Open-loop vs Closed-loop Anesthesia Control

Outside US Evidence from TCI

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The History of Target-Controlled Infusion

Target-controlled infusion (TCI) is a technique of infusing IV drugs to achieve a user-defined predicted (“target”) drug concentration in a specific body compartment or tissue of interest. In this review, we describe the pharmacokinetic principles of TCI, the development of TCI systems, and technical and regulatory issues addressed in prototype development. We also describe the launch of the current clinically available systems. (Anesth Analg 2016;XXX:00–00)
Rapidly Equilibrating Compartment

Central Compartment

Slowly Equilibrating Compartment

Drug Administration

$V_2$

$V_1$

$V_3$

$k_{12}$

$k_{21}$

$k_{13}$

$k_{31}$

$k_{10}$
Rapidly Equilibrating Compartment

Central Compartment

Slowly Equilibrating Compartment

Drug Administration

$I$

$V_2$

$k_{12}$ $k_{21}$

$V_1$

$k_{13}$ $k_{31}$

Effect Site $V_e$

$k_{1e}$ $k_{10}$

$k_{c0}$
Drug Effect

Effect Site Concentration

50% Effect

$E_0$

$E_{max}$

$C_{50}$

$n$
Drug Administration

$V_2$
Rapidly Equilibrating
Compartment

$V_1$
Central
Compartment

$V_3$
Slowly Equilibrating
Compartment

$k_{12} \quad k_{21}$

$I$

$k_{13} \quad k_{31}$

$k_{10} \quad k_{1e}$

$k_{e0}$

Effect Site Concentration

Drug Effect

50% Effect

$E_0$

$E_{max}$

$C_{50}$
Model Based Controller

- Desired Effect
Model Based Controller

Desired Effect

Drug Effect

Effect Site Concentration

- Desired Effect
- Effect Site Concentration
- Drug Effect
- 50% Effect
- $C_{50}$
- $E_{0}$
- $E_{max}$
- $n$
Model Based Controller

Desired Effect → Effect Site Concentration
Model Based Controller

Desired Effect

Effect Site Concentration

\[
\begin{align*}
V_e & \quad \text{Rapidly Equilibrating Compartment} \\
V_1 & \quad \text{Central Compartment} \\
V_3 & \quad \text{Slowly Equilibrating Compartment}
\end{align*}
\]

Drug Administration

\[
\begin{align*}
k_{21} & \\
k_{31} & \\
k_{10} &
\end{align*}
\]
Model Based Controller

Desired Effect → Effect Site Concentration → Infusion Rate
Model Based Controller

- Desired Effect
- Effect Site Concentration
- Infusion Rate

Observed Effect
Model Based Controller

- Desired Effect
- Effect Site Concentration
- Infusion Rate
- Observed Effect
Model Based Controller

- Desired Effect
- Observed Effect
- Effect Site Concentration
- Infusion Rate

TCI
Model Based Controller

Desired Effect

Observed Effect

Effect Site Concentration

Infusion Rate

TCI

Second Generation
Model Based Controller

Desired Effect

\[ \Delta \]

Observed Effect
Model Based Controller

Desired Effect

\[ \Delta \]

Observed Effect

\[ Ce_{50} \]
Model Based Controller

Desired Effect

Observed Effect

\[ \Delta \]

\[ E_0 \]

\[ E_{\text{max}} \]

\[ n \]

\[ C_{e_{50}} \]
Model Based Controller

Desired Effect

Observed Effect

\[ \Delta \]

\[ Ce_{50} \]

\[ E_0 \]

\[ E_{\text{max}} \]

\[ n \]

\[ V_1 \]

\[ k_{10} \]

\[ k_{12} \]

\[ k_{21} \]

\[ k_{13} \]

\[ k_{31} \]
CLOSED-LOOP FEEDBACK CONTROL OF PROPOFOL ANAESTHESIA BY QUANTITATIVE EEG ANALYSIS IN HUMANS

H. SCHWILDEN, H. STOECKEL AND J. SCHUTTLER

If median EEG frequency was outside this range, the difference between the measured and predicted values served to adapt the model parameters. On the basis of the updated parameters, a new infusion scheme was calculated for achieving and maintaining a concentration inducing a median EEG frequency of 2.5 Hz.
Comparison of Some Control Strategies for Three-Compartment PK/PD Models

Chuanpu Hu, William S. Lovejoy, and Steven L. Shafer

This paper investigates several control strategies in the framework of a three-compartment PK model plus an effect site with a PD model. Using computer simulations under different assumptions, we show that a MAP (maximum \textit{a posteriori}) Bayesian type of strategy is effective, nevertheless in high-risk situations a stochastic control strategy hedging against estimation errors provides better performance at computational cost.
Comparison of Some Control Strategies for Three-Compartment PK/PD Models

Chuanpu Hu, William S. Lovejoy, and Steven L. Shafer
Comparison of Some Control Strategies for Three-Compartment PK/PD Models
Closed-loop controlled administration of propofol using bispectral analysis

E. Mortier, M. Struys, T. De Smet, L. Versichelen and G. Rolly

This study demonstrated that this adaptive model-based control of propofol by BIS, incorporating TCI technology combined with a PK–PD model, performed very well to sedate patients undergoing surgery under spinal anaesthesia.
Closed-loop controlled administration of propofol using bispectral analysis

E. Mortier, M. Struys, T. De Smet, L. Versichelen and G. Rolly
Estimation of Optimal Modeling Weights for a Bayesian-Based Closed-Loop System for Propofol Administration Using the Bispectral Index as a Controlled Variable: A Simulation Study

De Smet T, Struys MMRF, Greenwald S, Mortier EP, Shafer SL
Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts

Struys, MMRF, Sahinovic M., Lichtenbelt BJ, Vereecke HEM, Absalom AR

Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study

A Brain-Machine Interface for Control of Medically-Induced Coma

Shanechi MM, Chemali JJ, Liberman M, Solt K, Brown EN
Robust control of burst suppression for medical coma

Westover MB, Kim ES, Ching SN, Patrick L Purdon PL, Brown EN
Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Janda M, Simanski P, Bajorat J, Pohl B, Noeldge-Schomburg GFE, Hofmockel R
Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Concerns about PID style controllers (no model):

1. Requires continuous signal.
   a. Poor choice if desired effect is probability of response.
   b. Lost signal $\rightarrow$ maintain existing rate
      i. Drug concentrations will rise.
Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Concerns about PID style controllers (no model):

2. Works best at midpoint of signal
   a. At edges signal is refractory to changes in concentration
Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade

Concerns about PID style controllers (no model):

3. Doesn’t understand PK/PD
   a. It doesn’t learn about PK/PD model
   b. Can’t apply learned knowledge to new target
   c. Can’t apply learned knowledge to prior target
Target-controlled infusions (TCIs) have been used in research and clinical practice for >2 decades. Nonapproved TCI software systems have been used during the conduct of almost 600 peer-reviewed published studies involving large numbers of patients. The first-generation pumps were first approved in 1996, and since then an estimated 25,000 units have been sold and used. Second-generation pumps were first approved in 2003. During 2004 to 2013, >36,000 units were sold. Currently, TCI systems are approved or available in at least 96 countries. TCI systems are used to administer propofol and opioids for IV sedation and general anesthesia for millions of patients every year. In countries where TCI systems are approved, nonapproved software is still commonly used in studies of the pharmacology of hypnotics and opioids, because research software offers greater flexibility than approved TCI systems. Research software is also readily integrated into data management modules. Although TCI is a part of established practice around the world, TCI devices have not received regulatory approval in the United States. In the United States, TCI administration of propofol and opioids for sedation and anesthesia is only possible using research software in IRB-approved research studies. (Anesth Analg 2016;XXX:00–00)
Target-Controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schnider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)¶
Target-Controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schneider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)*‖

Algeria, Andorra, Argentina, Australia, Austria, Bahrain, Bangladesh, Belgium, Bolivia, Botswana, Brazil, Brunei, Bulgaria, Canadaa, Cayman Islands, China, Chile, Colombia, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, French Polynesia, Germany, Ghana, Greece, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Ireland, Israel, Italy, Japan, Jordan, Kuwait, Lebanon, Libya, Lithuania, Luxembourg, Malaysia, Malta, Martinique, Mauritania, Mexico, Moldova, Mongolia, Morocco, Namibia, Netherlands, New Caledonia, New Zealand, Niger, Norway, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Puerto Rico, Qatar, Reunion, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Swaziland, Sweden, Switzerland, Syria, Taiwan, Thailand, Tunisia, Turkey, UAE, Ukraine, United Kingdom, Venezuela, Vietnam, Zambia
Target-Controlled Infusion: A Mature Technology

Anthony R. Absalom, MBChB, FRCA, MD,* John (Iain) B. Glen, BVMS, PhD, FRCA,† Gerrit J. C. Zwart, MD,* Thomas W. Schneider, MD, PhD,‡§ and Michel M. R. F. Struys, MD, PhD, FRCA (Hons)*‖
The World is Using TCI

- Over 500 peer-reviewed articles in Medline on TCI
  - Not a single report of adverse event
    - Please tell me if you know of any AE’s with TCI
- Most are now using second generation systems
  - Incorporate patient covariates
  - Target the effect site
- Conservative estimate of routine clinical use:
  - 20 million cases
Target-controlled infusion (TCI) technology has been available in most countries worldwide for clinical use in anesthesia for approximately 2 decades. This infusion mode uses pharmacokinetic models to calculate infusion rates necessary to reach and maintain the desired drug concentration. TCI is computationally more complex than traditional modes of drug administration. The primary difference between TCI and conventional infusions is that TCI decreases the infusion rate at regular intervals to account for the uptake of drug into saturable compartments. Although the calculated infusion rates are consistent with manually controlled infusion rates, there are concerns that TCI administration of IV anesthetics could introduce unique safety concerns. After approximately 2 decades of clinical use, it is appropriate to assess the safety of TCI. Our aim in this article was to describe safety-relevant issues related to TCI, which should have emerged after its use in millions of patients. We collected information from published medical literature, TCI manufacturers, and publicly available governmental Web sites to find evidence of safety issues with the clinical use of TCI. Although many case reports emphasize that IV anesthesia is technically more demanding than inhaled anesthesia, including human errors associated with setting up IV infusions, no data suggest that a TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. This is analogous to the risk of selecting the wrong drug with current infusion pumps. We found no evidence that TCI is not at least as safe as anesthetic administration using constant rate infusions. (Anesth Analg 2016;XXX:00–00)
Safety of Target Controlled Infusions

Schnider TW, Minto CF, Struys MMRF, Absalom AR

We collected information from
Safety of Target Controlled Infusions

Schnider TW, Minto CF, Struys MMRF, Absalom AR

We collected information from

- published medical literature,
Safety of Target Controlled Infusions

Schnider TW, Minto CF, Struys MMRF, Absalom AR

We collected information from

- published medical literature,
- TCI manufacturers,
Safety of Target Controlled Infusions

Schnider TW, Minto CF, Struys MMRF, Absalom AR

We collected information from

- published medical literature,
- TCI manufacturers,
- publicly available governmental web sites
Safety of Target Controlled Infusions

Schnider TW, Minto CF, Struys MMRF, Absalom AR

We collected information from

- published medical literature,
- TCI manufacturers,
- publicly available governmental web sites

to find evidence of safety issues with the clinical use of TCI.
Safety of TCI

• Number of adverse events related to pharmacokinetic control in TCI:
Safety of TCI

- Number of adverse events related to pharmacokinetic control in TCI: 0
Safety of TCI

- “Not a single report has identified an adverse incident that was related to the TCI algorithm for a PK-based infusion.”
- Conservative estimate: 20 million cases
- Rule of 3, upper 95% confidence estimate of risk is 1 in 7 million
Safety of TCI

- At St. Gallen Hospital, where dual channel TCI has been used in nearly every case for 15 years, there have been several swaps of propofol / remifentanil syringes.
- Same thing happens with conventional pumps.
Safety of TCI

- Third generation devices present an opportunity to make pumps more "idiot-proof" by smart human engineering.
Regulatory Implications

• TCI devices give
  • approved drugs
  • by approved routes
  • for approved indications
  • at doses that conform to the package insert

• There should be minimal regulatory burden for TCI devices since the drug, route, indication, and doses are approved.
Next Steps for Closed Loop Anesthesia Controllers

- TCI is on the critical path for closed loop administration of anesthesia
  - Identify approval path for TCI
  - Collaboration of clinicians, engineers, industry, and FDA.
No need for clinical trials of TCI

- Propofol (Schnider) and remifentanil (Minto) models are “good enough.”
- Overwhelming evidence of safety from 20 years of routine clinical use, and > 20 million uses
  - Zero AEs related to TCI mode of drug delivery.
  - What hypothesis would be tested?
- Multiple FDA approved studies done with TCI for drug approval.
Next Steps for Closed Loop Anesthesia Controllers

• Focus on patient safety.
  • You computational brains to catch stupid human errors.

PCLC devices don’t need to be smarter than us.
The benefit comes from not being stupid.