



Perspective

PK/PD Foundations of Intravenous Anesthesia with Target-Controlled Infusion: From Hill's Concentration–Effect Theory to the AI-Based Perspectives

Alfredo Del Gaudio ¹, Ornella Piazza ² and Marco Cascella ^{2,*}

¹ Anesthesia and Resuscitation II, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, 71013 Foggia, Italy; freddydelgaudio@libero.it

² Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, 84081 Baronissi, Italy; opiazza@unisa.it

* Correspondence: mcascella@unisa.it

Abstract

Background: Pharmacokinetic/pharmacodynamic (PK/PD)-guided intravenous anesthesia and target-controlled infusion (TCI) have progressively transformed modern anesthetic practice from empirical drug administration toward individualized, model-informed precision anesthesia. Recent advances in neuromonitoring, closed-loop systems, and artificial intelligence (AI) are further expanding this paradigm. **Methods:** This Perspective article provides a conceptual and educational synthesis of the historical foundations, mathematical principles, clinical applications, and AI-based perspectives of PK/PD-guided intravenous anesthesia and TCI. **Results:** The concentration–effect relationship derived from Hill's equation represents the conceptual basis of modern anesthetic pharmacology. Contemporary TCI systems integrate PK/PD models, effect-site targeting, synergistic drug interactions, and multimodal monitoring to improve anesthetic precision and safety. Recent evidence supports the advantages of total intravenous anesthesia (TIVA) in postoperative recovery outcomes, including reduced postoperative nausea and vomiting, emergence delirium, and improved quality of recovery. Emerging developments include increasingly generalizable PK “supermodels,” adaptive closed-loop control systems, multimodal AI integration, and patient-specific digital twins that may eventually support simulation of physiological responses and optimization of drug administration. However, biological variability, monitoring limitations, signal artifacts, model uncertainty, and the need for prospective validation, regulatory oversight, and continuous clinician supervision remain major challenges to the routine implementation of AI-assisted individualized anesthesia. **Conclusions:** PK/PD-guided anesthesia and TCI increasingly represent a clinically relevant framework for precision anesthesia, integrating pharmacology, monitoring, adaptive control, and AI-assisted systems. Future developments may progressively reduce the discrepancy between predicted and observed clinical effects, moving anesthetic practice toward continuously adaptive, feedback-driven, and individualized anesthesia care.

Keywords: target-controlled infusion; total intravenous anesthesia; PK/PD modeling; precision anesthesia; closed-loop anesthesia; artificial intelligence; neuromonitoring



Academic Editor: Nikolaus L. Gravenstein

Received: 22 May 2026

Revised: 7 July 2026

Accepted: 16 July 2026

Published: 1 August 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](#)

[Attribution \(CC BY\)](#) license.

1. The Concentration–Effect Relationship: Historical and Conceptual Foundations

1.1. Historical Background

In the 1920s, Archibald Vivian Hill (1886–1977) laid the foundations of modern pharmacology and, probably, what we now identify as precision anesthesia. The British physiologist described the hemoglobin dissociation curve as a sigmoidal relationship between arterial oxygen concentration (CaO_2), plotted on the x-axis, and hemoglobin oxygen saturation, plotted on the y-axis. The curve is read from left to right and shows hemoglobin desaturation as O_2 concentration decreases. This compensatory mechanism helps maintain oxygen delivery to tissues when O_2 is limited. In this process, an increase in CaO_2 raises the concentration of oxygenated hemoglobin (HbO_2). At the point he identifies as 95% of the effect, hemoglobin is already saturated, and a further increase in concentration does not change saturation, which is already maximal. Beyond that value, no further increase in hemoglobin saturation occurs, and, therefore, no further increase in the curve, which becomes a straight line. In other words, a further increase in concentration yields no further effect [1]. Notably, Hill's insight led to substituting the parameters on the axes: concentration on the x-axis and effect on the y-axis. In this view, he described the concentration–effect curve, the cornerstone of modern pharmacology [2].

1.2. Clinical Interpretation of the Hill Concentration–Effect Relationship

This concept applies to anesthesia. Increasing hypnotic drug concentration over time is reasonable only until loss of consciousness is achieved. Once this occurs (the 95% effect point), there is no reason to increase drug concentration further. In this scenario, side effects such as hemodynamic instability, respiratory failure, and increased mortality can occur on the flat part of the curve [3].

The ascending portion of the curve may be considered the induction of anesthesia, where 50% of the concentration corresponds to 50% of the effect, while 95% of the concentration corresponds to 95% of the possible hypnotic effect. Once the point Egan et al. [4] described as the crest of the wave is reached, the goal is to help maintain a stable pharmacodynamic (PD) effect. This “surfing the wave” avoids increases or decreases in concentration. At this point, infusion mode becomes central for anesthetic maintenance. Delivering inhaled or intravenous (IV) anesthetics produces accumulation over time, increasing the dose and the effects. For example, for IV anesthesia, an infusion of $100 \mu\text{g}/\text{kg}/\text{min}$ translates into an effect-site concentration of $0.5 \mu\text{g}/\text{mL}$ after 1.5 min, $1 \mu\text{g}/\text{mL}$ after 2.5 min, $2 \mu\text{g}/\text{mL}$ after 10 min, and $3 \mu\text{g}/\text{mL}$ after 77 min. Thus, the infusion–concentration relationship changes continuously, affecting the curve [4] (Figure 1).

Target-controlled infusion (TCI), the standard PK/PD-guided drug delivery approach for total IV anesthesia (TIVA), integrates patient covariates, compartmental volumes, and pharmacokinetic (PK) rate constants to predict effect-site drug concentrations and dynamically adjust infusion rates over time. Modern TCI systems may operate using either plasma-targeting or effect-site-targeting algorithms. While plasma targeting predicts central compartment concentrations, effect-site targeting incorporates equilibration kinetics to minimize delays between predicted concentration and clinical effect, particularly during induction. For years, the accuracy of prediction and the limitations of a measured/predicted ratio were debated. Quantitative EEG-derived indices, such as Bispectral Index (BIS), Spectral Edge Frequency (SEF), and Index of Consciousness (iCON), combined with qualitative interpretation of Density Spectral Array (DSA), may facilitate safer and more precise titration of hypnotic agents through continuous assessment of both processed parameters and raw cortical oscillatory dynamics [5]. Beyond hypnosis monitoring, future integrated systems may incorporate nociception and antinociception indices, enabling simultaneous

titration of unconsciousness, analgesia, and autonomic stability. Consequently, the stability of infusion can help prevent overdose and ensure rapid patient awakening. This phase corresponds to the anesthesia maintenance. Evaluating the curve from right to left shows that the emergence phase corresponds to the descending portion of the curve [6].

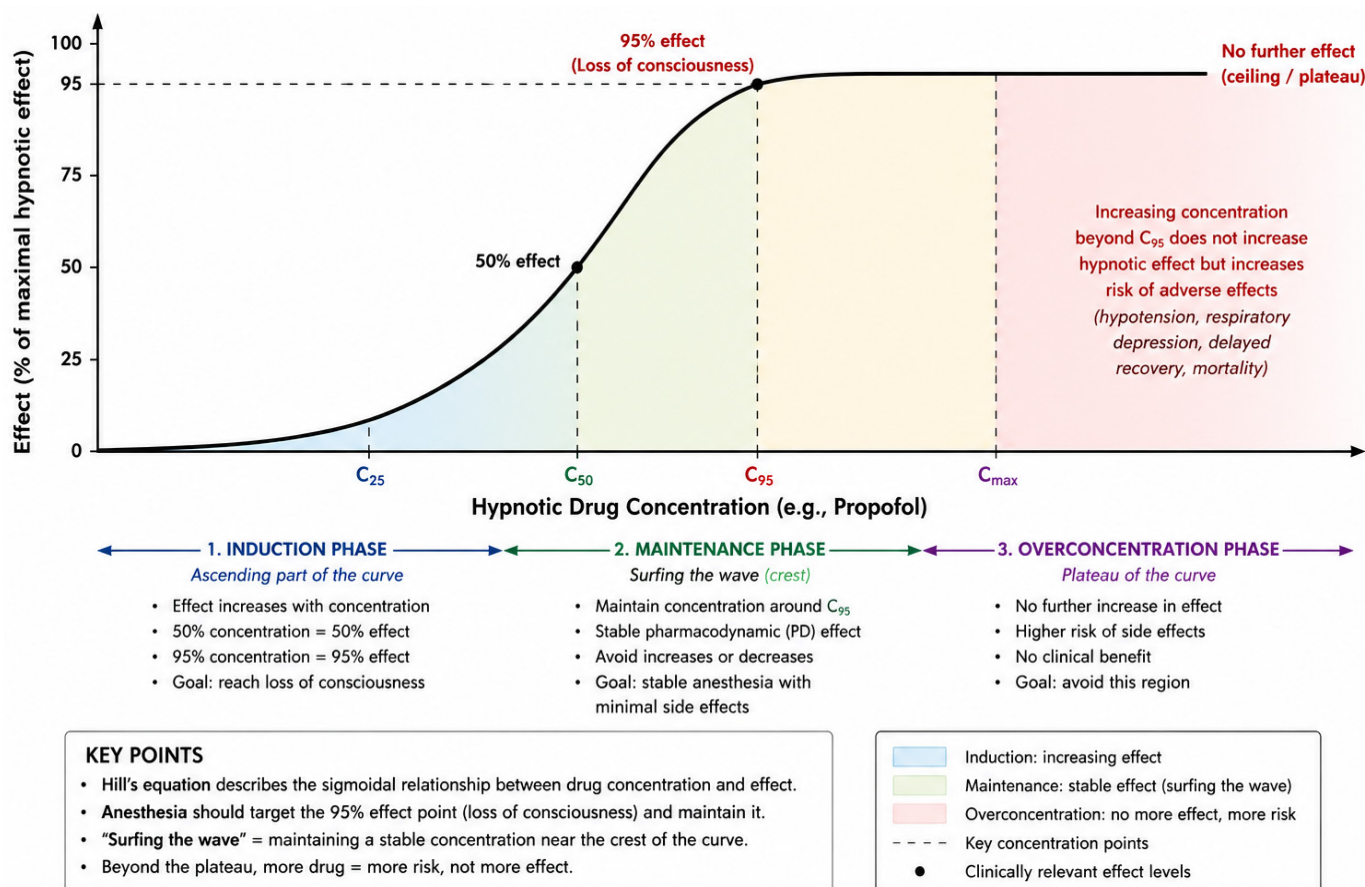


Figure 1. Clinical interpretation of Hill's concentration–effect curve during intravenous anesthesia. The sigmoidal concentration–effect relationship illustrates the evolution of anesthetic drug action from induction to maintenance and emergence. During induction, increasing effect-site concentration progressively enhances the hypnotic effect until approximately 95% of the maximal response is achieved, corresponding to loss of consciousness. The crest of the curve represents the optimal maintenance phase ("surfing the wave"), in which a stable pharmacodynamic effect is maintained while minimizing drug administration. Further increases in concentration beyond the plateau produce little or no additional hypnotic effect but substantially increase the risk of adverse events, including hemodynamic instability, respiratory depression, delayed recovery, and drug accumulation. The descending portion of the curve conceptually represents emergence from anesthesia as effect-site concentration decreases.

1.3. Mathematical Interpretation of the Hill Equation

Other analogies with Hill's curve can be emphasized. For example, the steepness of the curve must also be analyzed. Hill placed great importance on this aspect, introducing the γ coefficient, a key parameter in the mathematical formulation of the curve that expresses steepness. This coefficient describes the steepness of the concentration–effect relationship. A higher γ indicates that relatively small concentration changes around C_{50} produce larger changes in PD effect, resulting in a narrower transition between insufficient and excessive drug effect. This property should not be interpreted as the speed of drug onset. Rather, onset kinetics are determined by PK processes and effect-site equilibration, particularly the ke_0 rate constant and the time to peak effect (TTPE), which is drug-specific [7]. This

delay between plasma and effect-site equilibration is mathematically described by the ke_0 rate constant, which governs hysteresis between plasma concentration and clinical effect. In TCI systems, ke_0 is essential for estimating effect-site concentration and synchronizing drug delivery with the expected PD response. Additionally, evaluating the curve from right to left also means considering emergence from hypnosis or sedation, the descending phase. Moreover, the time variable is important as the decrement in time, the interval between stopping drug administration and eye opening, is the key parameter.

For the clinical reader, the Hill equation should be interpreted as a simple mathematical description of the relationship between drug concentration and pharmacological effect. Rather than emphasizing mathematical formalism, its relevance in anesthesia is primarily conceptual, providing a framework for understanding induction, maintenance, and emergence. The model assumes that drug effect increases progressively with effect-site concentration until a maximal response (E_{max}) is approached, beyond which further increases in concentration produce little additional clinical benefit while potentially increasing the risk of adverse effects. Clinically, this relationship explains why anesthetic management aims to achieve an appropriate effect-site concentration rather than simply administering higher drug doses. Thus, the Hill equation provides the pharmacological rationale underlying PK/PD-guided anesthesia and TCI. The basic equation is [2]:

$$E = E_0 + \frac{(E_{max} - E_0)C^\gamma}{C_{50}^\gamma + C^\gamma}$$

Clinically, E may represent the probability or magnitude of a PD endpoint, such as hypnosis or loss of consciousness, whereas C corresponds to the predicted effect-site drug concentration. The parameter C_{50} identifies the concentration associated with half of the maximal effect and is therefore a useful descriptor of drug potency. The Hill coefficient (γ) reflects how abruptly the transition from low to high drug effect occurs: higher values indicate a steeper concentration–effect relationship and a narrower transition zone between insufficient and excessive drug effect.

E_0 represents the baseline PD effect in the absence of drug exposure, whereas E_{max} represents the maximal achievable drug effect. Therefore, the difference ($E_{max} - E_0$) corresponds to the maximal drug-induced change from baseline rather than a temporal parameter. In anesthesia, the delay between plasma concentration and clinical response is instead explained by effect-site equilibration kinetics, particularly the ke_0 rate constant, which governs hysteresis between plasma concentration and PD effect.

This equation can also be expressed as [3]:

$$E = E_0 + \frac{(E_{max} - E_0)U^\gamma}{1 + U^\gamma}$$

In this formulation, U is the concentration normalized to potency. When $U = 1$, the drug concentration corresponds to C_{50} :

$$U = \frac{C}{C_{50}}$$

Expressing concentration as a multiple of C_{50} simplifies the comparison of drugs with different intrinsic potencies and facilitates the description of PD interactions (synergisms) [8]. For example, when hypnotics and opioids are administered together, the normalized concentration helps visualize synergistic effects independently of the absolute dose of each drug.

Against this background, this Perspective provides a conceptual and educational overview of the evolution of PK/PD-guided IV and TCI, tracing their development from

the concentration–effect principles established by Hill to contemporary model-informed anesthesia and emerging technologies. Rather than providing an exhaustive review, its aim is to offer an integrated framework linking pharmacological theory, current clinical TCI practice, neuromonitoring, and future adaptive anesthesia systems.

2. From Classical PK Models to General-Purpose Predictive Systems

2.1. PK/PD Evolution and Drug Synergism

Recent large-scale evidence has strengthened the clinical rationale for precision IV anesthesia. A 2024 meta-analysis, including 317 randomized trials and 51,107 patients, showed no consistent mortality benefit associated with TIVA, although clear advantages were observed in postoperative recovery profiles. Specifically, TIVA was associated with a lower incidence of postoperative nausea and vomiting (RR 0.61), reduced emergence delirium (RR 0.40), and a significantly higher quality of recovery (QoR-40 +6.45). Furthermore, some evidence also suggests a potential reduction in postoperative cognitive dysfunction (POCD), particularly in elderly surgical populations, although the certainty of evidence remains limited. These findings can support the shift toward individualized PK/PD-guided IV techniques [9]. Nevertheless, anesthesia has always relied on drug combinations. In the 1990s, Minto et al. [10] introduced the concept of the interaction of drug pairs, which does not result merely from combining two substances but from generating a third entity: synergism is more than a sum. This is demonstrated in the surface response diagrams illustrated in Minto's work: the concentration–effect curves of drugs A (hypnotic) and B (opioid) are shown, and additional curves are created for various dose combinations (A-dominant, 50/50, B-dominant). With each combination, a new “drug pair entity” emerges, with unique PK/PD characteristics as the effect-site concentrations shift.

A cross-section at 50% concentration and effect, projected on the axes, expresses the relationship between the two drugs: a hyperbola indicates synergism, a parabola indicates antagonism, and a straight line indicates additivity. Synergy can involve two or more drugs, continually generating new PD curves. In particular, synergistic potency (U) reduces the C50 of the new entity, thus increasing potency, as shown by a leftward curve shift. Ultimately, using multiple drugs yields a greater effect with lower doses and fewer side effects. These developments further expand the concept of model-informed precision anesthesia beyond traditional hypnotic-opioid combinations.

2.2. Emerging PK/PD Models

Beyond propofol and remifentanyl, dexmedetomidine has entered the landscape of model-based administration. The Hannivoort–Colin model integrates allometric scaling and provides a PK/PD characterization, including the drug's biphasic hemodynamic profile: hypotensive effects at effect-site concentrations < 2 ng/mL and hypertensive responses above this threshold. Unlike propofol, dexmedetomidine produces distinct EEG signatures (delta oscillations combined with sleep spindles), making quantitative BIS an unreliable endpoint because BIS values may remain paradoxically elevated despite clinically adequate sedation due to preserved spindle-rich EEG activity. Nevertheless, DSA can identify spindles, witnessing the kind of sedation and the level (spindles disappear with a dosage greater than 1.5–2 ng/mL). For this reason, the model predicts the probability of achieving a target MOAA/S score, offering a potentially more robust approach to sedation titration [11]. In this scenario, remimazolam represents a new generation of ultra-short-acting benzodiazepines with rapid onset (1–2 min), predictable offset (10–20 min), and context-insensitive recovery due to metabolism by nonspecific tissue esterases. Early evidence suggests favorable hemodynamic stability compared to propofol and good compatibility with neuromonitoring. Its reversibility with flumazenil and suitability for awake

neurosurgical procedures position it as a promising candidate for future PK/PD modeling and potentially TCI administration [12]. At present, in Europe, remimazolam is approved only for bolus administration in non-operating room anesthesia (NORA) procedures. However, in China and Japan, the drug is already being used in continuous infusion mode, supported by the clinically available Mazui TCI model. Despite these encouraging developments, several pharmacometric challenges still limit the widespread implementation of remimazolam TCI outside East Asia. Although several population PK/PD models have recently been developed, further external validation across ethnically diverse populations, broader BMI ranges, elderly and high-risk patients, and different clinical settings remains necessary [13]. Additional refinement of allometric scaling, characterization of PD endpoints, and prospective evaluation of model performance will likely be required before widespread regulatory approval of remimazolam TCI in Western countries [14]. Other models have been developed for rocuronium and norepinephrine [15], before and during general anesthesia [16].

2.3. Clinical Implications of Model-Informed Anesthesia

In summary, the concentration–effect relationship provides a unifying conceptual framework for understanding the pharmacological principles underlying IV anesthesia, helping clinicians interpret the rationale behind contemporary PK/PD-guided anesthetic practice. Within this framework, one of the principal objectives is to achieve and maintain an appropriate drug effect through controlled drug administration rather than relying solely on fixed infusion rates expressed in mL/h, $\mu\text{g/kg/min}$, or percentages of minute volume. Effect-site targeting offers a model-informed strategy for approximating stable predicted effect-site concentrations, while continuous clinical and instrumental monitoring remains essential to account for biological variability and dynamic physiological changes. Together, TCI, PD synergism, and multimodal monitoring provide complementary components of a model-informed approach that supports individualized anesthetic management throughout induction, maintenance, and emergence. Thus, concentration–effect relationships are not merely theoretical or mathematical concepts but represent the scientific foundation upon which contemporary PK/PD-guided anesthesia and TCI systems are built, with the potential to improve patient safety, treatment individualization, and perioperative outcomes (Table 1).

Table 1. Clinical Relevance of PK/PD-Guided Anesthesia and TCI.

PK/PD Concept	Clinical Relevance
Support stable effect-site concentration	May reduce the risk of overdose and hemodynamic instability
TCI-guided infusion	May improve the precision and reproducibility of anesthesia delivery
Drug synergism	Allows lower doses with fewer adverse effects
EEG-guided monitoring	Supports safer titration and emergence
Population PK/PD models	Facilitates individualized dosing in vulnerable patients
Closed-loop systems	May improve target maintenance and recovery profiles
AI-assisted prediction	May reduce the discrepancy between predicted and observed effects
Automated closed-loop control	May reduce clinician workload, supporting continuous adaptive titration

The conceptual and clinical framework of PK/PD-guided anesthesia, from drug administration to feedback-driven effect-site targeting and future AI-assisted closed-loop systems, is summarized in Figure 2.

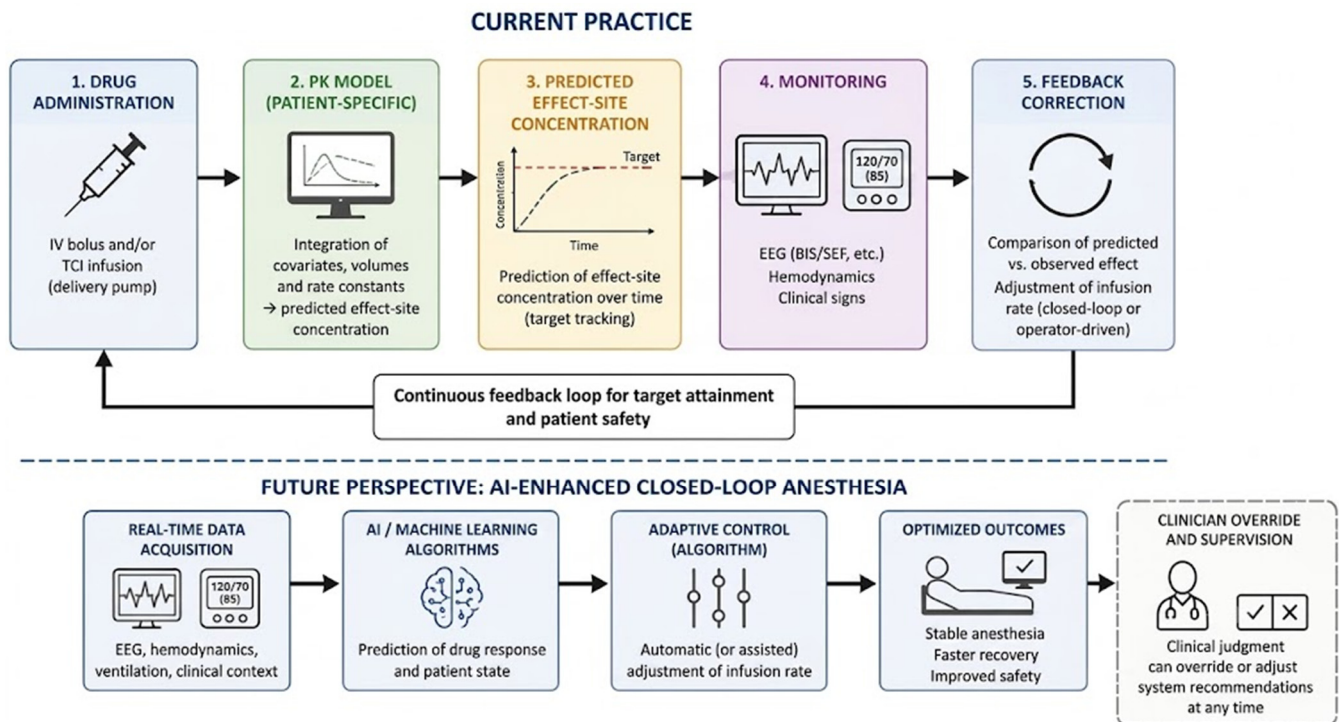


Figure 2. Conceptual workflow of PK/PD-guided anesthesia and future AI-assisted closed-loop systems. The figure illustrates the interaction between drug administration, population PK modeling, effect-site targeting, multimodal monitoring, and feedback correction. In real-world practice, this process is influenced by biological variability, signal noise, delayed physiological feedback, monitoring artifacts, sensor inaccuracies, inter-device variability, and the need for continuous clinician supervision and override. Accordingly, the workflow should be interpreted as a conceptual representation rather than a deterministic control architecture. Future AI-assisted systems may progressively reduce the discrepancy between predicted and observed clinical effects through adaptive closed-loop control, although clinical implementation will require prospective validation, robust artifact management, regulatory oversight, and continuous human supervision. Abbreviations: AI, artificial intelligence; BIS, Bispectral Index; EEG, electroencephalography; PK, pharmacokinetic; SEF, Spectral Edge Frequency; TCI, target-controlled infusion; IV, intravenous.

3. Future Perspectives: Closed-Loop Systems, AI, and Digital Twins

3.1. Closed-Loop Systems

Neurological monitoring and its reliability, both quantitative and qualitative, have partly reduced the need for precise prediction of effect-site concentration to approach a measured-to-predicted ratio increasingly close to unity. Nevertheless, achieving that result has always been of great interest [5,6]. Population PK modeling has progressively improved prediction accuracy by increasing sample size and the number of covariates contributing to individualized procedures. Biological variability remains the fundamental limiting factor of PD prediction [17]. This variability explains why neuromonitoring, such as quantitative and qualitative EEG, remains indispensable despite advances in PK/PD modeling. Rather than replacing monitoring, models and predictions frame a dynamic process in which continuous feedback is required to guide effect-site targeting, especially during induction and emergence.

These aspects underscore the challenging task of identifying the relationships between patient covariates (e.g., age, weight, and sex) and the volumes and clearances of multi-compartmental PK models applicable across broad populations from neonates to the elderly, from the underweight to the obese. These models address the issues of allometric scaling of body weight and size, body composition, sex differences, changes with advanced age,

and, for young children, changes with maturation and growth. General-purpose models for propofol, remifentanyl, and dexmedetomidine have been developed, and they greatly reduce the risk of biased model selection [17–19].

Based on these elements, the development of these “supermodels” moves clearly in this direction: unlike first-generation models built from a few dozen subjects with few covariates, the new models incorporate much larger datasets (e.g., 1033 subjects in the Eleveld propofol model). This improvement is made possible by including a large number of clinical studies, going beyond healthy volunteer data, and expanding covariates. This approach, together with the ability to incorporate allometric scaling, addresses two of the major limitations traditionally associated with TIVA/TCI administration: variability in the predicted-to-measured relationship and the need for multiple models tailored to different patient populations. Traditionally, model performance has been evaluated using metrics such as median performance error (MDPE), median absolute performance error (MDAPE), and wobble, which quantify bias, inaccuracy, and intraindividual variability of PK predictions. The ultimate goal is to achieve a universally applicable PK model for providing accurate effect-site predictions across heterogeneous patient populations, approaching a predicted-to-measured relationship of 1 [19].

Despite their clinical usefulness, PK/PD models remain approximations derived from population data and are affected by interindividual variability. Their performance may be reduced in patients with rapidly changing physiology, including shock, sepsis, major fluid shifts, obesity, hepatic or renal dysfunction, hypoalbuminemia, and extracorporeal membrane oxygenation (ECMO). In these settings, changes in volume of distribution, clearance, plasma protein binding, and tissue perfusion may alter the relationship between predicted and observed effect-site concentrations [20]. Pediatric and geriatric populations remain particularly challenging because developmental physiology, maturation, frailty, sarcopenia, multimorbidity, and polypharmacy may substantially influence PK/PD responses [19,21]. Accordingly, TCI should be regarded as a model-informed dosing strategy that complements, rather than replaces, continuous clinical assessment and physiological monitoring.

3.2. AI-Assisted Prediction

Artificial intelligence (AI) may further improve model performance by progressively reducing the discrepancy between predicted and observed clinical responses through the integration of PK/PD modeling and real-time monitoring. However, AI alone cannot eliminate biological variability or guarantee accurate prediction in every clinical scenario. Rather, AI-assisted systems should currently be regarded as decision-support tools that require continuous clinical supervision, prospective validation, and robust monitoring before broader implementation [22]. Moreover, AI-assisted anesthesia systems remain developmental and require prospective validation before routine clinical implementation. Major unresolved challenges include algorithmic bias, heterogeneity of training datasets, limited external validation, monitoring artifacts, lack of model explainability, cybersecurity vulnerabilities, regulatory approval, medico-legal accountability, and safe human–machine interaction [23].

On these bases, closed-loop anesthesia delivery systems represent one of the most promising developments toward AI-assisted precision anesthesia. A systematic review of 32 randomized trials demonstrated that closed-loop control of IV drugs improves time within target ranges for both sedation and hemodynamic variables and shortens recovery times compared with manual administration. These systems integrate real-time EEG-derived indices, nociception monitoring, hemodynamic variables, and ventilatory parameters within adaptive control architectures [24].

Control strategies currently include proportional–integral–derivative (PID) controllers, model predictive control systems, and machine learning–based adaptive algorithms capable of dynamically responding to interindividual physiological variability in real time [24]. In this framework, these approaches represent the early evolution of multi-input/multi-output (MIMO) platforms simultaneously modulating hypnotics, opioids, vasopressors, and fluid administration [25].

A further prerequisite for reliable closed-loop control is robust artifact detection and signal-quality assessment. Intraoperative EEG and physiological signals are frequently affected by electrocautery interference, patient movement, poor electrode contact, hemodynamic artifacts, and device-specific noise [5,6,26]. Without effective artifact rejection and signal validation, AI-assisted systems may misinterpret corrupted data and generate inappropriate drug-adjustment recommendations [25]. Consequently, signal quality control should be considered an integral component of future AI-assisted anesthesia platforms rather than a secondary technical feature [25].

While human supervision will remain essential, closed-loop control brings anesthetic drug delivery closer to the conceptual asymptote of unity, where predicted and measured effects converge. This is crucial, particularly for interpreting complex physiological responses and unexpected clinical scenarios. Future intelligent anesthesia platforms may also incorporate continuous runtime verification systems capable of detecting deviations between predicted and observed physiological responses in real time. Nonetheless, these technologies remain largely investigational and require prospective clinical validation. In this perspective, the “asymptote of one” could represent the progressive reduction in the discrepancy between predicted and observed clinical effects, achieved through the integration of PK/PD modeling, real-time monitoring, and AI-assisted adaptive control systems. Notably, rather than replacing anesthesiologists, these systems are expected to augment clinical decision-making, allowing physicians to focus on higher-level interpretation, safety oversight, and individualized patient management [27].

3.3. Digital Twins

Future developments may include patient-specific virtual replicas (digital twins) capable of continuously simulating anesthetic responses and dynamically optimizing drug administration based on real-time physiological feedback. These virtual patient replicas could integrate PK/PD modeling, EEG-derived signals, hemodynamic variables, respiratory parameters, laboratory data, and perioperative clinical information to ultimately support predictive and adaptive anesthesia management tailored to the individual patient. For example, digital twins may help anticipate physiological instability, improve effect-site targeting, reduce interindividual variability, and further narrow the gap between predicted and observed clinical responses [28].

Beyond these applications, the long-term evolution of digital twins will likely extend from intraoperative prediction toward continuously perioperative and updated clinical decision-support systems. Thus, by integrating longitudinal data streams, including preoperative assessment, intraoperative monitoring, electronic health records, and postoperative outcomes, future digital twins may dynamically revise patient-specific predictions and assist clinicians throughout the entire perioperative pathway rather than at isolated time points [29].

3.4. Toward ICU Implementation

All these aspects call for deeper scientific understanding, not only because TCI is progressively extending beyond the operating room into the intensive care unit (ICU), but also because its clinical implications are becoming increasingly relevant. TCI-guided

administration of propofol, remifentanyl, dexmedetomidine, and sufentanil could provide more stable and predictable sedation compared with manual titration. In ICU patients, first-generation or general-purpose PK/PD models may be less reliable because critically ill physiology differs substantially from stable intraoperative conditions. Severe fluid shifts, capillary leak syndrome, hypoalbuminemia, organ dysfunction, altered hepatic and renal clearance, vasopressor use, extracorporeal support, and rapidly changing tissue perfusion can significantly modify the volume of distribution and drug clearance [19,20,30]. Moreover, sedation targets in the ICU fluctuate over time according to ventilation, delirium, hemodynamic instability, procedures, and neurological status [31]. These factors explain why ICU implementation of TCI requires dedicated validation, robust PD endpoints, and continuous clinical reassessment [20]. On the other hand, the heterogeneity of PK datasets, the limited availability of robust PD endpoints, and the scarce validation of these models in critically ill populations underscore the need for further investigation before widespread adoption. Even so, the potential integration of TCI with closed-loop systems offers a remarkable opportunity for advancing individualized, feedback-guided sedation in critical care [20]. Future educational efforts should integrate PK/PD simulation tools, visual learning platforms, gamification strategies, EEG-guided tutorials, and interactive TCI simulators to facilitate the understanding of concentration–effect dynamics among trainees and clinicians [32].

Moreover, environmental considerations powerfully reinforce the shift toward IV techniques. Volatile anesthetics possess a dramatically high Global Warming Potential (GWP100), far exceeding that of CO₂. Reflecting this concern, the December 2024 amendment from the ESAIC Glasgow Declaration on Sustainability in Anaesthesiology and Intensive Care explicitly recommends reducing or eliminating nitrous oxide and desflurane and prioritizing agents with the lowest environmental footprint, namely, IV and regional anesthesia [33].

This Perspective has several limitations. First, it is not a systematic or narrative review and does not aim to provide an exhaustive synthesis of the literature. Second, several future applications discussed, including AI-assisted closed-loop systems and digital twins, remain largely developmental and require prospective clinical validation. Third, PK/PD models are population-derived tools and may be less accurate in patients with extreme or rapidly changing physiology. Finally, regulatory, ethical, cybersecurity, medico-legal, and implementation barriers currently limit the translation of fully adaptive systems into routine clinical practice.

4. Conclusions

PK/PD-guided TIVA and TCI represent clinically relevant tools for model-informed IV anesthesia. Current evidence supports their role in improving titration, reproducibility, and selected recovery outcomes, particularly when combined with appropriate neuromonitoring and clinical judgment. Emerging closed-loop systems and AI-assisted platforms may further improve feedback-supported drug delivery, but they remain dependent on robust validation, artifact management, regulatory approval, and continuous clinician supervision. Digital twins and fully adaptive anesthesia systems should currently be regarded as promising future perspectives rather than established clinical tools.

Author Contributions: Conceptualization, A.D.G.; methodology, M.C.; software, M.C.; validation, O.P.; data curation, M.C.; writing—original draft preparation, A.D.G.; writing—review and editing, A.D.G. and M.C.; visualization, M.C.; supervision, O.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: M.C. is an editorial board member of Anesthesia Research. The other authors declare no conflicts of interest. The manuscript was handled independently by the journal editorial office, and the involved author did not participate in the editorial decision-making process.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
PK/PD	Pharmacokinetic/Pharmacodynamic
TCI	Target-Controlled Infusion
AI	Artificial Intelligence
CaO ₂	Arterial Oxygen Concentration
O ₂	Oxygen
HbO ₂	Oxygenated Hemoglobin
IV	Intravenous
EEG	Electroencephalography
BIS	Bispectral Index
SEF	Spectral Edge Frequency
iCON	Index of Consciousness
DSA	Density Spectral Array
PD	Pharmacodynamic
TTPE	Time to Peak Effect
E _{max}	Maximum Effect
C ₅₀	Concentration Producing 50% Effect
TIVA	Total Intravenous Anesthesia
RR	Relative Risk
QoR-40	Quality of Recovery-40
POCD	Postoperative Cognitive Dysfunction
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NORA	Non-Operating Room Anesthesia
MDPE	Median Performance Error
MDAPE	Median Absolute Performance Error
PID	Proportional–Integral–Derivative
MIMO	Multiple Input/Multiple Output
ICU	Intensive Care Unit
GWP100	Global Warming Potential 100-Year
ESAIC	European Society of Anaesthesiology and Intensive Care

References

1. Somvanshi, P.R.; Venkatesh, K.V. Hill Equation. In *Encyclopedia of Systems Biology*; Dubitzky, W., Wolkenhauer, O., Cho, K.H., Yokota, H., Eds.; Springer: New York, NY, USA, 2013. [\[CrossRef\]](#)
2. Prinz, H. Hill coefficients, dose—Response curves and allosteric mechanisms. *J. Chem. Biol.* **2010**, *3*, 37–44. [\[PubMed\]](#)
3. Goutelle, S.; Maurin, M.; Rougier, F.; Barbaut, X.; Bourguignon, L.; Ducher, M.; Maire, P. The Hill equation: A review of its capabilities in pharmacological modelling. *Fundam. Clin. Pharmacol.* **2008**, *22*, 633–648. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Egan, T.D.; Shafer, S.L. Target-controlled infusions for intravenous anesthetics: Surfing USA not! *Anesthesiology* **2003**, *99*, 1039–1041. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Laferrière-Langlois, P.; Morisson, L.; Jeffries, S.; Duclos, C.; Espitalier, F.; Richebé, P. Depth of Anesthesia and Nociception Monitoring: Current State and Vision for 2050. *Anesth. Analg.* **2024**, *138*, 295–307. [\[CrossRef\]](#) [\[PubMed\]](#)

6. Purdon, P.L.; Sampson, A.; Pavone, K.J.; Brown, E.N. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. *Anesthesiology* **2015**, *123*, 937–960. [[CrossRef](#)] [[PubMed](#)]
7. Proekt, A.; Kelz, M.B. Explaining anaesthetic hysteresis with effect-site equilibration. *Br. J. Anaesth.* **2021**, *126*, 265–278. [[CrossRef](#)] [[PubMed](#)]
8. Greco, W.R.; Bravo, G.; Parsons, J.C. The search for synergy: A critical review from a response surface perspective. *Pharmacol. Rev.* **1995**, *47*, 331–385. [[CrossRef](#)] [[PubMed](#)]
9. Kampman, J.M.; Hermanides, J.; Hollmann, M.W.; Gilhuis, C.N.; Bloem, W.A.; Schraag, S.; Pradelli, L.; Repping, S.; Sperna Weiland, N.H. Mortality and morbidity after total intravenous anaesthesia versus inhalational anaesthesia: A systematic review and meta-analysis. *eClinicalMedicine* **2024**, *72*, 102636. [[CrossRef](#)] [[PubMed](#)]
10. Minto, C.F.; Schnider, T.W.; Egan, T.D.; Youngs, E.; Lemmens, H.J.; Gambus, P.L.; Billard, V.; Hoke, J.F.; Moore, K.H.; Hermann, D.J.; et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology* **1997**, *86*, 10–23. [[CrossRef](#)] [[PubMed](#)]
11. Colin, P.J.; Hannivoort, L.N.; Eleveld, D.J.; Reijntjens, K.M.E.M.; Absalom, A.R.; Vereecke, H.E.M.; Struys, M.M.R.F. Dexmedetomidine pharmacokinetic-pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. *Br. J. Anaesth.* **2017**, *119*, 200–210. [[CrossRef](#)] [[PubMed](#)]
12. Zhang, H.; Li, H.; Zhao, S.; Bao, F. Remimazolam in General Anesthesia: A Comprehensive Review of Its Applications and Clinical Efficacy. *Drug Des. Devel Ther.* **2024**, *18*, 3487–3498. [[CrossRef](#)] [[PubMed](#)]
13. de Jong, B.T.; Eleveld, D.J.; Mason, K.P.; Struys, M.M.R.F. Clinical Pharmacokinetics and Pharmacodynamics of Remimazolam. *Clin. Pharmacokinet.* **2025**, *64*, 1263–1282. [[CrossRef](#)] [[PubMed](#)]
14. Chen, Y.; Zhang, Z.J.; Zhang, X.F.; Peng, Y.; Jiao, Z.; Wu, J.X. Model-Informed Precision Dosing of Remimazolam in General Anesthesia Patients. *Drug Des. Devel Ther.* **2025**, *19*, 5099–5109. [[CrossRef](#)] [[PubMed](#)]
15. Masui, K.; Ishigaki, S.; Tomita, A.; Otake, H. Rocuronium pharmacodynamic models for published five pharmacokinetic models: Age and sex are covariates in pharmacodynamic models. *J. Anesth.* **2018**, *32*, 709–716. [[CrossRef](#)] [[PubMed](#)]
16. Li, Y.; Koomen, J.V.; Eleveld, D.J.; van den Berg, J.P.; Vos, J.J.; de Keijzer, I.N.; Struys, M.M.R.F.; Colin, P.J. Population Pharmacokinetic Modelling of Norepinephrine in Healthy Volunteers Prior to and During General Anesthesia. *Clin. Pharmacokinet.* **2024**, *63*, 1597–1608. [[CrossRef](#)] [[PubMed](#)]
17. Eleveld, D.J.; Proost, J.H.; Cortínez, L.I.; Absalom, A.R.; Struys, M.M. A general purpose pharmacokinetic model for propofol. *Anesth. Analg.* **2014**, *118*, 1221–1237. [[CrossRef](#)] [[PubMed](#)]
18. Cortínez, L.I.; De la Fuente, N.; Eleveld, D.J.; Oliveros, A.; Crovari, F.; Sepulveda, P.; Ibacache, M.; Solari, S. Performance of propofol target-controlled infusion models in the obese: Pharmacokinetic and pharmacodynamic analysis. *Anesth. Analg.* **2014**, *119*, 302–310. [[CrossRef](#)] [[PubMed](#)]
19. Eleveld, D.J.; Koomen, J.V.; Absalom, A.R.; Su, H.; Hannivoort, L.N.; Struys, M.M.R.F. Allometric Scaling in Pharmacokinetic Studies in Anesthesiology. *Anesthesiology* **2022**, *136*, 609–617. [[CrossRef](#)] [[PubMed](#)]
20. Introna, M.; Carozzi, C.; Gentile, A.; Girasole, R.; Gemma, M.; Koomen, J.V.; Struys, M.M.R.F.; van Den Berg, J.P. Target controlled infusion in the intensive care unit: A scoping review. *J. Clin. Monit. Comput.* **2025**, *40*, 501–515. [[CrossRef](#)] [[PubMed](#)]
21. Coetzee, E.; Absalom, A.R. Pharmacodynamic Changes in the Elderly: Impact on Anesthetics. *Anesth. Clin.* **2023**, *41*, 549–565. [[CrossRef](#)] [[PubMed](#)]
22. Gambus, P.; Shafer, S.L. Artificial Intelligence for Everyone. *Anesthesiology* **2018**, *128*, 431–433. [[CrossRef](#)] [[PubMed](#)]
23. Cascella, M.; Tracey, M.C.; Petrucci, E.; Bignami, E.G. Exploring Artificial Intelligence in Anesthesia: A Primer on Ethics, and Clinical Applications. *Surgeries* **2023**, *4*, 264–274. [[CrossRef](#)]
24. Spataru, A.; Eiben, P.; Pluddemann, A. Performance of closed-loop systems for intravenous drug administration: A systematic review and meta-analysis of randomised controlled trials. *J. Clin. Monit. Comput.* **2024**, *38*, 5–18. [[CrossRef](#)] [[PubMed](#)]
25. West, N.; van Heusden, K.; Görges, M.; Brodie, S.; Rollinson, A.; Petersen, C.L.; Dumont, G.A.; Ansermino, J.M.; Merchant, R.N. Design and Evaluation of a Closed-Loop Anesthesia System With Robust Control and Safety System. *Anesth. Analg.* **2018**, *127*, 883–894. [[CrossRef](#)] [[PubMed](#)]
26. Cascella, M. Mechanisms underlying brain monitoring during anesthesia: Limitations, possible improvements, and perspectives. *Korean J. Anesth.* **2016**, *69*, 113–120. [[CrossRef](#)] [[PubMed](#)]
27. Daga, R.G.; Sukhadeve, A.; Suthar, A. Closed-Loop Anesthesia: Advances in Automated Drug Delivery and Perioperative Monitoring. *J. Pharm. Bioallied Sci.* **2026**, *18*, S4–S6. [[CrossRef](#)] [[PubMed](#)]
28. AbdElSalam, M.; Bensalem, S.; Delacourt, A.; He, W.; Katsaros, P.; Kekatos, N.; Ruiz, R.N.; Peled, D.; Ponchant, M.; Ryad, I.; et al. Digital twin for the formal analysis of a depth of anesthesia controller. *Simulation* **2025**, *101*, 341–360. [[CrossRef](#)]
29. Wang, H. Towards digital twin-enabled perioperative care: Extending the potential of multimodal deep learning for cardiovascular risk stratification. *Int. J. Surg.* **2026**, *112*, 10786–10787. [[CrossRef](#)] [[PubMed](#)]

30. Roberts, J.A.; Abdul-Aziz, M.H.; Lipman, J.; Mouton, J.W.; Vinks, A.A.; Felton, T.W.; Hope, W.W.; Farkas, A.; Neely, M.N.; Schentag, J.J.; et al. Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *Lancet Infect. Dis.* **2014**, *14*, 498–509. [[CrossRef](#)] [[PubMed](#)]
31. Hume, N.E.; Zervas, I.; Wong, A.; Klein-Fedyshin, M.; Smithburger, P.L.; Buckley, M.S.; Devlin, J.W.; Kane-Gill, S.L. Clinical Impact of the Implementation Strategies Used to Apply the 2013 Pain, Agitation/Sedation, Delirium or 2018 Pain, Agitation/Sedation, Delirium, Immobility, Sleep Disruption Guideline Recommendations: A Systematic Review and Meta-Analysis. *Crit. Care Med.* **2024**, *52*, 626–636. [[CrossRef](#)] [[PubMed](#)]
32. Cascella, M.; Cascella, A.; Monaco, F.; Shariff, M.N. Envisioning gamification in anesthesia, pain management, and critical care: Basic principles, integration of artificial intelligence, and simulation strategies. *J. Anesth. Analg. Crit. Care* **2023**, *3*, 33. [[CrossRef](#)] [[PubMed](#)]
33. Gonzalez-Pizarro, P.; De Robertis, E.; Buhre, W. Amendment to the Glasgow Declaration. *Eur. J. Anaesthesiol.* **2024**, *41*, 937–938. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.