UMC Utrecht

# Dosing Errors in infusion

## Theoretical background

**Roland Snijder**

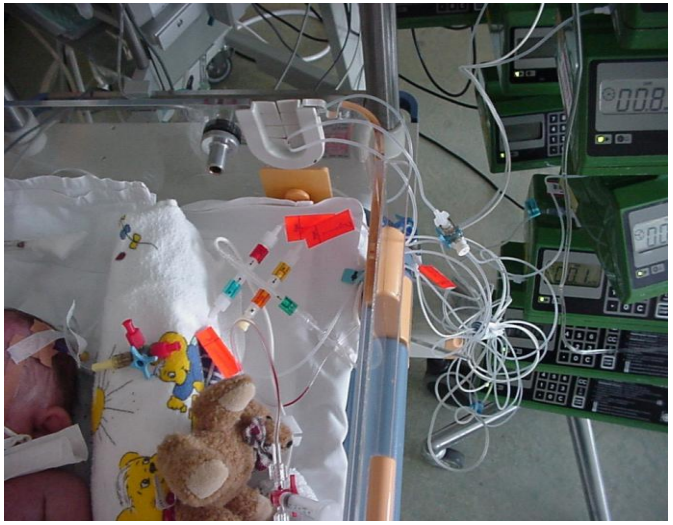
# Dosing Errors: clinical relevance

Especially dangerous in critical patients such as neonates.

Low flow rates

High concentrations

Potent medications with small half-lifes



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# Outline

Goal: To fully understand and quantify infusion dosing errors.

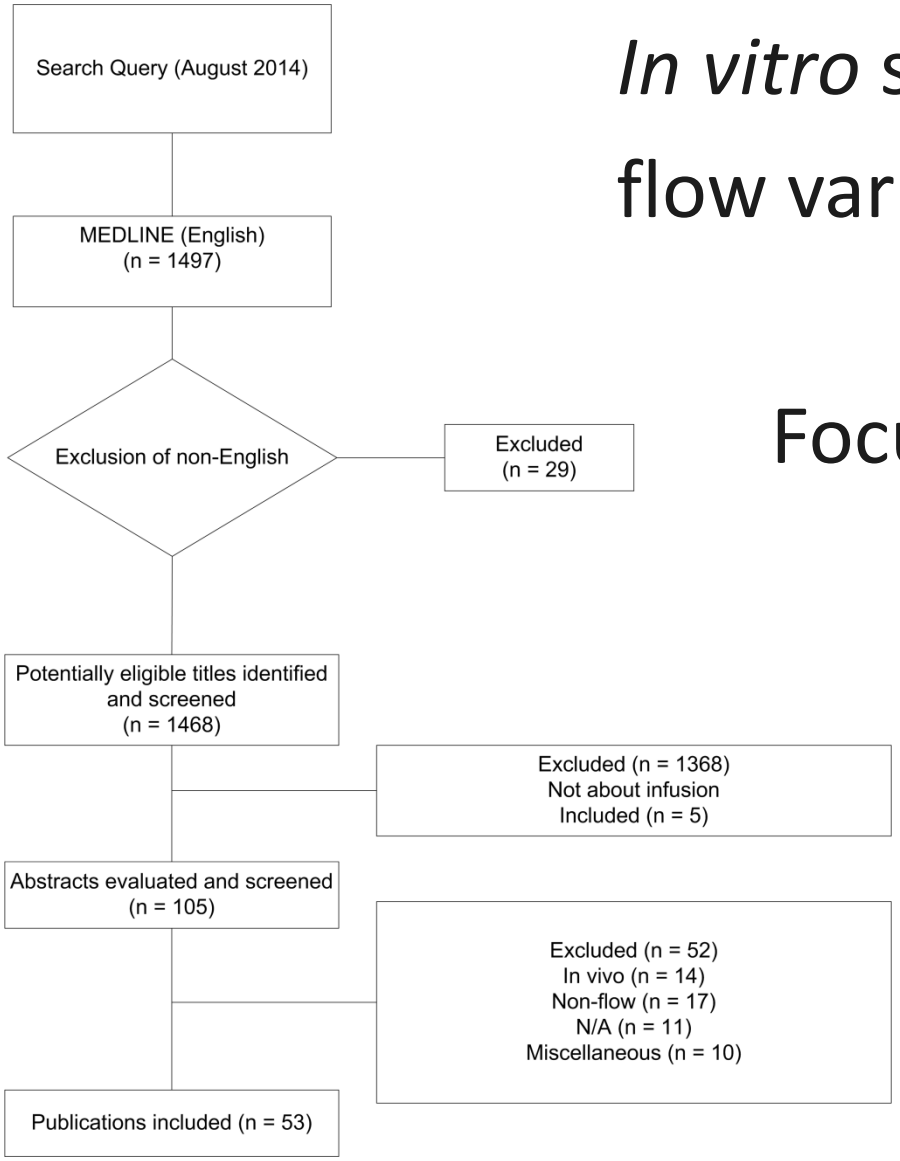
Why?

- Simulating / predicting dosing errors

How?

- Dosing errors in literature
- Measuring dosing errors

# Methods: systematic literature review




*In vitro* studies investigating flow variability / dosing errors

Focus on physical causes

RA Snijder, et al. biomedical engineering / Biomedizinische Technik

# Physical Causes: what does literature tell us?

**Main outcome**

- Most important physical phenomena:
  - **compliance**
  - **resistance**
  - **dead volume**

- Other effects also mentioned:
  - Temperature and viscosity
  - Diffusion
  - Air bubbles
  - Turbulence (very high flow rates)

# Physical Causes: what does literature tell us?

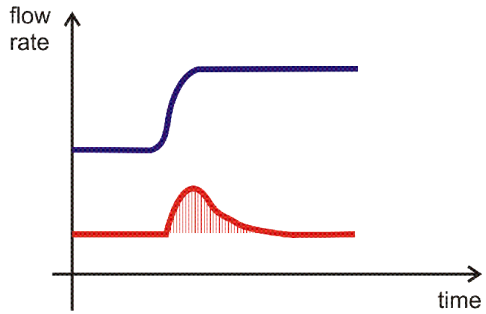
**Flow rate change**

Others

Height difference

Physical Effect

Dosing Error




Types of dosing errors due to *compliance, resistance and dead volume*

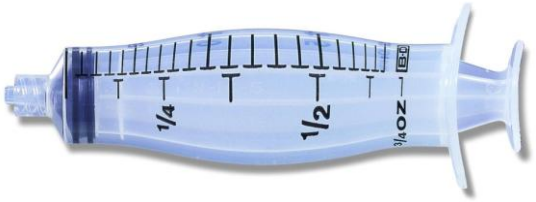
1. **Start-up phenomena**
2. **Backflow**
3. **Dead volume: push-out effects**

# Compliance/Resistance: start-up phenomena

**Start-up phenomena: clinical perspective**

- Delayed treatment of symptoms
- Thrombosis in arterial lines

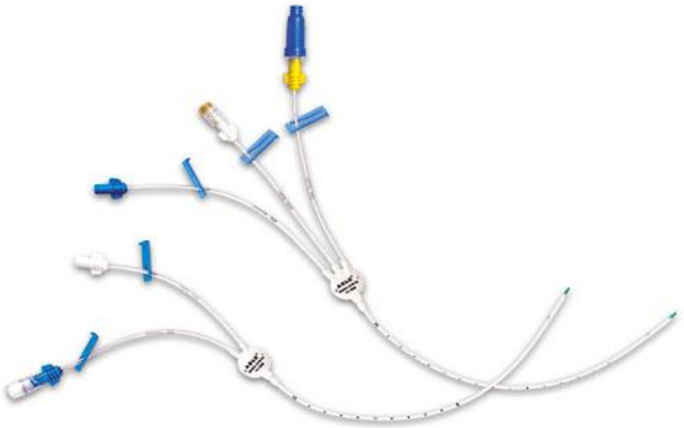
# Compliance/Resistance: start-up phenomena

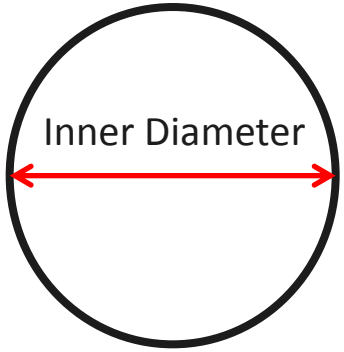



- **Compliance and Resistance**

[Volume per pressure]

- Compliance expands components
- Resistance 'resists' the flow
- This is mostly caused by narrow tube such as vascular access devices.

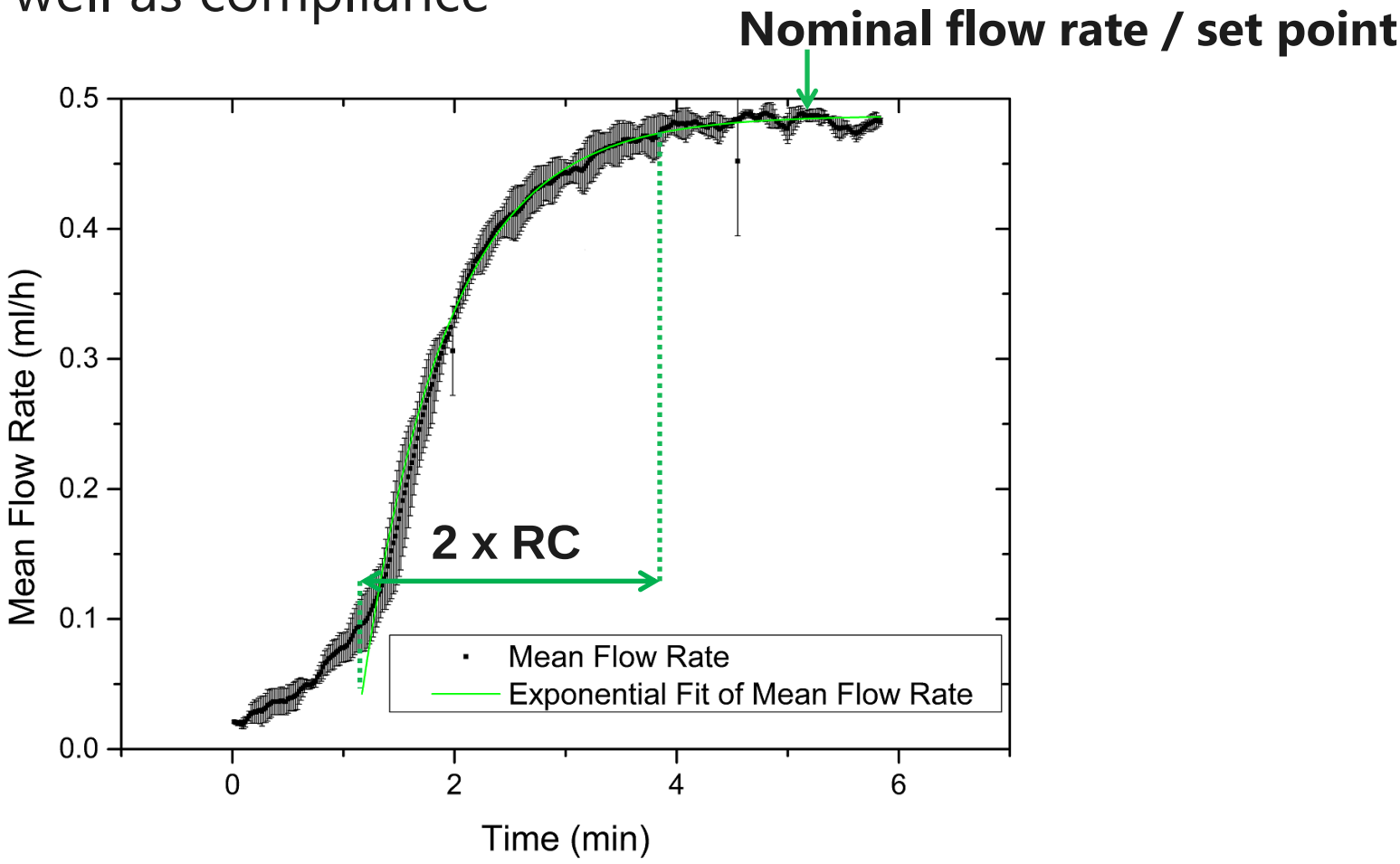





[Pressure per ml/h]

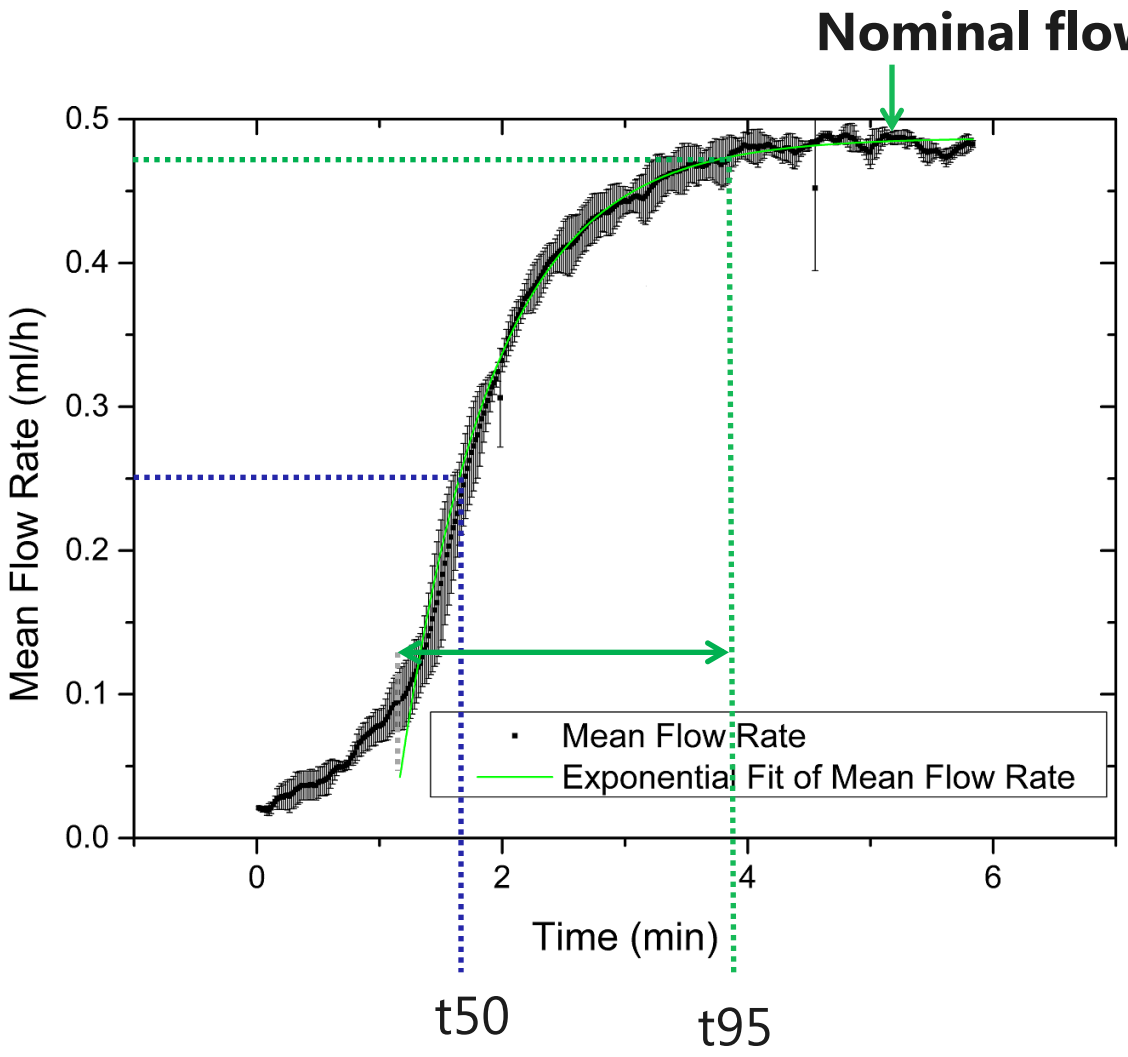
# Compliance/Resistance: start-up phenomena

Narrow tubes may result in longer start-up delays as well as compliance




**RC-time = compliance x resistance ~ minute.**

# Compliance/Resistance: start-up phenomena

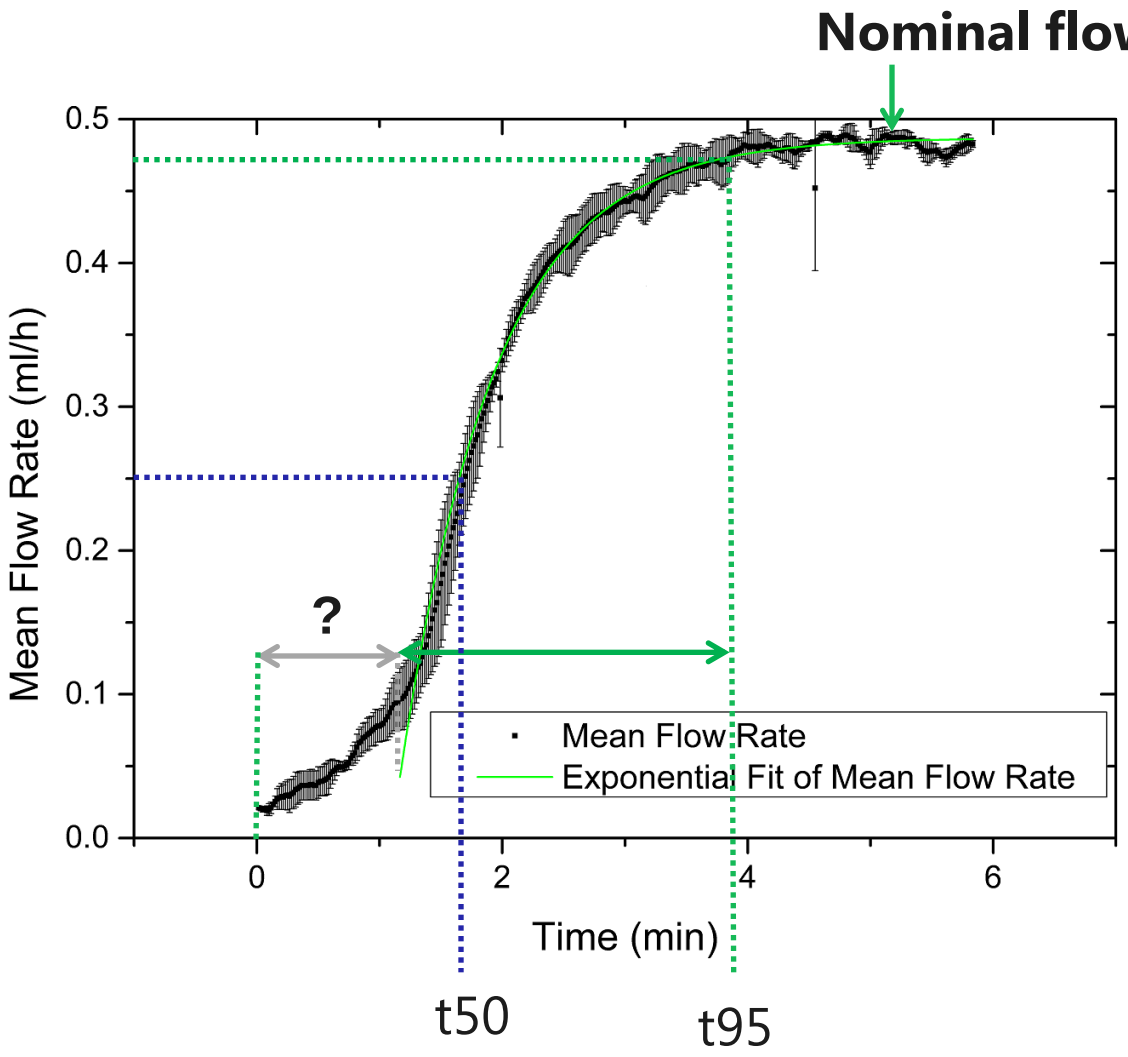



95% (3.9 ± 0.5 min)

50% (1.7 ± 0.1 min)

Time to first drop: ~seconds

# Compliance/Resistance: start-up phenomena



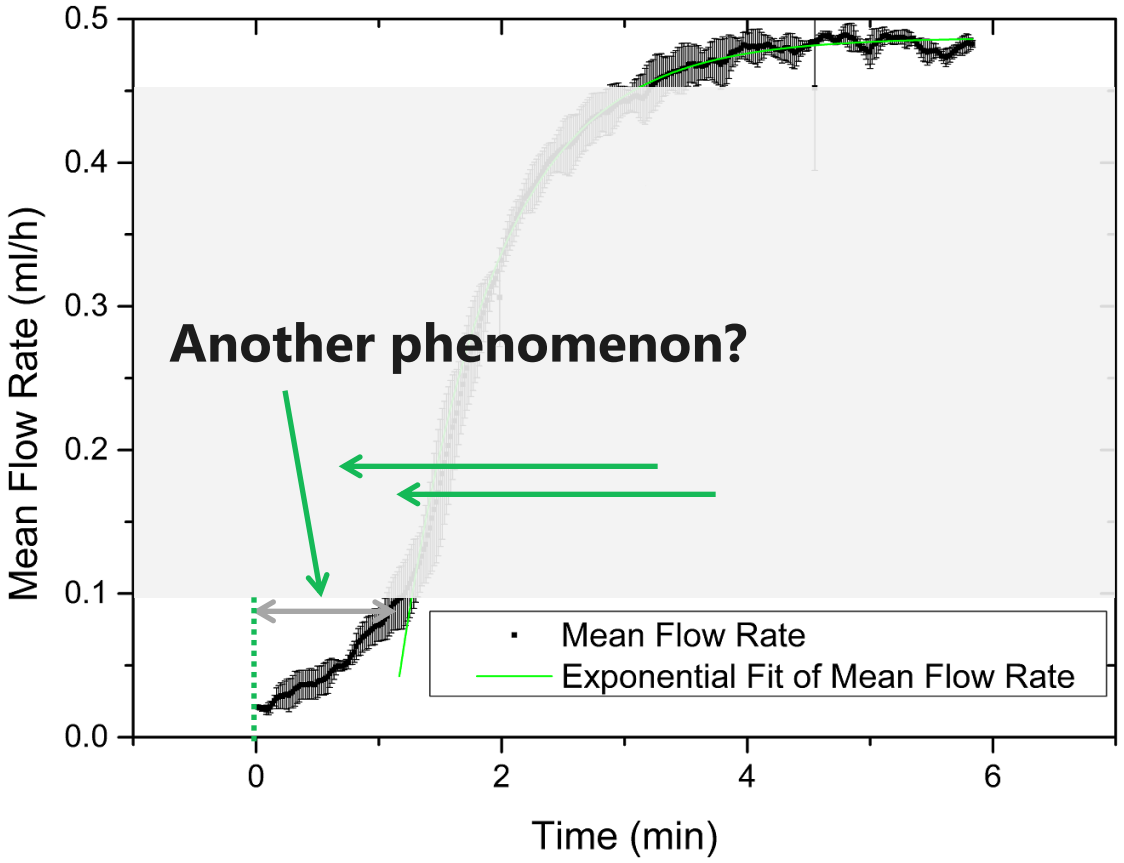

95% (3.9 ± 0.5 min)

50% (1.7 ± 0.1 min)

Time to first drop: ~seconds

# Compliance/Resistance: start-up phenomena

- Most of the start-up time could be defined by an exponential fit
- A second phenomenon also contributes to the start-up time



# Compliance/Resistance: start-up phenomena

## Literature

**Other causes contributing to start-up times:**

- Gap between the plunger and the pump [Lönnqvist (1997), Neff (2001)]
- Friction between plunger and the syringe wall [Timmerman (2015)]
- Priming / initial bolus may eliminate the additional start-up phenomenon [Neff (2001), Kim (2013)]

**Typical Start-up time of syringe pump flow rates:**

- 3.6 – 75 minutes [Neff (2007)]
- Usually several minutes [Neff, Weiss, Kim, Schmidt, Sarraf]
- Compliance mostly located in syringe [Kim (2013)]
- but also in other components, such as, the pump it self [Neff (2001)]

- *Literature values in line with our measurements*

# Compliance/Resistance: start-up phenomena

## Compliance values

**Literature (50 ml syringes)**

- 0.93 – 1.83 ml / bar [Neff (2001)]
- 0.9 – 1.35 ml / bar [Weiss (2000)]
- Smaller syringe sizes less compliant

**Our findings (50 ml syringe)**

- 1.54 – 2.10 ml / bar [Batista et al.]
- Smaller syringe sizes less compliant

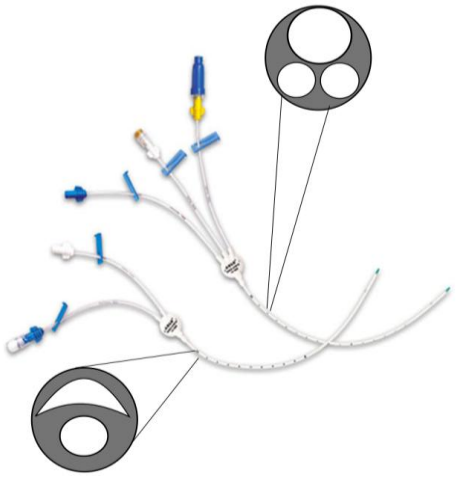
*Literature values in line with our measurements*

# Compliance/Resistance: start-up phenomena

## Resistance values

### Literature (Catheters)

- Typically smaller compared compliance [Angle (1997)]
- Hagen-Poiseuille: good estimation but limited [Jayanthi(2005)]
- Multi-lumen inner shape not always round [Angle (1997)]



### Our findings (50 ml syringe)

- *Literature values in line with our measurements*

# Compliance/Resistance: backflow

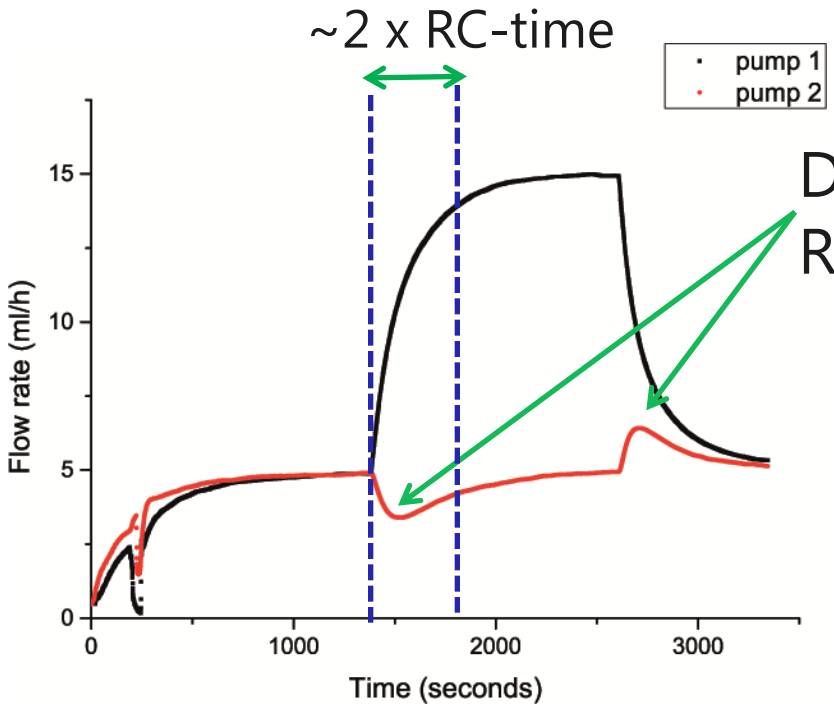
**Backflow: Clinical perspective**

- Delayed treatment of symptoms
- Blood inside infusion system

# Compliance/Resistance: backflow

Start-up time of syringe pump flow rate in literature:

- In multi-infusion
- Possible backflow [Decaudin (2009), Ellgar (2011) and many others]
- Anti-reflux valves might prevent backflow
- Valves may also introduce additional start-up time [van der Eijk (2014), McCarroll (2000)]




Dosing Errors due to Compliance / Resistance

**Valves** (Vygon (UK))

# Dead volume

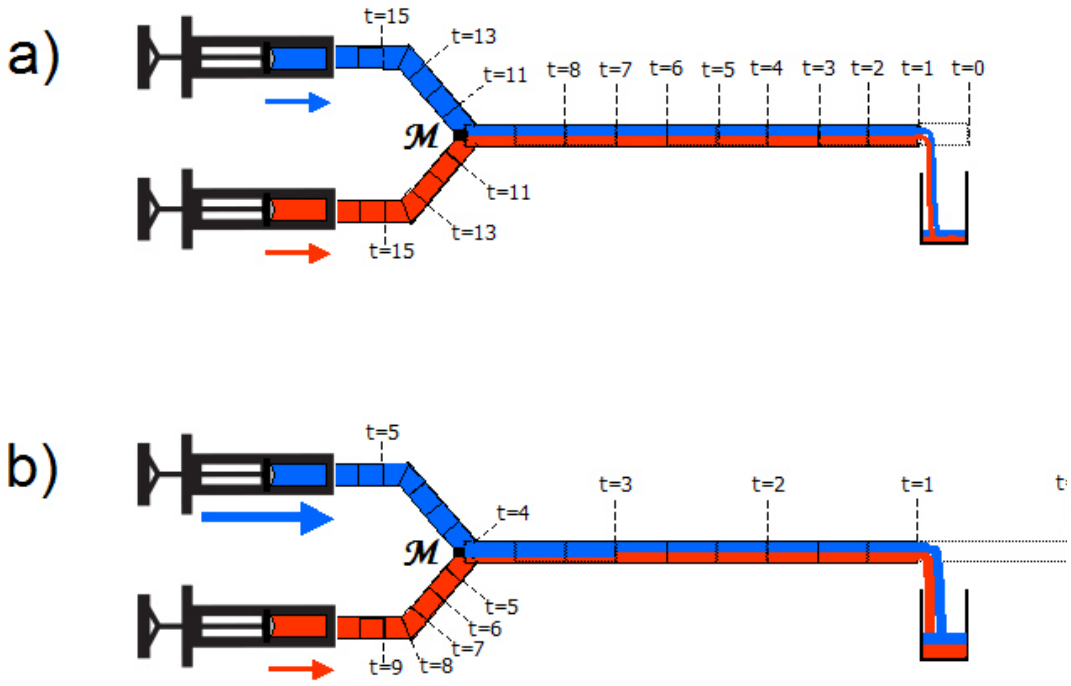
## Dead volume: Clinical perspective

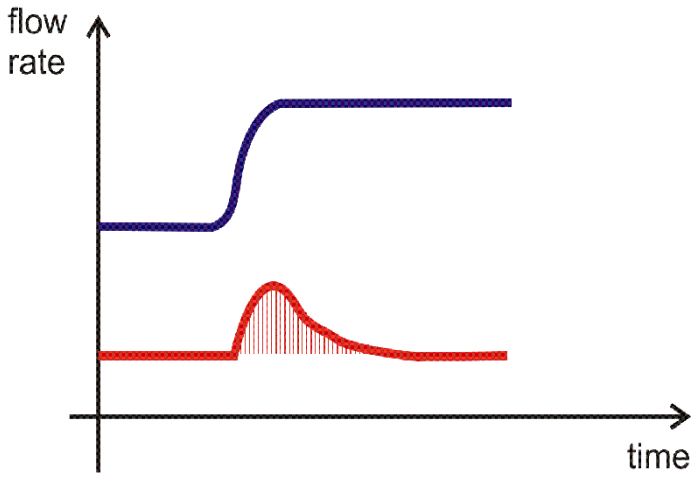
- Delayed treatment of symptoms: Delayed onset of drug delivery *on top* the onset flow rate
- Dosing Errors: Push-out effect

# Dead volume

**Internal Volume or 'Dead Volume':**

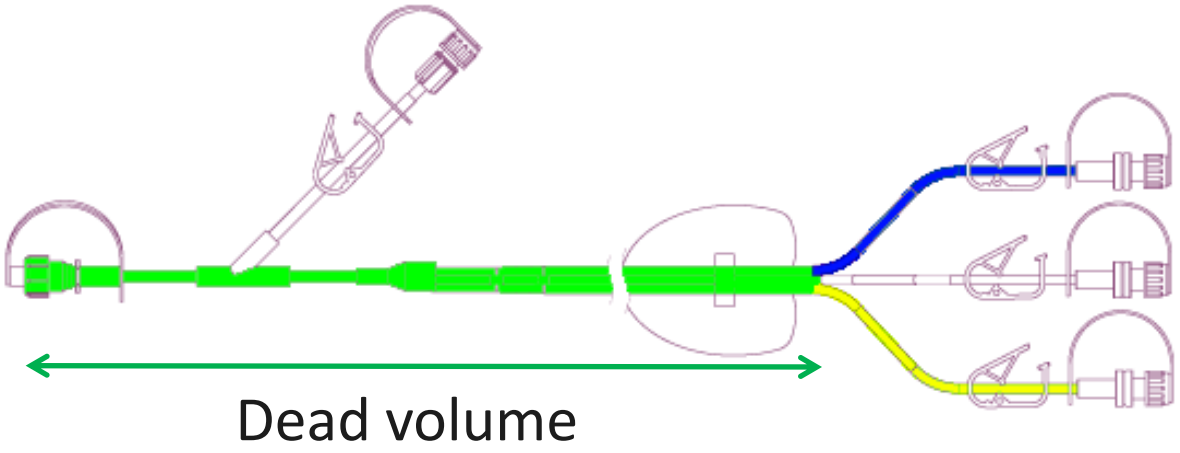
The volume between the mixing point and the point of outflow, i.e. the patient




Konings, et al.

# Dead volume: push-out effect

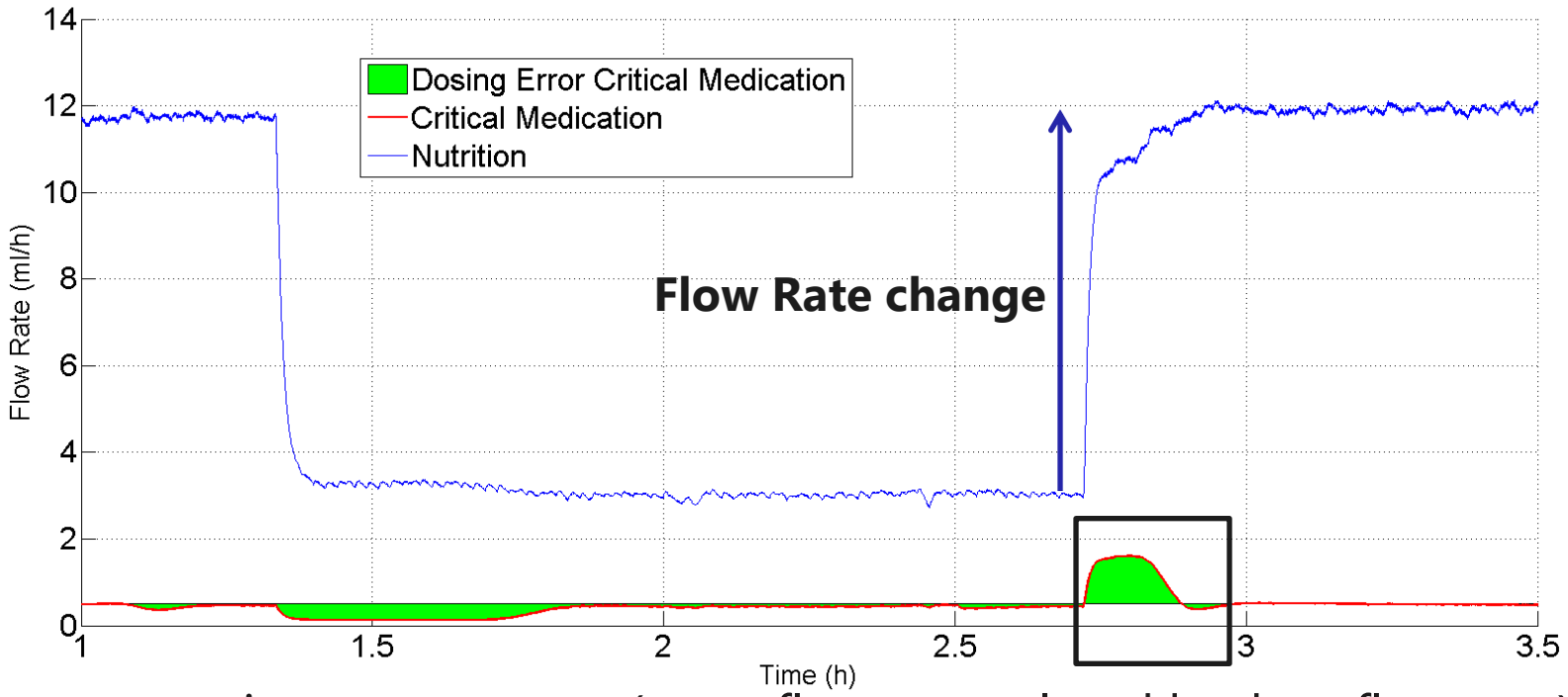



Dead Volume time (h) = dead volume (ml) / flow rate (ml/h)

- 6 minutes calculated [Oualha (2014)]
- 15 – 18 minutes measured [Oualha (2014)]
- So maybe not so straight forward

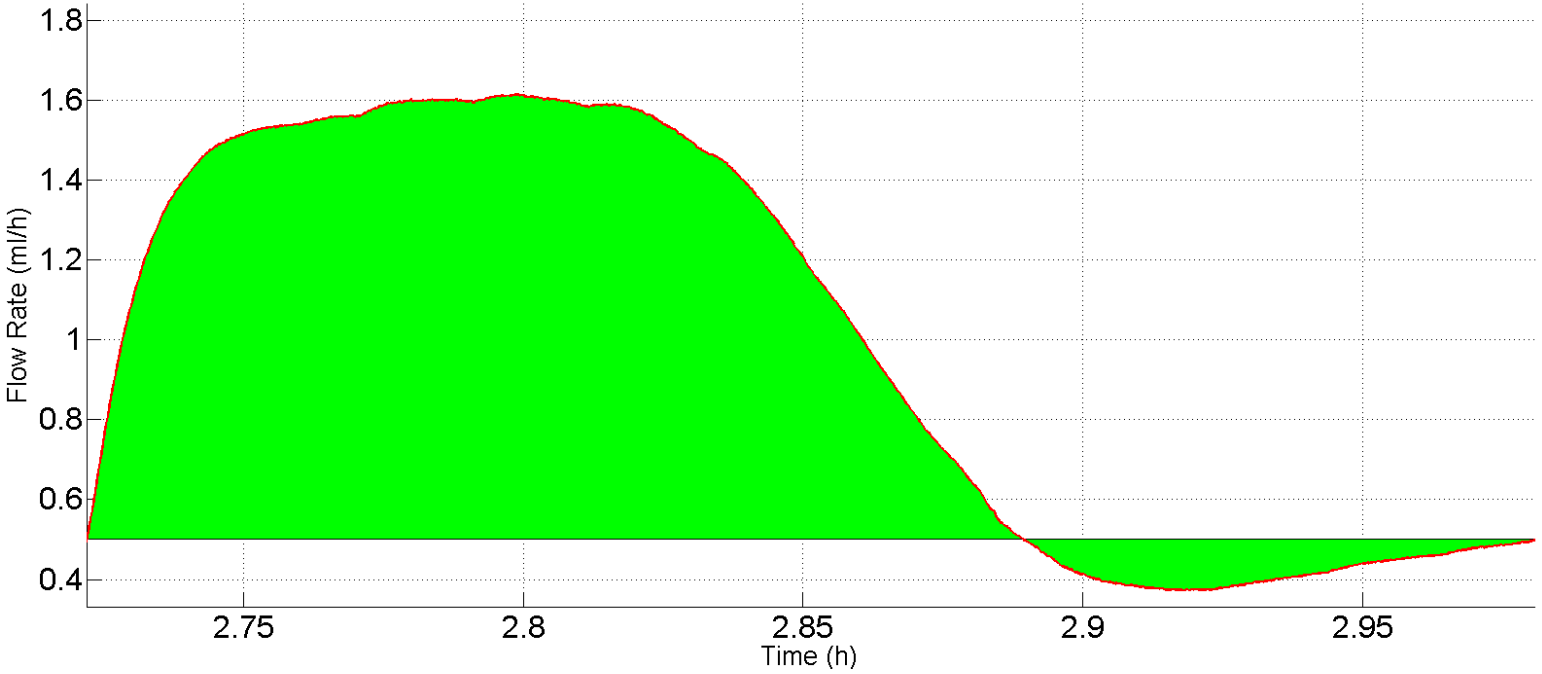
# Dead volume: push-out effect

Dosing Errors due to **dead volume (mostly)** but also **compliance and resistance**




Spectrometric measurement (mass flow rate related back to flow rate)

# Dead volume: push-out effect

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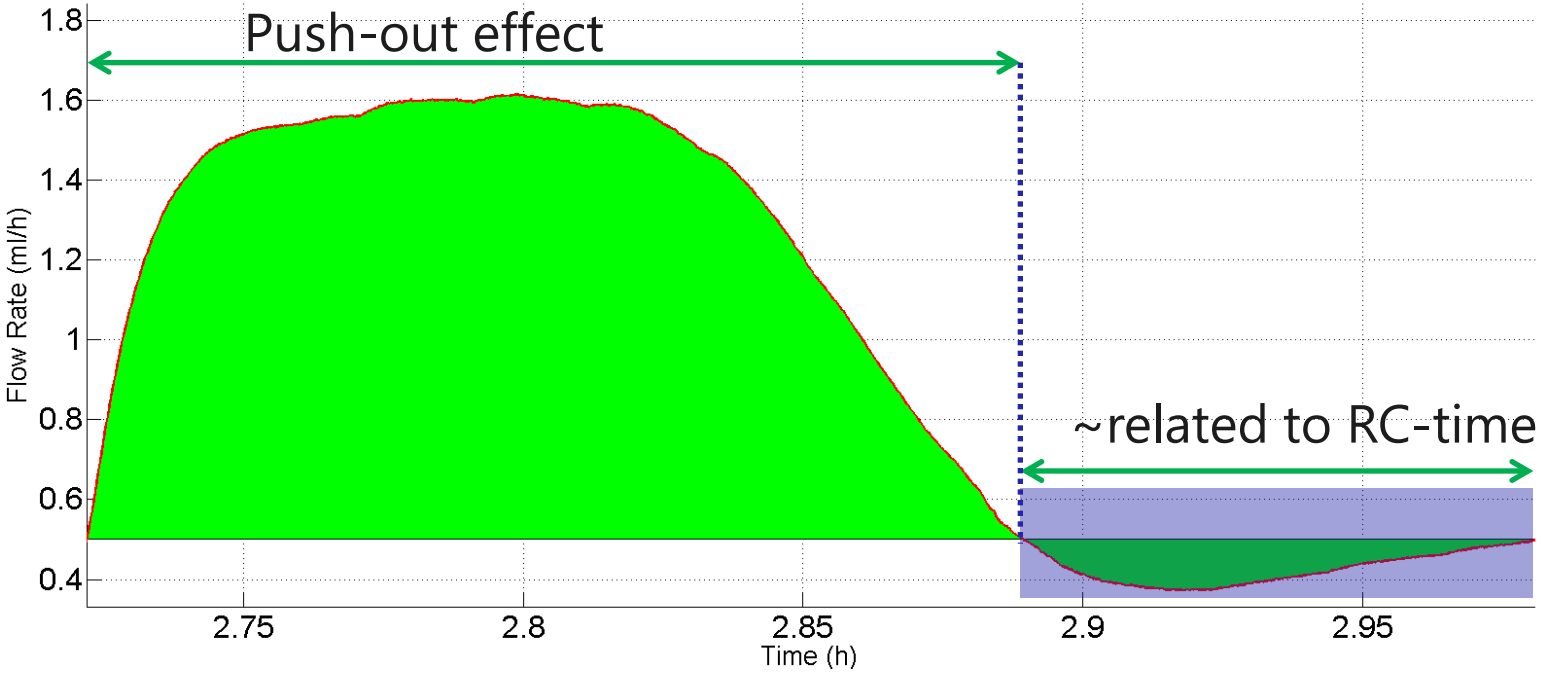


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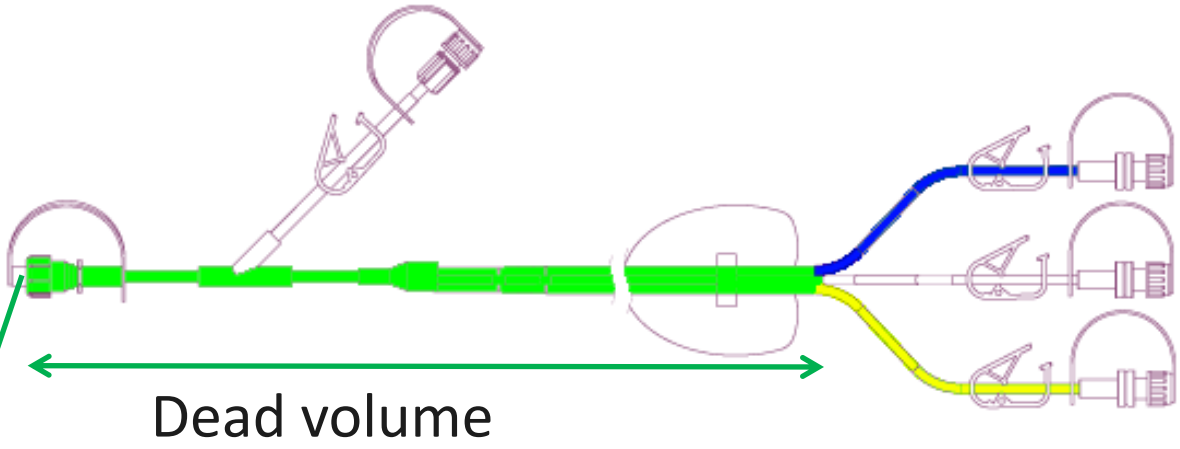
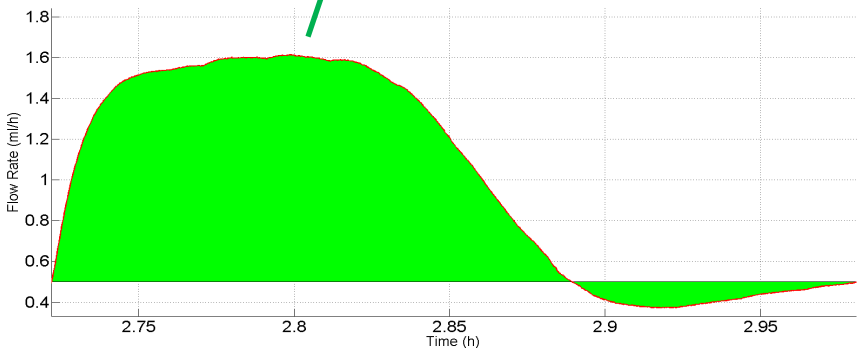
# Dead volume: push-out effect



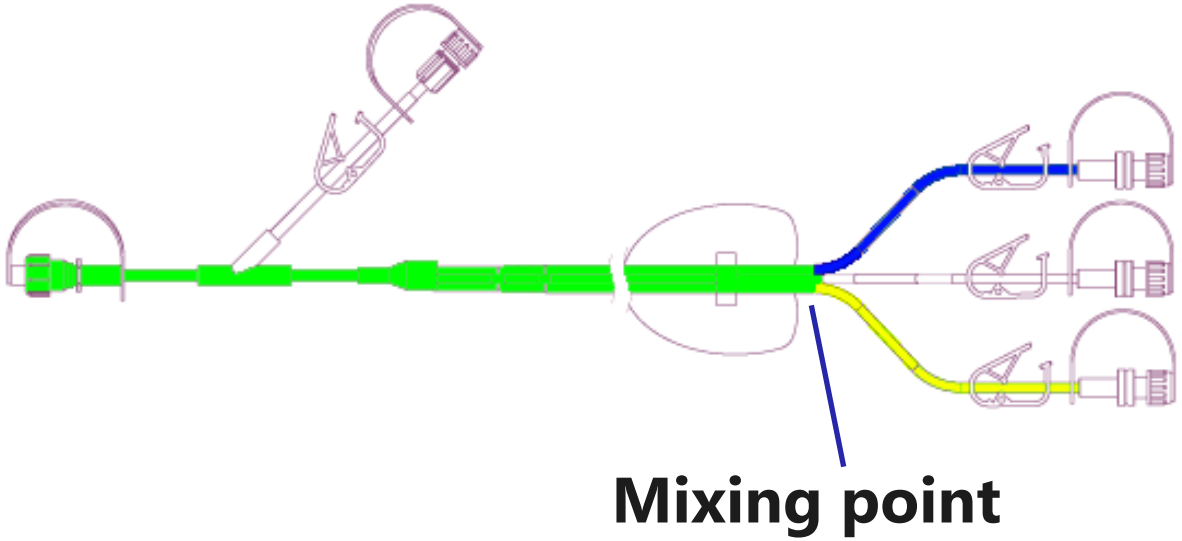

Area Under the Curve (AUC) related to dead volume and ratio of flow rate change

Minimize dead volume to reduce dosing errors [Decaudin, Lannoy, Lovich]

# Dead volume: mixing effect

## Literature

- How do the medications mix when they mix?



# Dead volume: mixing effect

## Literature

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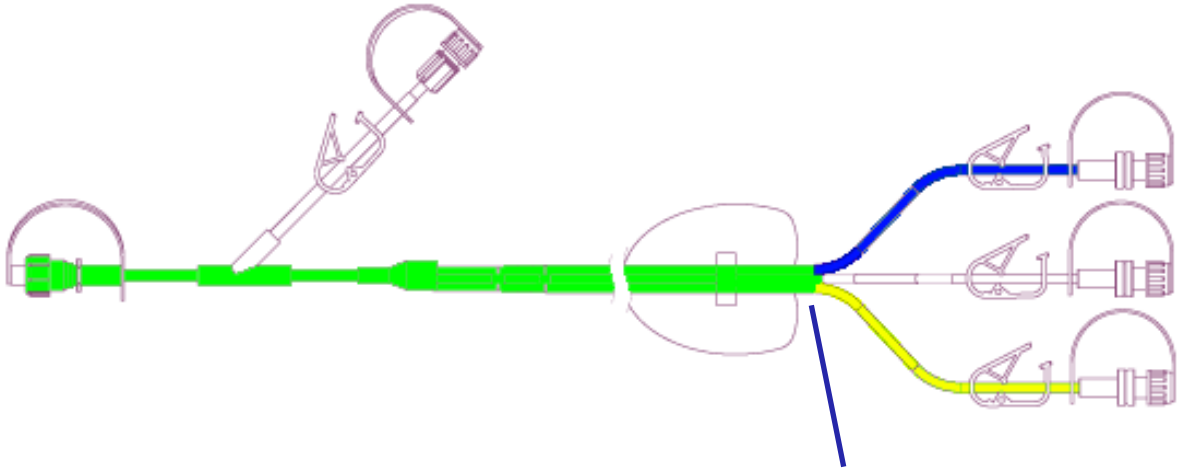


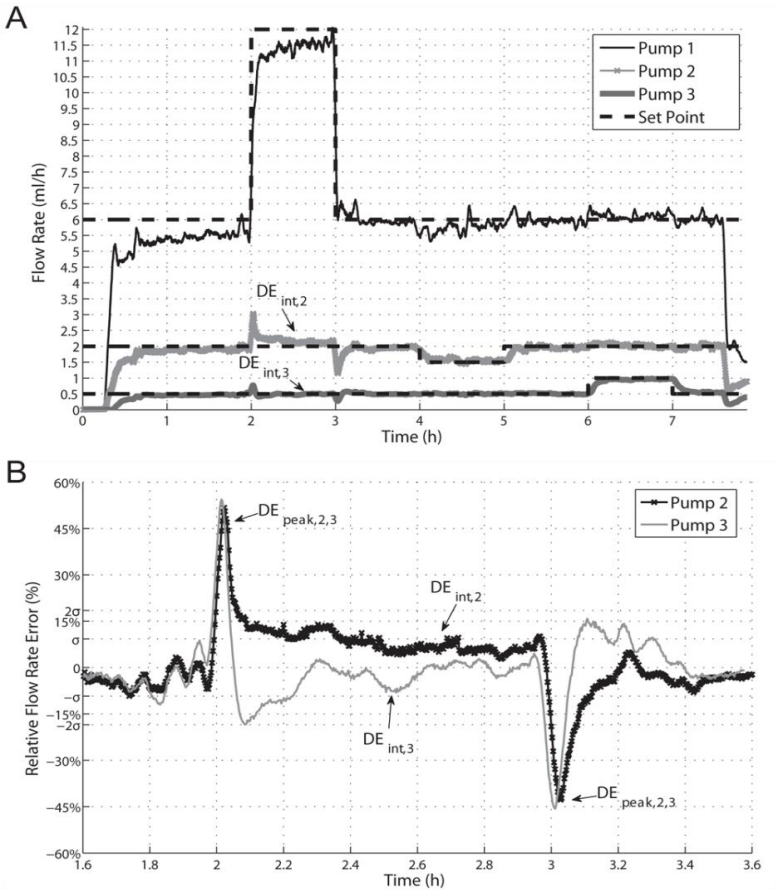

**Two extremes:**

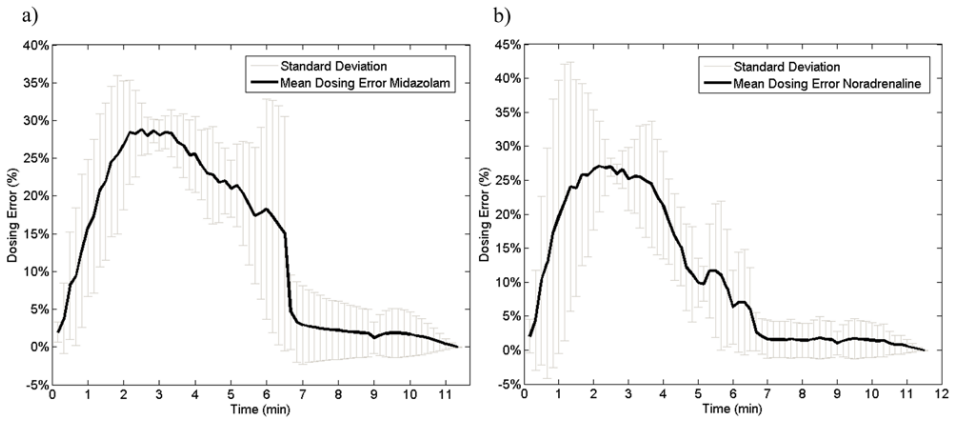
- Plug flow
- Well-mixed

- In reality somewhere in between [Lovich (2006)]
- Dependent on flow rate
- Diffusion may only a minor effect, but mentioned in literature [Lovich (2006), Oualha(2014)]

# Dead volume: push-out effect

## Our findings



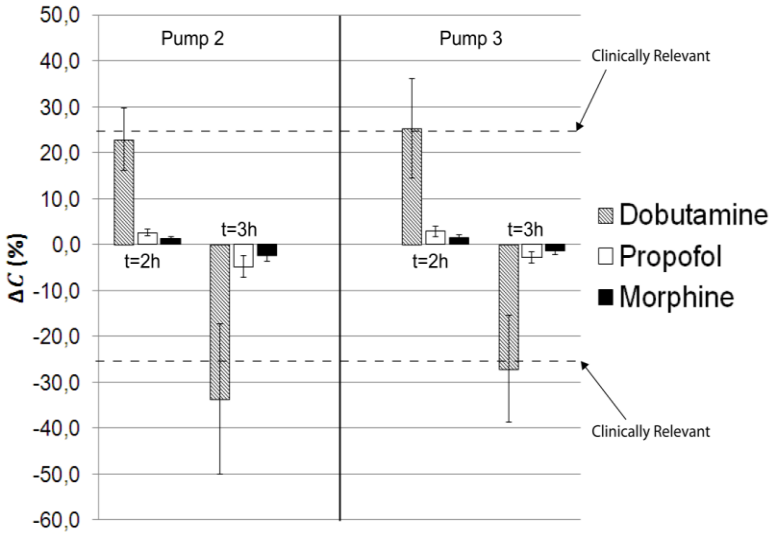

a) Mean AUC 27.5% ± 10.4%
b) Mean AUC 25.4% ± 6.19%

**Highest dosing errors:**
**+48.1% ± 10.5% (P ≤ 0.0001)**

# Dosing Errors: Clinical Relevance

## Dosing Errors: are they clinically relevant?

Tested using a simple one-compartment




| 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)**

# Simulation

- Simulation of compliance/ resistance [Murphy (2011)]
- Simulation of dead volume [Lovich (2005), Lovich (2006), Ma (2011) ]
- Two pumps max

We have developed a simulation model

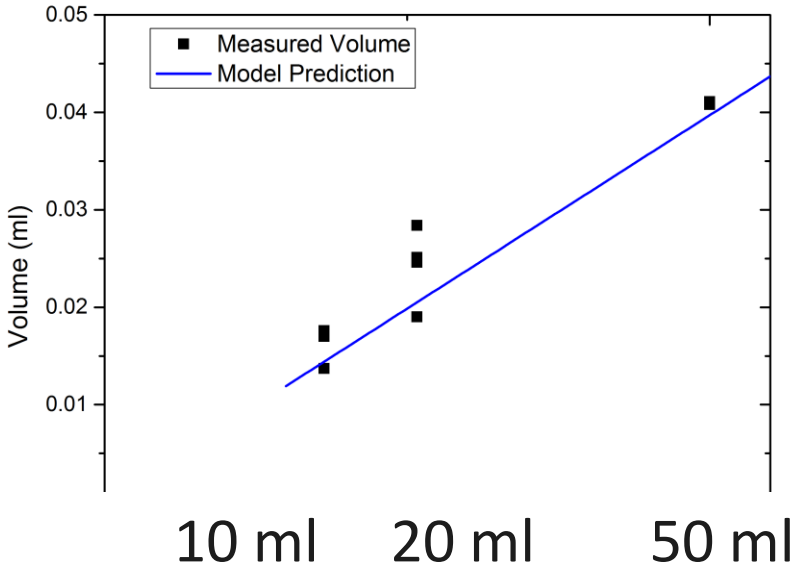
- Capable of simulating n pumps
- Capable of simulating dead volume as well as compliance / resistance

# Simulation

A peak at the results

| **Model** | **Measurement** |
| --- | --- |
| RC dosing error 0.03972 ml | 0.0408, 0.0409, 0.0411 ml (n=3 measurement) |
| Dead volume time 831 | 823, 813 seconds |

Typical RC values varying (10, 20 and 50 mL syringe)



# Conclusion

- Dosing errors are mainly a superimposed combination of compliance, resistance, dead volume and possible mixing effects
- In order to simulate dosing errors it is necessary to fully under understand these errors