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Measurement and Modelling: what did we learn about infusion dosing errors?

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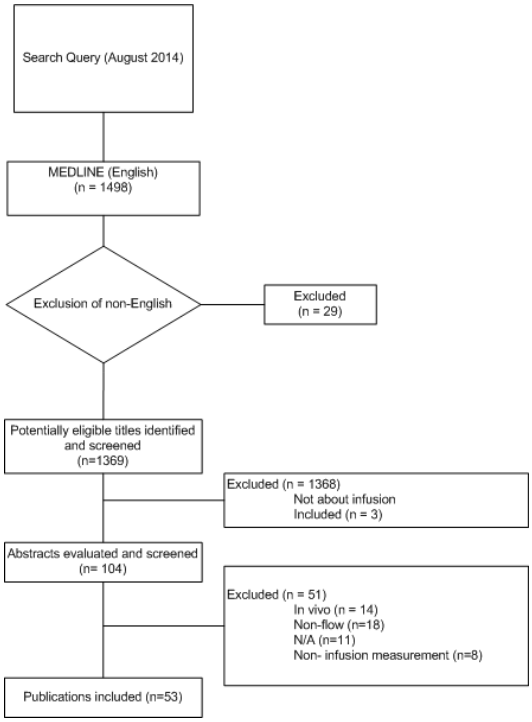
Dosing Errors

Dosing errors
- What are the physical causes?
- How can we measure them?
- Are they clinically relevant?
- Preventing dosing errors?

Review of Infusion Measurement



- Flow variability often leads to dosing errors
- Often when multiple pumps are combined on one central line (multi-infusion)
- Especially on neonatology where **low flows** and **high concentrations** are used

Dosing Errors: why?

Two distinctive physical parameters found

As we have seen in the presentation of dr. Timmerman

1. **Compliance: RC-behavior**
2. **Dead space volume**

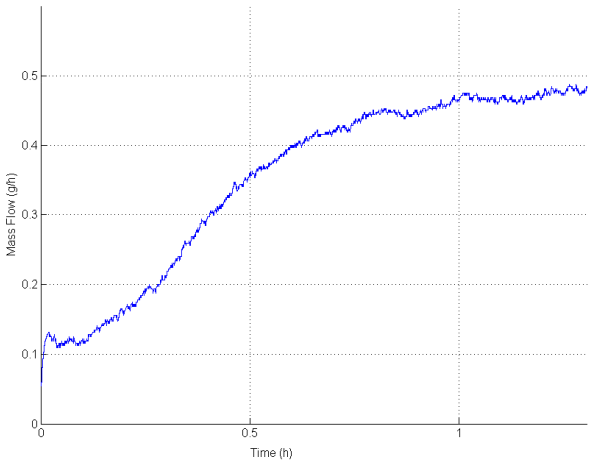
Dosing Errors: why?

Two distinctive physical parameters found

(1) Compliance (RC-behavior)

$$C = \frac{\Delta V}{\Delta P}$$

- **Resistance**
- **Capacitance**



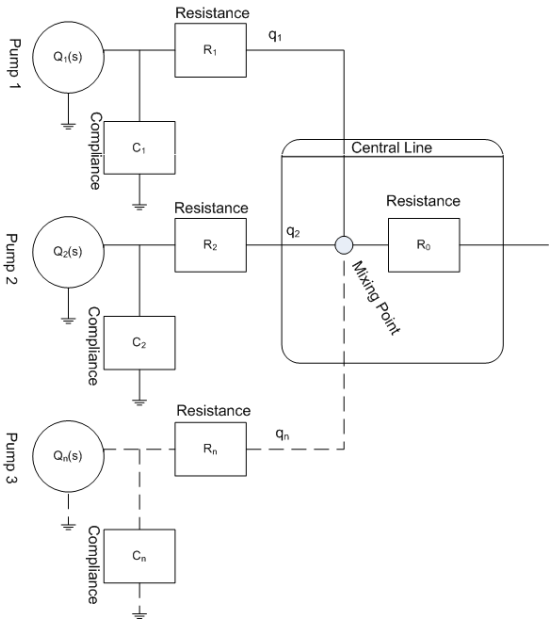
Dosing Errors: measuring and modelling

Two distinctive physical parameters found

(1) Compliance (RC-behavior)

- Modelling a multi-infusion system
- We are developing a fully analytical model

capable of simulating internal volume



Dosing Errors: measuring and modelling

Two distinctive physical parameters found

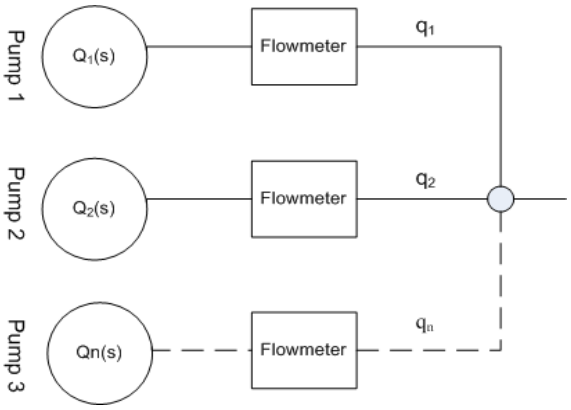
(1) Compliance (RC-behavior)

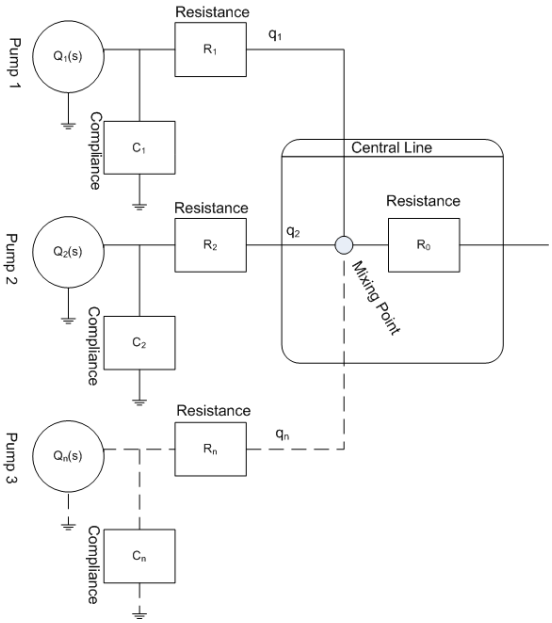
- Modelling a multi-infusion system
- We are developing a fully analytical model

capable of simulating internal volume

- Measuring single flows,
- Not too low flows gravimetrically
- Using in-line **flowmeters i.e. Coriolis or Thermal**

For multi-infusion RC-effects



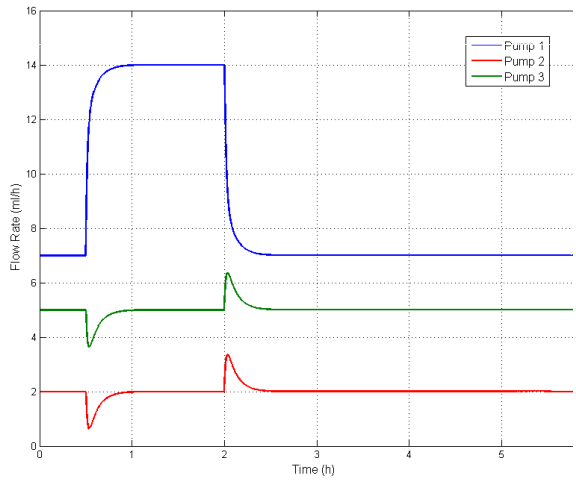


Dosing Errors: measuring and modelling

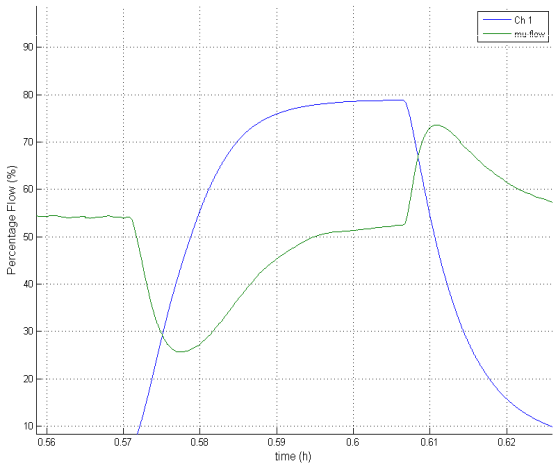
Two distinctive physical parameters found

(1) Compliance (RC-behavior)

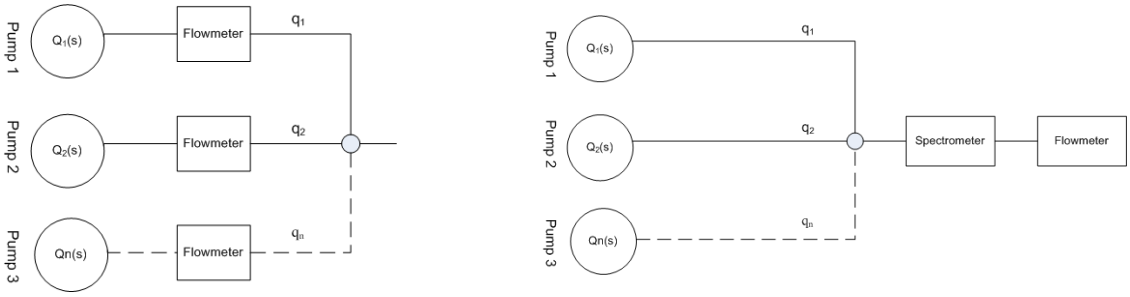
Simulation



Measurement with µ-flow L01
(not a validation measurement)



Discussion: Improving Measurement



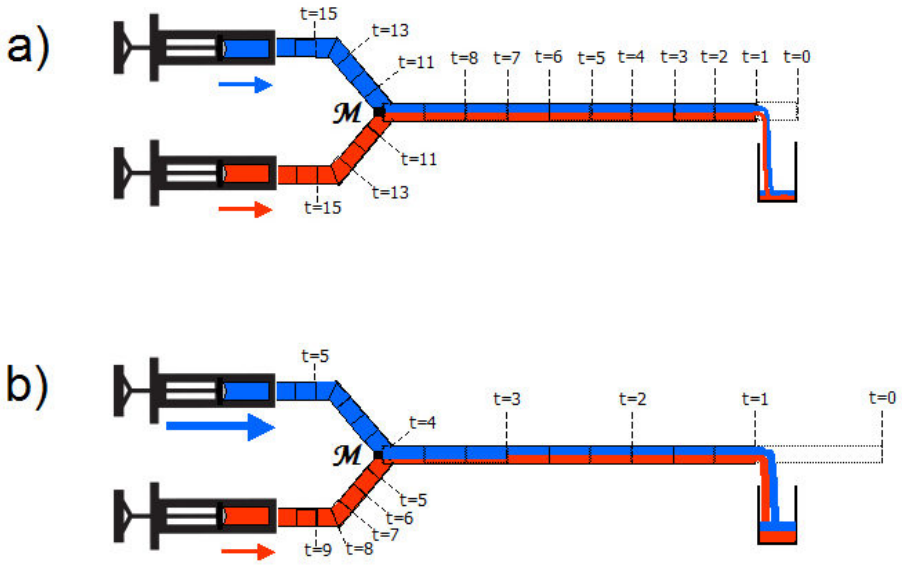
- Flowmeters less noise than gravimetric methods
- However, large resistance, i.e.

- Normal intravenous pressure: P = 5.9 mmHg (0.0079 bar)
- For our M12P we found: R = 5.41 mmHg / ml

Dosing Errors: why?

Two distinctive physical parameters found

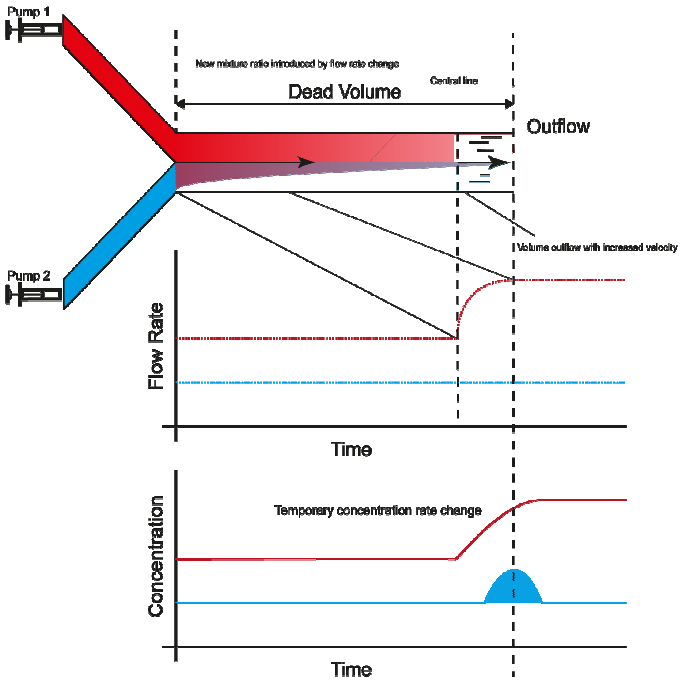
(2) Internal Volume or 'Dead Volume'



Dosing Errors: why?

Two distinctive physical parameters found

(2) Internal Volume or 'Dead Volume'

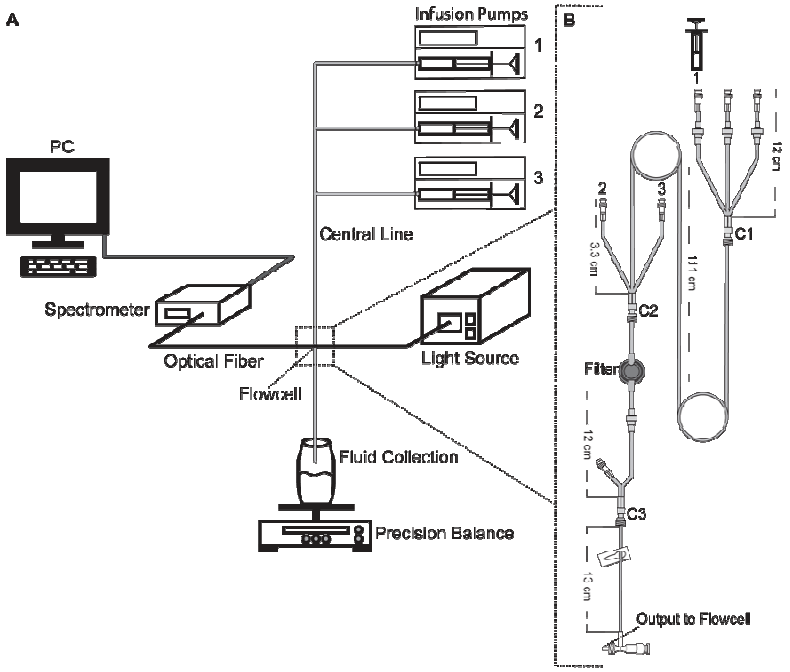


Dosing Errors: measuring

Two distinctive physical parameters found

(2) Internal Volume or 'Dead Volume'

Spectrometry (absorption photo-spectrometric)



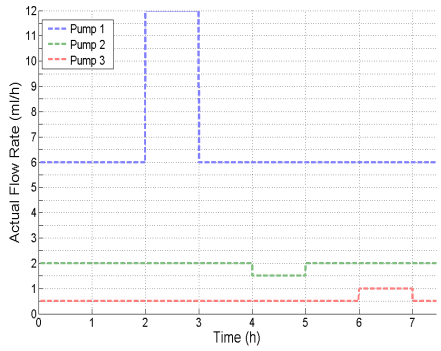
Dosing Errors: measuring

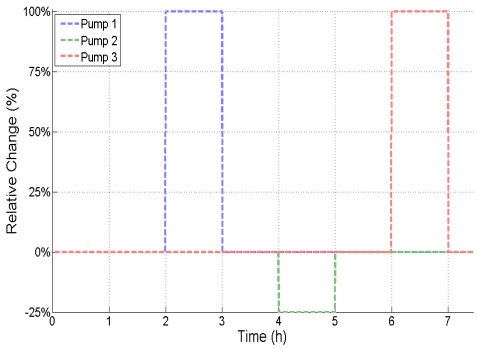
Two distinctive physical parameters found

(2) Internal Volume or 'Dead Volume'

Pump	Pharmaceutical simulated	Dye	C (mg/ml) *	Flow (relative change) †			
				t=0	t=2h	t=4h	t=6h
1	Electrolytes	Tartrazine (TT)	0.020	6	12	6	6
				(-)	(100%)	(0%)	(0%)
2	High alert med. ‡	Indigo Carmine (IC)	0.100	2	2	1.5	2
				(-)	(0%)	(-25%)	(0%)
3	Electrolytes or High alert med.‡	Allura Red (AR)	0.200	0.5	0.5	0.5	1
				(-)	(0%)	(0%)	(100%)

*note that the actual concentration was based on physical properties of the dyes.
†Actual flow rate (ml/h) and relative change initiated (%).
‡High alert medication: i.e. inotrope, analgesic or anesthetic.

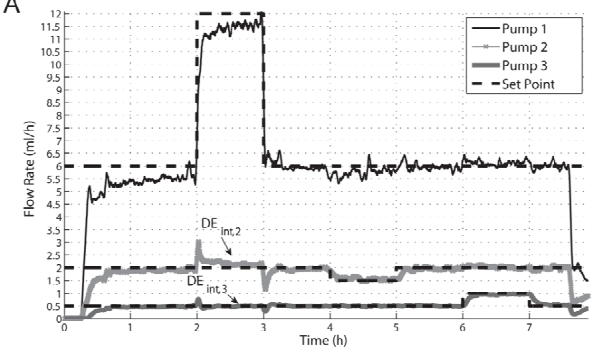




Dosing Errors: measuring

Dosing Errors due to **dead volume (mostly)**

A



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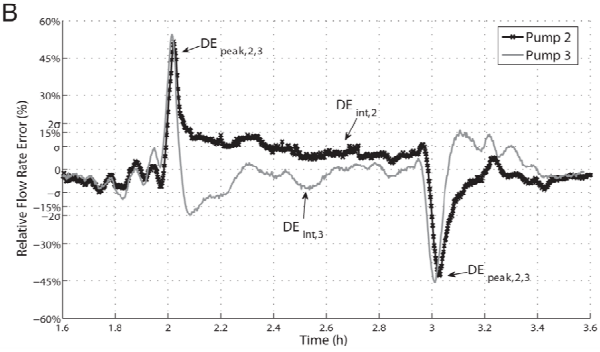


Remember: low flows high concentrations!

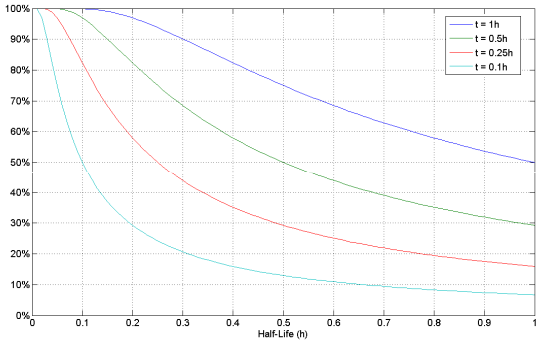
Results

Dosing Errors: are they clinically relevant?

Dosing Errors: clinical relevance

Dosing Errors: are they clinically relevant?

$$k_e = \frac{ln\,2}{t_{1/2}}$$



Type	Common Pharmaceutical	Half-life ($t_{1/2}$)
Inotrope	Dopamine	1-2 minutes
	Dobutamine	1-2 minutes
	Noradrenaline	1-2 minutes
Anesthetic	Propofol	30-60 minutes
Analgesic	Morphine	2-3 hours

- Short half-life, fast onset, usually. Small half-life small therapeutic index
- Inotropics: max over-dose:
- **~24.1% ± 6.5% (over-dose)**
- **~-16.3% ± 11.3% (under-dose)**

Dosing Errors: Clinical Relevance

Are they clinically relevant?

- Inotropes overdose in neonates: potentially life-threatening
  - Hypertension (Cloudhurry, 2011)
  - Peri-intraventricular hemorrhages (Alderliesten,2013)
- Inotrope under-dose
  - Hypotension [Gill, 1993]

- Start-up delay in agreement with literature (Decaudin, 2009; Lovich, 2005; Neff, 2001)

Discussion: preventing dosing errors

Some feasible innovations

- **In-line measurement**
- **In-line pressure regulation (controlling the RC behavior)**
  - **Consider costs**
  - **Disposable regulators (or be able to sterilize)**
- **Reduce internal (dead) volume**
- **Managing internal (dead) volume**

Conclusions

- Compliance and internal (dead) volume cause dosing errors
- Dead volume can be measured using a spectrometric method
- Compliance and resistance can be measured using flowmeters
- Dosing errors were found to be clinically relevant
- Innovations preventing dosing errors may be feasible.

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