its effects, they might be unaware of the delay caused by  $T_{\text{no medication}}$ .

From the equations generated by the model (Appendix I), the mechanism behind this volume can be understood and is explained as follows. The slow syringe S was exchanged, however, no pressure build-up has been realized inside the new syringe of the slow pump S. Consequently, after the new syringe is connected to the infusion set, the direction of the least pressure will be towards this newly attached syringe. The storage of this volume is allowed because the syringe is somewhat compliant, i.e. some parts of the syringe are compressible, most notably the plunger. This, in turn, allows a volume of fluid ( $V_{\text{backflow}}$ ) to be pushed back from the infusion set, beyond the mixing point, into the infusion line S during the compression of the syringe connected to the line S. This volume of fluid consists of the “non-critical drug” originating from infusion line F, instead of the “critical drug” from the infusion line S (Appendix I). Therefore it will take some time,  $T_{\text{no medication}}$ , before the critical medication reaches the mixing point again, and hence the total time that no critical drug S is fed into the mixing point amounts to  $T_{\text{exchange}} + T_{\text{no medication}}$ .

As the results show,  $T_{\text{no medication}}$  is dependent on the hardware properties of the infusion system. Specifically, the amount of the backflow allowed is strongly dependent

on the compliance of syringe S ( $C_2$ ). This is because the compressibility of the syringe allows the fluid from the fast syringe, fluid F, to flow back in the direction of the slow syringe, syringe S (Appendix I). Therefore, smaller syringes, which are typically much less compliant, will result in less potential backflow. Moreover, the resistance of the catheter ( $R_L$ ) has a substantial impact on  $T_{\text{no medication}}$ , if the resistance of the catheter is low, the affinity for the fluid to flow back into syringe S is lower. These results are immediately evident from Figure 4. In fact, the results show that in the *in vitro* experiment, the problems are only clinically relevant with catheters smaller than 4 Fr. Additionally,  $T_{\text{no medication}}$  is dependent on the ratio of the flow rates between the fast and the slower pump (Appendix I). In the presented typical clinical case of this simulation, the flow rates of pump S and F were 0.5 and 12 ml/h. Consequently, it takes considerably longer to push the non-critical drug F out of the infusion line S, than the time that was required to push the drug into line S.

Clinicians should also consider the dangers if the syringe is outside of the pump. In this case the plunger is not fixated, which may allow free flow to occur [28]. Moreover, during the experiments it was empirically observed that the volume of drug F, introduced in line S due to backflow, might be even larger in this case as the plunger is simply allowed to be pushed backwards, out of the syringe. The extent of this is dependent on the pressure coming from pump F and the friction of the plunger in the syringe, which also may have a significant impact [29] and may differ per syringe type.

As mentioned, besides delays caused by  $T_{\text{exchange}}$  and  $T_{\text{no medication}}$  there is also  $T_{\text{deadvolume}}$ , which is caused by the dead volume of the infusion set. Therefore, the (near) absence of drug S will occur only after  $T_{\text{deadvolume}}$ , the time required for the fluid to travel through the dead volume from the mixing point to the catheter tip into the patient's blood stream.  $T_{\text{deadvolume}}$  is dependent on the physical parameters: quantity of the dead volume, the total flow rate ( $U_{\text{total}}$ ), the laminar flow profile as described by Poiseuille and (predominantly radial) diffusion [22, 30–33]. In the *in vitro* experiment, the dead volume of the infusion set was approximately 0.4 ml, resulting in a  $T_{\text{deadvolume}}$  of at least 58 seconds. However, due to the physical parameters it will take longer to reestablish the intended dosing rate. Nevertheless,  $T_{\text{no medication}}$  was substantially larger than  $T_{\text{deadvolume}}$  in the simulation of the *in vitro* experiment with 2034 seconds. Contrary,  $T_{\text{no medication}}$  is smaller in the cases of the 4 and 7-Fr catheter. However, the



additional delay of  $T_{\text{no medication}}$  may still amount to almost a minute, which may be unwanted in the case of, for example, a patient with severe hypotension. This mechanism therefore shows that delays in multi-infusion systems are caused by a multitude of physical effects.

During the experiments, it was empirically observed that the drug F will enter infusion line S. In the case of this laminar flow drug solutions closer to the walls of the infusion line move more slowly in the axial direction, towards the patient and remain more unaffected by the flow of drug F. This fundamental principle is explained by Poiseuille [22]. Therefore the  $T_{\text{no medication}}$  simulated and measured is a worst case scenario, in practice some critical medication may still be delivered.

**Protocol (B)** From the simulation results, the errors resulting from the syringe exchange of the fast syringe can be explained as follows. During the exchange of the fast pump F, the slow pump S is stopped, but not clamped. As a result, due to compliance effects, the critical drug solution from the pump S, not diluted by the fast pump F, oozes into the common line beyond the mixing point. The volume of  $V_{\text{undiluted}}$  depends on the  $T_{\text{exchange}}$  and many other factors, such as the initial flow (before  $T_{\text{exchange}}$ ) of the pump F, the mechanical compliances  $C_1$  and  $C_2$  of syringes F and S, respectively, and the resistances  $R_1$ ,  $R_2$ , and  $R_L$  of lines F, S, and the catheter, respectively (see Figure 2 and Appendix I) [22].

The effects of this procedure may be even more counter-intuitive as protocol A. Consequently, the probability that an adverse effect will occur may also be greater. From the results it is evident that the quantity of  $V_{\text{undiluted}}$  is strongly dependent on the resistance and compliance. Again, with catheter-diameters larger than 4-Fr, the effects are minimal and smaller syringes also minimize the amount of  $V_{\text{undiluted}}$ . However, even in a situation with zero compliance and resistance, a quantity  $V_{\text{undiluted}}$  will be produced if pump F is not stopped, although this amount is substantially smaller than the amount that results from the infusion system's compliance. The clinical relevance of  $V_{\text{undiluted}}$  is dependent on the time required to deliver this volume to the patient, which in turn is dependent on the current flow rate. For example, if the largest measured  $V_{\text{undiluted}}$  of 0.17 ml is administered with 0.5 ml/h it is, in fact, administered with the intended dosing rate in 1224 seconds. However, in the typical clinical case,  $V_{\text{undiluted}}$  was administered with a flow rate of 12.5 ml/h in 49 seconds, which means that this quantity was administered with an excess dosing rate of 2400 %. It must be stated that such short dosing errors are typically clinically relevant for drugs with short onset times, e. g. noradrenaline and dopamine. In addition, a high concentration of the critical drug S,

typically used for patients who cannot handle fluids, also increases the probability for an adverse event.

## Limitations and future research

The spectrometer was not used in protocol A because a higher accuracy could be achieved by using only the flowmeter. However, it should be noted that while the flow rate of pump S is increased, the flow rate of pump F could be decreased slightly, due to compliance and resistance effects, therefore impacting  $T_{\text{no medication}}$  as measured in the *in vitro* experiment. Nevertheless, because the flow rate from pump F is much higher, this effect is negligible and using only the flow meter allows the acquisition of  $T_{\text{no medication}}$  relatively accurately.

A discrepancy could be observed between the experimental and simulated values. All *in vitro* results were systematically underestimating the simulated results, which suggest an overestimation of the compliance of this particular infusion setup, as described in the typical clinical case. Although the input values that we measured were typically quite accurate with relatively small confidence intervals and  $R^2 > 0.98$  (see Appendix II), repeated measurements of, e. g. multiple catheters/syringes of the same type, may give an additional error to the input values of the model. The output values of the model have a linear sensitivity to errors in the input parameters (R and C). In the case errors in the input parameters would be added, the simulated output may be approximated more closely by the *in vitro* experiment. Furthermore, the experimental *in vitro* results in protocol A did follow the expected exponential curve. We did not have the instruments available to measure the physical properties of the infusion setup in the typical clinical case in more detail, which is a likely cause for the discrepancy. Furthermore, only the results of the *in vitro* experiments using the 50 ml syringe and the non-rigid set, corresponding to a neonatal situation, were presented. The signal to noise ratio prevented us from obtaining usable results for a 10 ml syringe, which indicated that the measured quantities were too low. Obtaining usable experimental results for the smaller syringes would further validate the results of the theoretical simulation model. It is recommended to conduct these experiments with better instruments in future research.

In clinical practice, TPN or NaCl may be administered using a volumetric or gravity driven pump. These pumps do not have compliance in a similar fashion as syringes. Volumetric pumps are typically connected through specific infusion lines with a compliant part inside the actuator cartridge, which enables the commonly used peristaltic mechanism to operate, while the rest of the infusion line

is less compliant. Although typical infusion lines were shown to be compliant [25], the impact of the infusion lines used in volumetric pumps on the physical mechanism described in this study was not investigated. Nevertheless, since in protocol A,  $T_{\text{no medication}}$  is mostly related to the compliance of syringe S ( $C_2$ , see Figure 2) there will probably not be any substantial differences in the results. Likewise, in protocol B, the compliance of syringe S is also the most important parameter, in combination with the resistance of the catheter. Another noteworthy point is the flow rate of pump F (12 ml/h). This was chosen to observe the effects studied in this paper with sufficient confidence in the *in vitro* experiments. The flow rate is somewhat high as the flow rate in the NICU is preferred to be kept as low as possible. The formula for  $T_{\text{no medication}}$  in Appendix I can be used to calculate other flow rate combinations. In clinical practice this flow rate may also be produced by multiple pumps instead of just one syringe pump. However, in all these situations, the overall results of this study will be maintained.

## Conclusion

It was shown that a syringe exchange produces dosing errors as well as substantial delay times in certain cases. This may have severe implications for patient safety. The quantity of the dosing error is dependent on the exchange duration and the physical properties of the infusion hardware used, most notably the syringes and the catheter. Smaller syringes, catheters with larger inner-diameters and less compliant infusion systems in general, result in smaller dosing errors during a syringe exchange. It is recommended to consider these factors when selecting infusion hardware. By clamping all infusion lines during a syringe exchange, most of the unwanted results can be prevented or mitigated. In fact, this is more important than performing the syringe exchange procedure quickly since the extra delay due to compliance effects can be unexpectedly large, as has been shown in this study. It is therefore advised to clamp or otherwise block all infusion lines that are co-administering drugs through the same infusion set and catheter lumen as the syringe that is exchanged.

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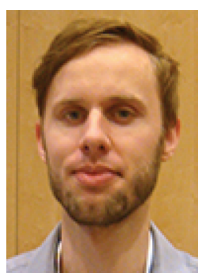
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## Bionotes



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