Motivation and Clinical Relevance
Metrology for Drug Delivery
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The Clinical Cause

- Infant with acute blood pressure problem
- Dopamine infused to raise blood pressure
- No result
- Increasing dopamine flow rate
- No result
- Increasing dopamine again
- Overshoot
- No relation found with dopamine setpoint
- Decreasing dopamine flow rate
- No result
- Etc..

Clinical relevance: widespread use of infusion

- Almost every patient receives IV Therapy
- Many different applications
- Many users
- Many errors/ adverse events
- Potentially high impact
**Therapeutic range**

![Therapeutic range graph]

Small therapeutic range: Set point deviations are more relevant

**Half life of drugs**

- Serum concentration is determined by
  - Administered dose
  - Half life of drug
- Short half life drugs
  - can be more easily controlled in theory
  - are more sensitive to dose/ flowrate changes

Clinical relevance of flow rate accuracy

- Small therapeutic range
- Small drug half life
  - Vasopressors
  - Inotropics
  - Certain anesthetics
- Condition of the patient
  - Fluid intake restriction
- Drug concentration

Control mechanism infusion

Driving mechanism:
- Displacement of plunger by step motor

Control mechanism
- Change in step motor velocity

Setpoint parameter
- Flow rate

Non plunger displacement induced flowrate changes are not noticed by the system

> poor measurability
> poor controllability
Standards and regulations

- Pumps: IEC/EN 60601-2-24
  - Describes “trumpet curve”
- Syringes: ISO 7886-2
  - Describes maximum compliance (compressibility)
  - Describes maximum “dead volume”

No specific regulations for low flowrate/ specific applications

No protocols describing maximum internal volume

No output measurements of entire system (pump+ syringe+ infusion line and catheter)

In-vitro experiment: “push-out” effect

Blue:
Set point increased

Green:
“push-out effect”
Same direction
In-vitro experiment: “compliance” effect

- Mass flow rate
- System compliance results in start up time

Red: Compliance Effect
Blue: Set point increased

Opposite direction

This time is long enough to cause thrombosis

Computer simulation (method)

- Schematic representing a multi-infusion set-up with N pumps. Network Q1, Q2 .. Qn are sources (pumps). qn is the flow rate output of pumpn- (before the mixing point)
- Electric analogue for multi-infusion setup to simulate the outflow
- Standard analytical methods (Laplace domain)
- System of 3 pumps was calculated
Results of computer simulation (compliance effect)

- initial situation: steady state values
- At t=0.5, pump #1 is set to 14
- the flow rates of the parallel pumps #2 and #3 react to the pressure difference caused by the flow rate changes of pump #1, in the form of altered storage of fluid in the compliance (capacitor effect) of the (plunger of the) syringe

Equal lengths

Combining the results

**In-vitro experiment: “push-out” effect**
- Blue: Set point increased
- “push-out effect” _Same direction_

**In-vitro experiment: compliance effect**
- Blue: Set point increased
- compliance effect _Opposite direction_

**Computer simulation: compliance effect**
- Blue: Set point increased
- compliance effect _Opposite direction_
- Equal lengths
Implications of results 1

“push-out effect”  
Same direction  
compliance effect  
Opposite direction

Mathematical fact:

IF:

• Two opposite effects that play a role  
• Effects may be of same order of magnitude  
• Strength of effects depends on many factors

THEN:

Direction and strength of total net result may be hard to predict and counter-intuitive

Implications of results 2

Results of computer simulation (compliance effect)

Equal lengths (absolute : ml/h)

Implications:

Impact on “red” medication relatively high as a percentage of the red set point value
Discussion

• The in-vitro experiments, as well as the computer simulation, of a 3-pump multi-infusion set-up, show:
  • Internal volume effect produces a deviation in *the same direction* as the direction of the change in flow rate set point (of another pump, e.g. the "blue" pump),
  • Syringe compliance effect produces a deviation in *the opposite direction* with respect to the direction of the flow rate set point change
  • Syringe compliance effects are particularly important at low flow rates
  • At low flow rates, deviations have a higher clinical relevance

Conclusions

• In-vitro experiments as well as computer simulations show that the direction as well as the strength of the net compound deviations in multi-infusion are highly unpredictable and often counter-intuitive.
  • Accurate measurement of the mechanical compliances in the multi-infusion set-up adds to controllability and thus to safety
  • Increased focus and effort should be directed to the metrology of mechanical compliances at low flow rates.
  • Regulation concerning mechanical compliances should be updated and more strictly specified, especially for low flow rates
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