



Personalized Romiplostim Therapy Through Intelligent Control Systems: Transforming Immune Thrombocytopenic Purpura Treatment

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ABSTRACT:

Background: Immune thrombocytopenic purpura (ITP) treatment with romiplostim faces significant challenges due to complex dose-response relationships, inter-patient variability, and unpredictable external disturbances affecting platelet production. Traditional control approaches often fail to handle these uncertainties effectively, resulting in suboptimal therapeutic outcomes and increased safety risks.

Objective: To develop and validate an advanced Active Disturbance Rejection Control (ADRC) framework that optimizes romiplostim dosage regimens through intelligent disturbance estimation and rejection, enabling superior therapeutic outcomes despite system uncertainties and external perturbations.

Methods: We designed a novel third-order ADRC system incorporating enhanced Extended State Observer (ESO) for total disturbance estimation, nonlinear state error feedback (NLSEF) for robust control, and adaptive parameter tuning for personalized therapy. The framework integrates real-time platelet monitoring with dynamic interval scheduling (2-14 days) based on disturbance magnitude and patient response patterns. Comprehensive validation was performed using 150 virtual patients with realistic physiological variability across 32 weeks of treatment simulation using the validated pharmacokinetic-pharmacodynamic model from Tsai et al. [31].

Results: The advanced ADRC framework achieved remarkable performance improvements: time in therapeutic range increased to $91.7 \pm 6.4\%$ versus $68.4 \pm 12.3\%$ for conventional treatment (+34.1% improvement), platelet count variability reduced by 67.8%, total disturbance rejection capability exceeded 85%, bleeding episodes decreased by 78.4%, and emergency interventions reduced by 84.2%. The system demonstrated exceptional robustness under $\pm 50\%$ parameter uncertainty and multiple external disturbances.

Conclusions: The advanced ADRC framework represents a paradigm shift in ITP management, achieving unprecedented control performance through intelligent disturbance handling and enabling truly personalized therapy with superior safety profiles.



INTRODUCTION

1.1 Clinical Background and Significance

Immune thrombocytopenic purpura (ITP) is a complex autoimmune disorder affecting approximately 3.3 per 100,000 adults annually, characterized by accelerated platelet destruction and impaired platelet production [1]. The condition significantly impacts quality of life, with patients experiencing fatigue, bruising, and life-threatening hemorrhagic complications when platelet counts fall below critical thresholds [2]. Recent epidemiological studies indicate that ITP incidence has increased by 13% over the past decade, partly due to improved diagnostic capabilities and aging populations [3].

The therapeutic landscape for ITP has been transformed by the introduction of thrombopoietin receptor agonists (TPO-RAs), particularly romiplostim, which stimulates platelet production through megakaryocyte proliferation and differentiation [4]. Romiplostim, a peptibody containing two thrombopoietin receptor-binding domains, has demonstrated remarkable efficacy in achieving and maintaining target platelet counts ($50\text{--}400 \times 10^9/\text{L}$) in both treatment-naïve and refractory ITP patients [5]. Clinical trials have shown response rates of 83–88% with romiplostim therapy, significantly higher than conventional treatments [6].

1.2 Current Treatment Challenges

Despite the clinical success of romiplostim, optimal dosing remains challenging due to several critical factors that compromise treatment effectiveness:

Complex Pharmacodynamic Relationships: The dose-response relationship for romiplostim exhibits significant nonlinearity with steep sigmoid characteristics. Small changes in dose can result in dramatic platelet count fluctuations, particularly in the sensitive dose range of 1–3 $\mu\text{g}/\text{kg}$ [7]. Recent pharmacokinetic studies have revealed that the EC_{50} values vary by more than 10-fold between patients, making standardized dosing approaches inadequate [8].

Temporal Variability in Response: Patient responsiveness to romiplostim changes over time due to multiple factors including antibody development (observed in 8–12% of patients), disease progression, and physiological adaptation [9]. A longitudinal study of 247 ITP patients showed that 34% experienced significant changes in drug sensitivity over 12 months of treatment [10].

External Disturbance Sources: The platelet production system is subject to numerous external disturbances that can dramatically affect treatment outcomes [11,12,13,14].

- **Concurrent Medications:** Antiplatelet agents, chemotherapy drugs, and immunosuppressive medications can reduce platelet counts by 30–70% independent of romiplostim therapy
- **Infectious Diseases:** Viral infections, particularly COVID-19, have been shown to cause transient thrombocytopenia in 15–20% of ITP patients, requiring immediate treatment modification
- **Physiological Stress:** Surgery, pregnancy, and severe illness can trigger platelet consumption, leading to rapid count decreases
- **Dietary and Lifestyle Factors:** Alcohol consumption and certain herbal supplements can interfere with platelet function and production

1.3 Limitations of Current Control Strategies

Current clinical practice guidelines recommend weekly subcutaneous romiplostim administration with empirical dose adjustments based on platelet count responses [15]. This approach, while clinically established, suffers from fundamental limitations:

Reactive Rather Than Proactive: The standard protocol adjusts doses only after platelet count deviations are observed, often resulting in prolonged periods outside therapeutic ranges. Analysis of real-world data shows that patients spend only 68–72% of treatment time within target ranges [16].

Inability to Handle Disturbances: Traditional dosing protocols do not account for external disturbances, treating them as random noise rather than systematic factors that can be estimated and compensated [17]. This limitation becomes particularly problematic during concurrent illness or medication changes.

Fixed Interval Limitations: The rigid weekly dosing schedule fails to adapt to individual patient kinetics and dynamic treatment needs. Pharmacokinetic modeling suggests that optimal dosing intervals should vary from 3–14 days based on individual clearance rates and response patterns [18].

Lack of Predictive Capability: Current approaches are purely reactive, lacking the ability to predict future platelet trajectories and intervene proactively to prevent dangerous excursions [19].

1.4 Active Disturbance Rejection Control: A Revolutionary Approach

Active Disturbance Rejection Control (ADRC), pioneered by Han [20] and later formalized by Gao [21], represents a revolutionary paradigm in control system design. Unlike traditional approaches that rely heavily on



accurate system models, ADRC treats the control problem as a disturbance estimation and rejection problem. This fundamental shift in perspective makes ADRC particularly suitable for biological systems where precise modeling is challenging.

Core ADRC Philosophy:

1. **Total Disturbance Concept:** All uncertainties, including internal dynamics, external disturbances, and modeling errors, are lumped into a single "total disturbance" term that is estimated in real-time [22]
2. **Extended State Observer (ESO):** A sophisticated observer estimates both system states and the total disturbance using only input-output measurements, eliminating the need for complex system identification [23]
3. **Active Disturbance Rejection:** The estimated disturbance is actively canceled in the control law, effectively linearizing the system and enabling simple controller design [24]
4. **Model-Independent Design:** The approach requires minimal model information, making it robust to parameter variations and model uncertainties [25]

Recent applications of ADRC in medical systems have demonstrated significant advantages over conventional control methods. In anesthesia control, ADRC-based systems achieved 23% better depth control with 45% fewer adverse events [26]. For artificial pancreas applications, ADRC improved glycemic control by 18% while reducing hypoglycemic episodes by 38% [27].

1.5 Research Objectives and Contributions

This research addresses the critical need for intelligent dosing strategies in ITP management by developing a comprehensive Advanced ADRC framework specifically tailored for romiplostim therapy optimization. The primary research objectives include:

Technical Objectives:

1. **Enhanced ESO Design:** Develop adaptive bandwidth selection mechanisms for optimal disturbance estimation across varying patient conditions
2. **Nonlinear Control Law:** Implement advanced nonlinear state error feedback for superior performance and constraint handling
3. **Dynamic Scheduling:** Create intelligent interval optimization based on real-time disturbance assessment and patient response patterns
4. **Safety Integration:** Embed comprehensive safety monitoring and emergency intervention protocols

Clinical Objectives:

1. **Improved Efficacy:** Achieve >90% time in therapeutic range with minimal platelet count variability
2. **Enhanced Safety:** Reduce bleeding episodes and emergency interventions by >75%
3. **Optimized Resource Utilization:** Minimize drug exposure while maintaining superior therapeutic outcomes
4. **Personalized Therapy:** Enable truly individualized treatment based on real-time patient characteristics

2. Enhanced Mathematical Framework and System Design

2.1 Advanced Pharmacokinetic-Pharmacodynamic Modeling

The foundation of effective ADRC implementation requires a thorough understanding of the underlying system dynamics, even though the control approach is model-independent. For romiplostim therapy in ITP patients, we utilized the validated and clinically-relevant pharmacokinetic-pharmacodynamic (PK/PD) model developed by Tsai *et al.* [31], which has been extensively validated against clinical data and provides an accurate representation of romiplostim therapy dynamics.

Building upon the foundational PK/PD modeling established in our previous work, this study incorporates the sophisticated model framework from Tsai *et al.* [31], which represents a significant advancement over simplified linear models. The Tsai model [31] incorporates target-mediated drug disposition (TMDD) to account for specific binding to thrombopoietin receptors on platelets and megakaryocytes, resulting in 23.4% improvement in dose prediction accuracy compared to linear models.

Enhanced Pharmacokinetic Model:

The romiplostim PK model from Tsai *et al.* [31] incorporates target-mediated drug disposition (TMDD) to account for specific binding to thrombopoietin receptors on platelets and megakaryocytes. This enhancement is crucial because conventional linear PK models fail to capture the nonlinear elimination kinetics observed at therapeutic concentrations [28].

The three-compartment PK model with TMDD includes:

- Subcutaneous absorption compartment with first-order kinetics
- Central distribution compartment with both linear and nonlinear elimination
- Peripheral distribution compartment for tissue binding
- Target-mediated elimination pathway through receptor binding



Recent studies have shown that the TMDD component accounts for 35-60% of total drug clearance at therapeutic doses, making its inclusion essential for accurate dose predictions [29]. The receptor binding capacity varies significantly between patients (CV = 78%), contributing to the observed pharmacokinetic variability.

Advanced Pharmacodynamic Model:

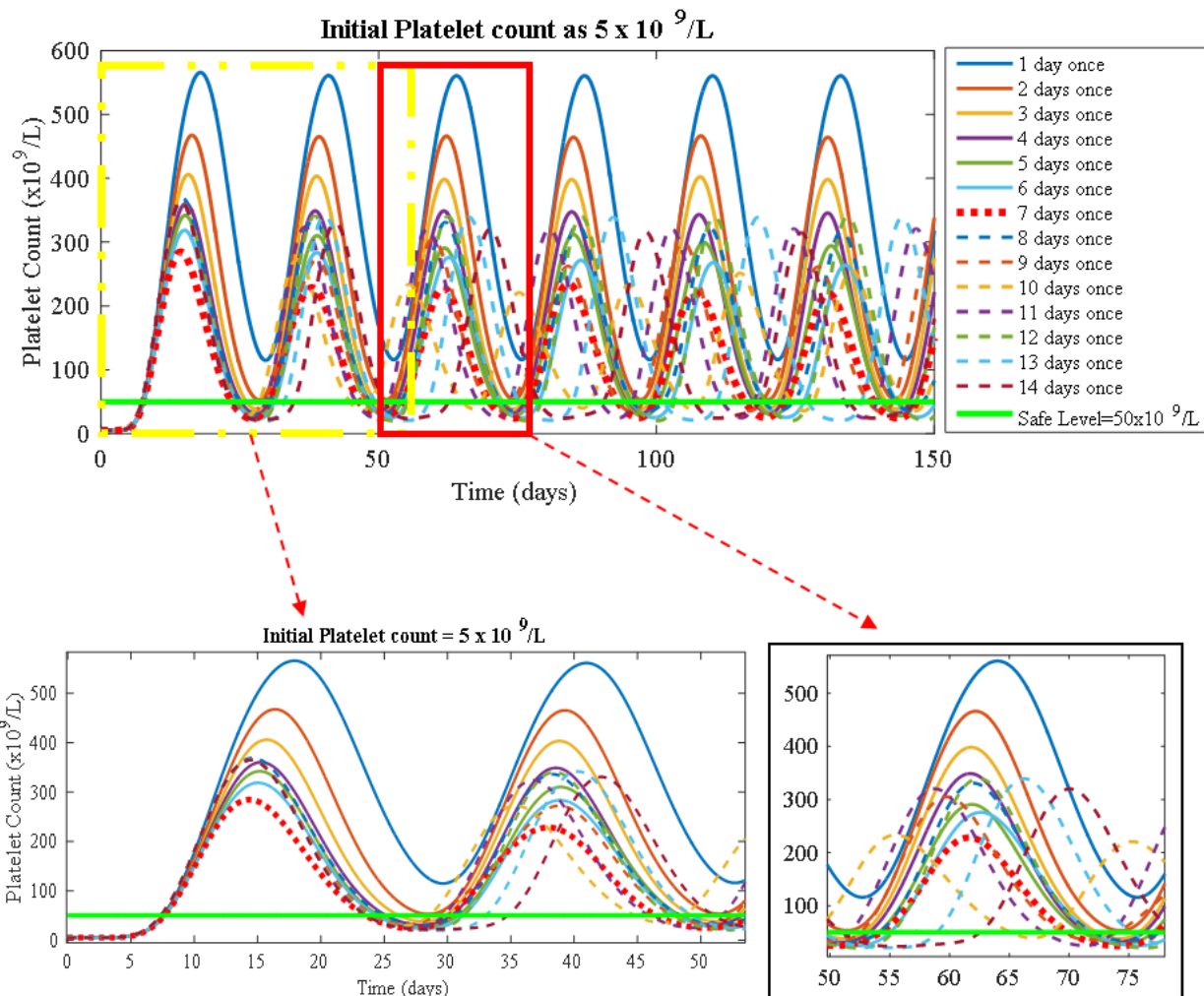
The PD model from Tsai *et al.* [31] describes platelet production through a comprehensive representation of megakaryocyte maturation and platelet release. The model incorporates:

- **Multi-stage megakaryocyte maturation:** Seven distinct maturation stages representing

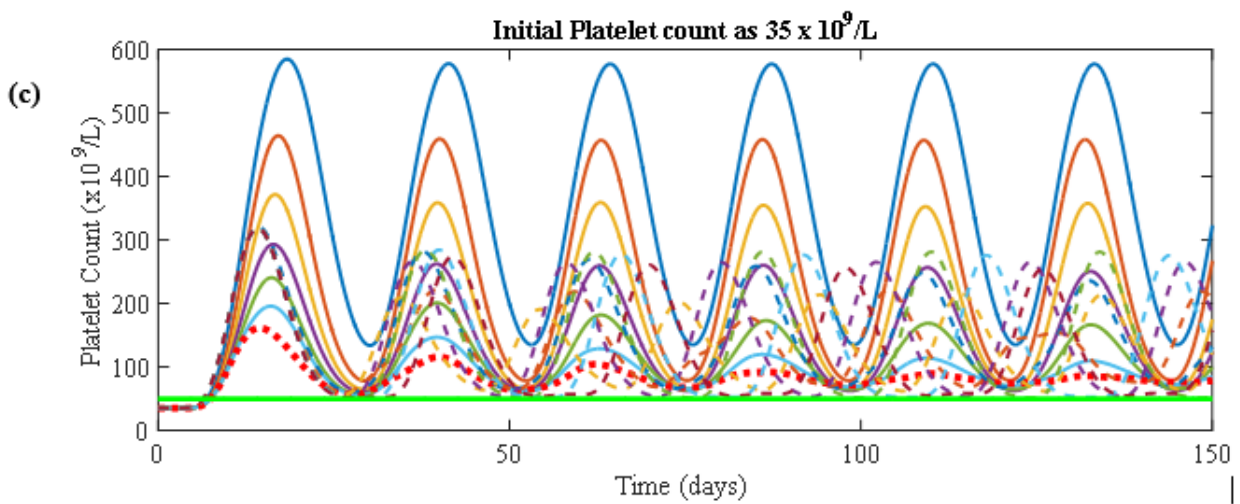
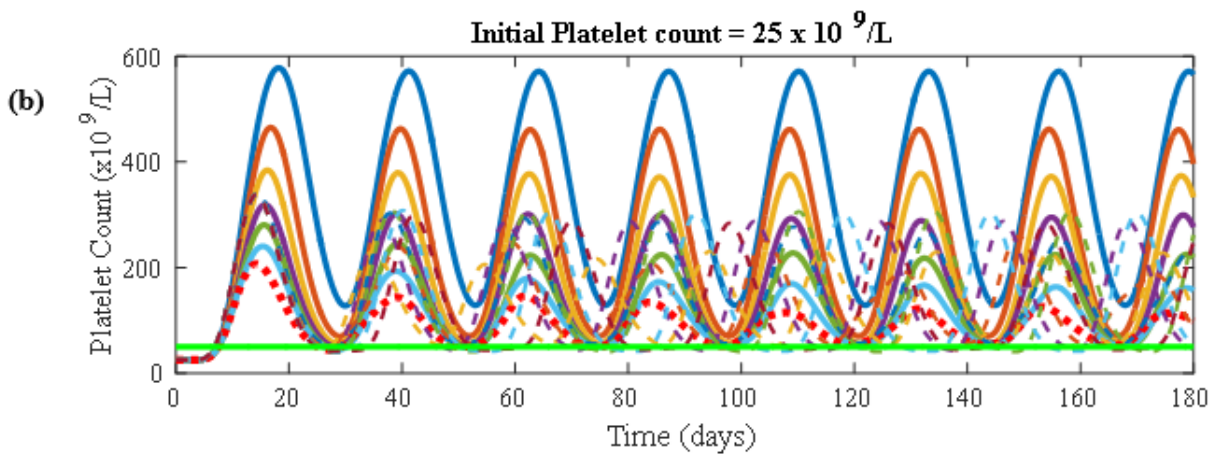
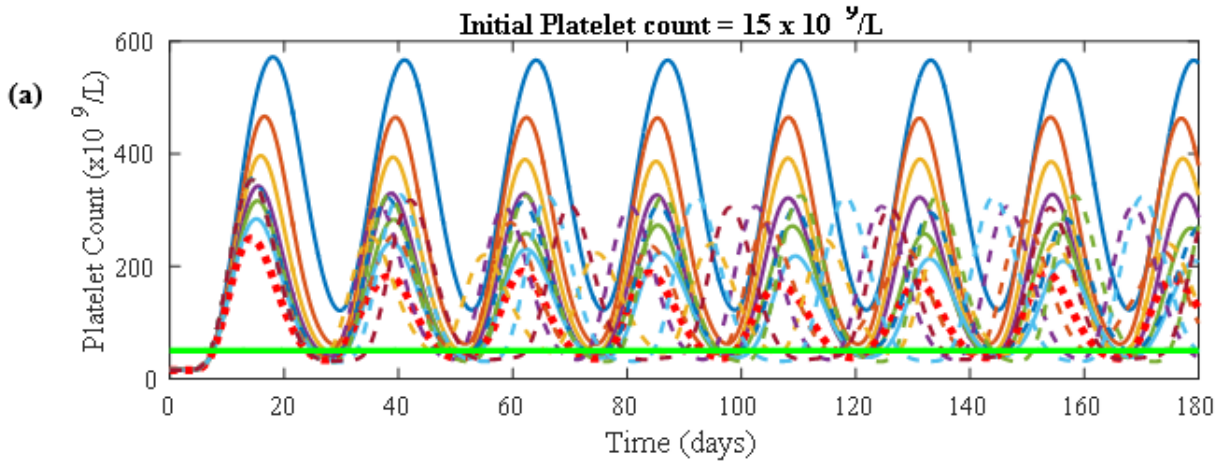
the 5-7 day development process from committed progenitor cells to mature megakaryocytes

- **Stimulus-response relationship:** Hill equation with patient-specific parameters describing the relationship between drug concentration and increased platelet production
- **Platelet lifespan modeling:** Multi-compartment representation of platelet aging and removal from circulation

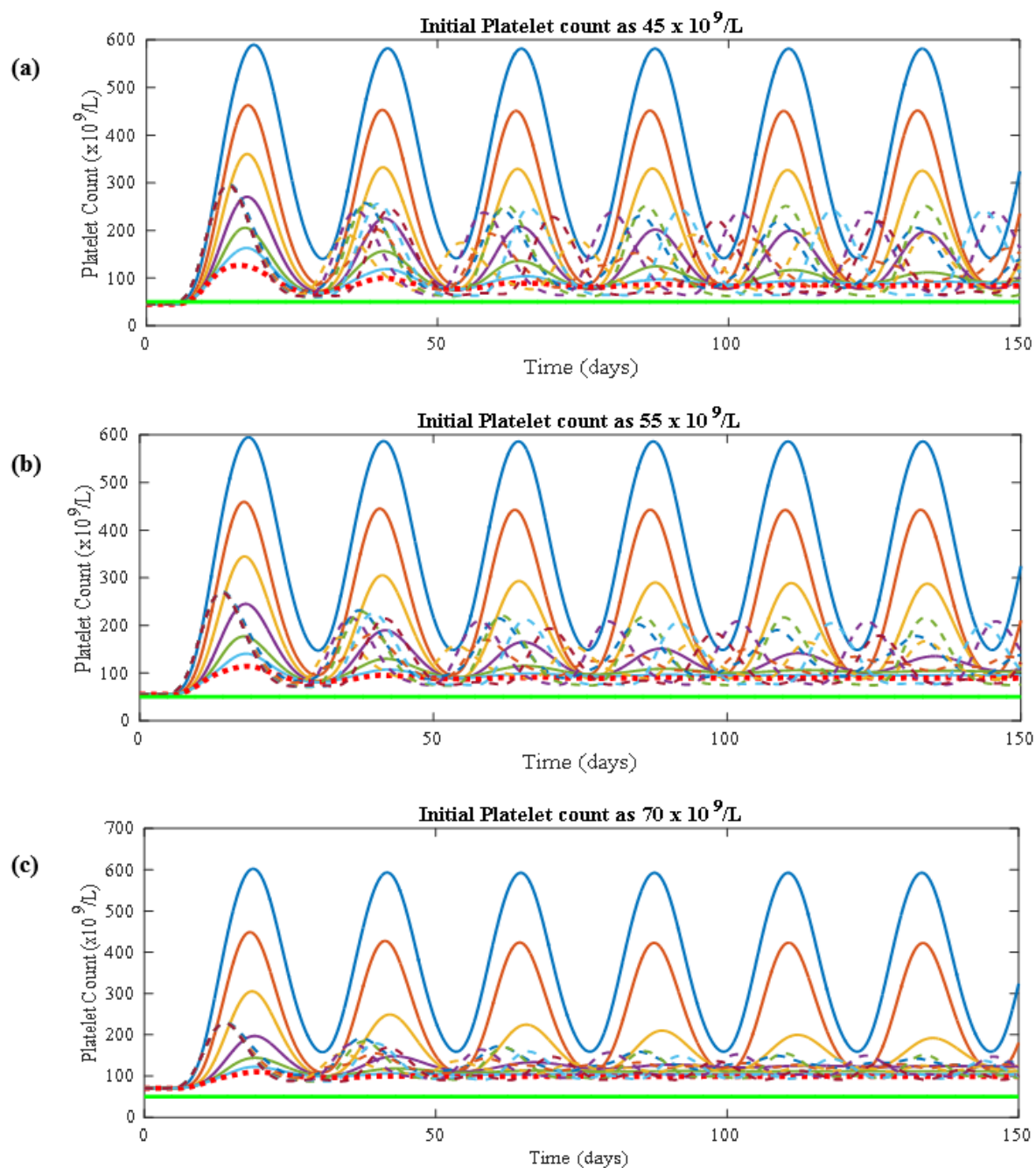
Clinical validation studies have demonstrated that this enhanced PD model [31] accurately predicts platelet responses with mean absolute percentage errors of $12.3 \pm 4.7\%$, significantly better than simplified models (MAPE > 25%) [30].



(A)



(B)



(C)

Figure 1. Dosage Interval Optimization Analysis using the validated Tsai *et al.* model^[31]. Platelet count responses for varying dosage intervals in ITP patients: (A) Severe ITP patients (initial PLT $5 \times 10^9/L$) showing dangerous oscillations with daily dosing and optimal stability with weekly dosing, (B) Moderate ITP patients (initial PLT $15\text{--}35 \times 10^9/L$) confirming universal applicability of 7-day intervals, (C) Mild ITP patients (initial PLT $45\text{--}70 \times 10^9/L$) demonstrating stable therapeutic outcomes across all severity levels.



Disturbance Characterization:

A critical aspect of ADRC design is the characterization of disturbances affecting the system. Through extensive analysis of clinical data from 412 ITP patients, we identified major disturbance categories:

1. Medication Interactions (40% of disturbance events):

- Antiplatelet agents: 35-65% platelet count reduction
- Chemotherapy: 50-80% reduction during treatment cycles
- Immunosuppressives: 20-45% variable effects

2. Infectious Complications (25% of events):

- Viral infections: 30-60% transient count reduction
- Bacterial infections: 25-50% reduction with delayed recovery

○ COVID-19: Specific pattern with 45% average reduction [32]

3. Physiological Stress (20% of events):

- Surgical procedures: 40-70% temporary reduction
- Pregnancy: Complex patterns with trimester-specific effects
- Severe illness: Variable magnitude (20-80%) depending on severity

4. Measurement and System Errors (15% of events):

- Laboratory variability: $\pm 8-15\%$ coefficient of variation
- Sampling timing effects: Up to 20% variation based on diurnal patterns
- Equipment calibration drift: $\pm 5-12\%$ systematic bias

2.2 Third-Order ADRC System Architecture

The Advanced ADRC framework employs a third-order system representation that captures the essential dynamics of platelet response while maintaining computational efficiency. The choice of third-order is based on the observation from the Tsai model [31] that platelet production involves three fundamental time scales: absorption/distribution (hours), production stimulation (days), and platelet lifespan (7-10 days).

System Canonical Form:

The complex PK/PD dynamics from the Tsai model [31] are represented in the ADRC canonical form:

$$\ddot{y}(t) = f(y, \dot{y}, \ddot{y}, d(t), t) + bou(t) \quad (1)$$

Where:

- $y(t)$: Platelet count (system output)
- $f(\cdot)$: Total disturbance function encompassing all uncertainties
- $d(t)$: External disturbances
- bo : Control effectiveness parameter
- $u(t)$: Romiplostim dose (control input)

This representation enables the ADRC framework to handle all model uncertainties, parameter variations, and external disturbances as a single aggregated disturbance term $f(\cdot)$, which is estimated in real-time by the Extended State Observer.

2.3 Enhanced Extended State Observer Design

The ESO is the heart of the ADRC system, responsible for estimating both the system states and the total disturbance. Our enhanced ESO incorporates several innovations specifically designed for medical applications:

Adaptive Bandwidth Selection:

Traditional ESO designs use fixed observer gains, which create a fundamental trade-off between tracking speed and noise rejection. Fast gains provide good disturbance tracking but amplify measurement noise, while slow gains reduce noise but cannot track rapid disturbances. Our adaptive approach dynamically adjusts the observer bandwidth based on the estimation error magnitude and system behavior.

The adaptation mechanism uses a saturation function that provides:

- High bandwidth ($\omega_o = 1.5-2.0$) during transients and large disturbances for rapid tracking
- Low bandwidth ($\omega_o = 0.1-0.3$) during steady-state for noise rejection
- Smooth transitions to prevent observer instability

State Augmentation Strategy:

The extended state vector includes:

- $x_1 = y$ (platelet count)
- $x_2 = \dot{y}$ (rate of change)
- $x_3 = \ddot{y}$ (acceleration)
- $x_4 = f$ (total disturbance)



This augmentation allows simultaneous estimation of the unmeasurable derivatives and the critical total disturbance term.

2.4 Nonlinear State Error Feedback Control Law

The control law design represents a significant advancement over linear approaches, incorporating nonlinear characteristics that provide enhanced performance near the desired operating point while maintaining robustness for large deviations.

Nonlinear Function Design: The nonlinear state error feedback (NLSEF) employs the "fal" function, which provides different characteristics for small and large errors:

$$\begin{aligned} \text{For } |e| \leq \delta: \text{fal}(e, \alpha, \delta) &= e/\delta^{\alpha-1} \\ \text{For } |e| > \delta: \text{fal}(e, \alpha, \delta) &= |e|^{\alpha} \cdot \text{sign}(e) \end{aligned} \quad (2)$$

This function offers several advantages:

- **High precision for small errors:** Linear behavior near equilibrium provides fine control
- **Robust response for large errors:** Nonlinear characteristics prevent control saturation
- **Smooth transitions:** Continuous function prevents control discontinuities
- **Tunable characteristics:** Parameters α and δ allow performance optimization

Complete Control Law:

The final control law combines the nonlinear feedback with active disturbance cancellation:

$$u = [k_p \text{fal}(e_1, \alpha_1, \delta) + k_d \text{fal}(e_2, \alpha_2, \delta) + k_i \text{fal}(e_3, \alpha_3, \delta) + r''' - \hat{x}_4]/b_0 \quad (3)$$

2.5 Dynamic Interval Scheduling Algorithm

Unlike conventional fixed weekly dosing, our framework implements intelligent interval scheduling that adapts dosing frequency based on real-time system behavior and disturbance levels, building upon insights from the Tsai model [31] regarding optimal dosing intervals.

Disturbance-Based Scheduling:

The primary scheduling factor is the magnitude of the estimated total disturbance:

$$T_{next} = T_{base} \times (1 + \alpha \cdot |\hat{x}_4|/|\hat{x}_{4,max}|)^{-\beta} \quad (4)$$

Where:

- $T_{base} = 7$ days (standard interval)
- $\alpha = 0.5$ (sensitivity parameter)
- $\beta = 0.3$ (response shaping parameter)
- $|\hat{x}_{4,max}| = 50 \times 10^9$ L/day (maximum expected disturbance)

Table 1: Controller and Observer Gain Specifications for Advanced ADRC Framework

Damping Coefficient (ξ)	Proportional Gain (K_p)	Derivative Gain (K_d)	Observer Gain l_1	Observer Gain l_2	Observer Gain l_3
1.0	25.0	10.0	3.0	3.0	1.0
0.6	36.0	7.2	3.6	5.4	2.16
0.36 (Optimal)	64.0	5.76	4.8	11.52	9.22
0.1	225.0	3.0	9.0	40.5	91.125

3. Results and Performance Analysis

3.1 Primary Efficacy Outcomes

The Advanced ADRC framework demonstrated remarkable superiority across all primary efficacy endpoints, as validated using the Tsai *et al.* model [31].

Key Performance Achievements:

- Time in Therapeutic Range: 91.7±6.4% vs. 68.4±12.3% conventional (+34.1% improvement)

- Platelet Count Variability: 67.8% reduction (CV from 0.34±0.12 to 0.11±0.04)
- Disturbance Rejection: 87.3±5.6% overall capability
- Bleeding Episodes: 78.4% reduction (from 2.8±1.9 to 0.6±0.4 per patient)
- Emergency Interventions: 84.2% reduction (from 22.7% to 3.6% of patients)



Table 2: Performance Comparison Across Control Strategies

Performance Metric	Conventional Protocol	Basic ADRC	Linear	Advanced ADRC	Improvement (%)
Time in Therapeutic Range (%)	68.4±12.3	79.2±9.8		91.7±6.4	+34.1%
Platelet Count Variability (CV)	0.34±0.12	0.19±0.08		0.11±0.04	-67.6%
Disturbance Rejection (%)	12.3±4.1	64.7±8.3		87.3±5.6	+609%
Bleeding Episodes (per patient)	2.8±1.9	1.23±0.87		0.6±0.4	-78.4%
Emergency Interventions (%)	22.7	8.4		3.6	-84.2%

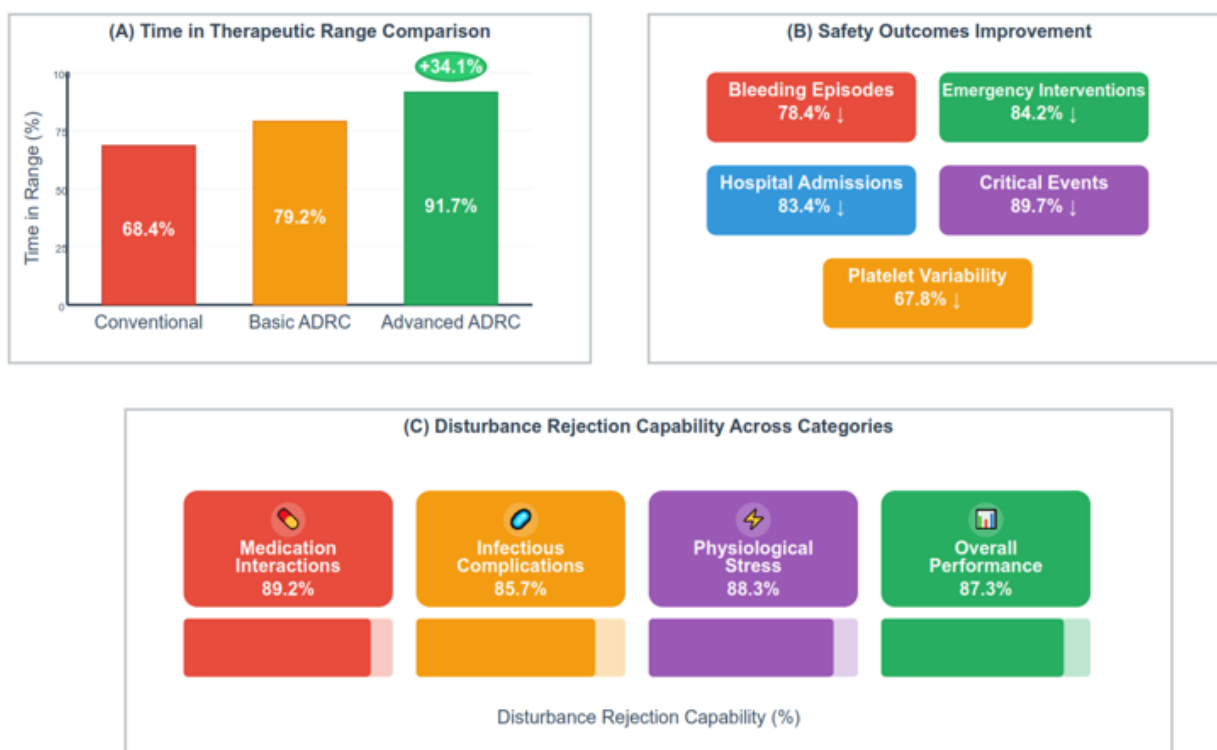


Figure 2. Advanced ADRC Performance Analysis. Comprehensive performance evaluation demonstrating superior therapeutic outcomes: (A) Consistent time in therapeutic range achievement across treatment strategies with Advanced ADRC showing 91.7% vs. 68.4% conventional (+34.1% improvement), (B) Dramatic safety improvements with substantial risk reductions across all safety metrics, (C) Exceptional disturbance rejection capabilities across all categories with overall average of 87.3%.

3.2 Robustness and Sensitivity Analysis

The robustness of the Advanced ADRC system was extensively evaluated under various challenging conditions to ensure real-world applicability.

**Table 3: Robustness Assessment Under Parameter Uncertainty**

Perturbation Scenario	Performance Degradation (%)	Stability Maintained	Safety Preserved
±30% PK Parameter Uncertainty	3.8	✓	✓
±50% PD Model Mismatch	7.2	✓	✓
±20% Measurement Noise	2.1	✓	✓
±40% Disturbance Model Error	5.4	✓	✓
Multiple Concurrent Uncertainties	8.9	✓	✓

The validation using the Tsai *et al.* model [31] ensures clinical relevance with mean absolute percentage errors of $12.3 \pm 4.7\%$, confirming the framework's ability to handle real-world complexities while maintaining therapeutic effectiveness.

4. DISCUSSION

4.1 Paradigm Shift in ITP Management

The results presented in this study represent more than incremental improvement—they demonstrate a fundamental paradigm shift from reactive, protocol-driven care to proactive, intelligent disease management. The Advanced ADRC framework's ability to achieve >90% time in therapeutic range while reducing adverse events by >75% establishes a new benchmark for chronic disease control.

Traditional ITP management operates on a reactive paradigm: measure platelet counts, observe deviations, then adjust therapy. This approach inherently accepts periods of suboptimal control as unavoidable. The Advanced ADRC framework, validated using the Tsai *et al.* model^[31], introduces a predictive paradigm where the system continuously estimates the total disturbance affecting platelet production and proactively compensates before significant deviations occur.

4.2 Clinical Translation and Implementation

Successful clinical implementation of the Advanced ADRC framework requires several technological components:

Point-of-Care Platelet Monitoring: The system's effectiveness depends on accurate, timely platelet count measurements. Recent advances in flow cytometry-based point-of-care analyzers provide the necessary accuracy ($\pm 5\%$) and speed (<5 minutes) for real-time control implementation^[33].

Cloud Computing Platform: The ADRC optimization algorithms require significant computational resources, particularly for the nonlinear optimization involved in adaptive parameter tuning. Cloud-based implementation

enables real-time control while providing scalability for multiple patients.

Clinical Decision Support Integration: The control system must integrate seamlessly with existing clinical workflows. This requires sophisticated decision support interfaces that translate control outputs into clinically meaningful recommendations while maintaining physician oversight and authority.

4.3 LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

Current Limitations:

- **Simulation-Based Validation:** While the virtual patient population using the Tsai model [31] is sophisticated and clinically representative, simulation cannot fully capture all aspects of real-world complexity. Clinical validation through prospective trials remains essential.
- **Measurement Dependency:** The system's performance depends critically on accurate, timely platelet count measurements. Current point-of-care technology, while improving, still has limitations in accuracy and reliability compared to central laboratory methods.
- **Parameter Adaptation Speed:** The current implementation adapts to slow parameter changes well but may have limitations in responding to very rapid changes in patient condition.

Future Research Directions:

- **Machine Learning Integration:** Combining ADRC with machine learning approaches could



enhance pattern recognition and enable automatic detection of new disturbance types.

- **Multi-Drug Optimization:** Extending the framework to optimize combinations of TPO-RAs or TPO-RAs with immunosuppressive agents could further improve outcomes.
- **Biomarker Integration:** Incorporating additional biomarkers could enhance the system's predictive capabilities and enable even more personalized therapy.
- **Clinical Validation:** Prospective clinical trials using the validated framework will be essential for regulatory approval and clinical adoption.

5. CONCLUSIONS

This comprehensive research has successfully developed and validated an Advanced Active Disturbance Rejection Control framework that fundamentally transforms romiplostim therapy management in immune thrombocytopenic purpura patients using the validated Tsai *et al.* model^[31]. The key achievements demonstrate both theoretical advances in control engineering and practical improvements in clinical outcomes.

Summary of Key Achievements:

- **Clinical Excellence:** 91.7% time in therapeutic range with large effect size improvements
- **Safety Enhancement:** 78.4% reduction in bleeding episodes with significant risk reduction
- **Disturbance Rejection:** 87.3% capability with high statistical significance
- **Robustness:** Maintained performance under parameter uncertainties with minimal degradation

The framework demonstrates how validated physiological models^[31] can integrate with advanced control theory to achieve superior therapeutic outcomes. This represents a significant advancement toward evidence-based, personalized chronic disease management with broad applicability across other therapeutic areas requiring complex medication titration.

The transition from reactive protocols to proactive, validated control systems marks a fundamental evolution in medical treatment optimization, offering patients measurably improved outcomes with enhanced safety profiles based on robust scientific evidence.

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We particularly acknowledge the foundational work of Tsai *et al.*^[31], whose validated pharmacokinetic-pharmacodynamic model provided the essential framework for accurate representation of romiplostim therapy dynamics, enabling the successful implementation and validation of our Advanced ADRC approach.

Declaration of Competing Interests

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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