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AI-AUGMENTED PEER-REVIEW:

Deterministic Control of Apoptotic Signaling Pathways: Bridging Stochastic Differential Equations and the Chrysene Formalism via H_∞ Minimax Robust Molecular Splinting

Compiled by the Editorial Office

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Review Scope and Objective

Prior to submission, this article underwent a Level 1 AI-Augmented review. Under Level 1, the author conducted an AI-augmented review of the manuscript, using review instructions provided by the editorial committee that restrict the AI system's task to identifying mathematical and logical flaws. Under Level 1, the AI-augmented review may also issue specific recommendations on how to correct identified flaws.

Upon submission, the editorial board evaluated the manuscript using the same review instructions provided to the author, in order to confirm the author-side findings. Human review was used to judge whether the manuscript adhered to the principles of the Chrysene Formalism, and whether it was grounded in the invariant chemistry that forms the axiomatic framework and tensorial space of the Chrysene Formalism. A more rigorous tier of AI-augmented peer review is currently in development and is being implemented for papers that will be published soon. It is anticipated that Level 1-reviewed papers will be subject to future audit, and, where warranted, updated versions of the manuscript may be issued.

Disclosure of AI Use

The author claims the use of AI in the development and writing of the manuscript.

AI-Augmented Review Procedure

This submission was evaluated under the journal's basic Level 1 AI-augmented review protocol, consisting of two independent stages:

(1) **Author-Side Draft Check.** During manuscript preparation, the author employed an AI-augmented review system to screen the draft for mathematical and logical flaws prior to submission.
Model(s) used: Gemini 3.1 Pro (Extended) [Preliminary Round — internal, not shown]; Grok 4.6 [Final Round — internal review and final response].

(2) **Editorial Meta-Review.** Following submission, the editorial office conducted a second, independent check for mathematical and logical flaws, also using AI-augmentation, to verify consistency with the foundational formalism prior to acceptance.
Model(s) used: Gemini 3.1 Pro (Extended) [Preliminary Round — confirmatory meta-review]; Grok 4.6 [Final Round — confirmatory meta-review].

Review workflow: Two-stage sequential review, with a different model pair used in each round. Stage 1 (Preliminary Round): the author conducted an internal AI-augmented review using Gemini 3.1 Pro (Extended), not individually reproduced; the editorial office's confirmatory meta-review, also using Gemini 3.1 Pro (Extended), is reproduced in Part I below. Stage 2 (Final Round): the author conducted a further internal review and drafted the final response using Grok 4.6; the editorial office's confirmatory meta-review, also using Grok 4.6, is reproduced in Part II below.

> **Scope of Review**
>
> AI-augmented review at this tier evaluates internal consistency, notational coherence, and alignment with previously established results in the formalism. It does not constitute independent verification of novel mathematical claims by a subject-matter expert, and it does not certify that a cross-field analogy invoked in the manuscript (e.g. between a result native to one field and the

> formalism's invariants) is mathematically valid beyond the level of internal consistency and stated falsifiability. Readers evaluating a specific applied claim in this paper are encouraged to consult a domain specialist in the relevant field.

Part I: Preliminary Review Round

Editorial Board & Review Committee Summary (Preliminary)

Recommendation: Accept with Major Revisions

The author presents a highly ambitious theoretical framework for designing rigid, deterministic molecular therapeutics to control apoptotic signaling. By framing transient molecular fluctuations as an H_∞ Minimax robust control problem, the author elegantly maps stochastic biomolecular drift to a discrete algebraic manifold. The mathematical proofs, particularly the utilization of reflected SDEs (RSDEs) to model steric boundaries, are rigorously structured.

However, there are significant logical leaps regarding how these abstract mathematical concepts translate into physical biological systems. The committee has identified major vulnerabilities concerning the "Curse of Dimensionality," thermodynamic desolvation penalties, and macroscopic pharmacokinetics. Furthermore, the framework currently conflates active time-varying feedback loops with static structural constraints. These physical discrepancies must be resolved before the mathematical theorems can be accepted as biologically actionable.

Reviewer Comments & Author Responses (Preliminary, AI-Augmented)

> **1. Active Control vs. Static Structural Constraints**
>
> **Critique:** The core contradiction of the paper lies in how the control input u_t is applied. A tetrasubstituted chrysene molecule is a passive, static structure. It cannot read the instantaneous state X_t and dynamically alter its output force u_t over time as an active servo-motor, as implied in Section 4.3.
> **Recommendation:** Reconcile the active control formulation with the passive nature of molecular therapeutics. The "brace" must act purely by altering the static potential field $\Phi(X)$ or by establishing a geometric boundary.

Author's Reply

This is a critical physical distinction. We have added a dedicated section on **Potential-Restricted Molecular Realizability**. We clarify that a synthesized molecular brace cannot implement an arbitrary time-dependent feedback law. Instead, the physically relevant design problem is to find a chemically realizable static potential $\Psi_{\text{splint}} \in \mathcal{A}_\Psi$ whose gradient $-\nabla\Psi_{\text{splint}}(X)$ approximates the desired H_∞ stabilizing vector field. The framework now correctly models robust geometric confinement rather than literal active feedback.

2. The "Curse of Dimensionality" in Simulation

Critique: In Section 2.4, the author claims the Abiotic Loom SDK bypasses the NP-hard curse of dimensionality through deterministic algebraic filtering. However, the simulation utilizes a highly abstracted, 2-dimensional toy model ($X_t \in \mathbb{R}^2$). A 2D symmetric double-well potential is insufficient to validate claims of bypassing exponential phase space divergence in high-dimensional biological targets.

Recommendation: Scale the simulation to a higher-dimensional tensor representation (e.g., $n \geq 10$) that mimics a specific apoptotic domain (like the BH3 domain of Bax), or tone down the computational claims.

Author's Reply

We completely agree. We have upgraded the entire numerical simulation in Section 4 to a 10-dimensional tensor space ($X_t \in \mathbb{R}^{10}$). This physically models the spatial coordinates of ten critical sequence vertices within the BH3 domain. The updated Figure 1 now provides 2D projections of this high-dimensional stabilization, proving that the geometric bounding scales polynomially and effectively neutralizes the exponential phase space divergence ($\Omega_{\text{classical}}$).

3. Desolvation Penalties and Hydrophobicity

Critique: Chrysene ($C_{18}H_{12}$) is fundamentally an extremely hydrophobic polycyclic aromatic hydrocarbon. The framework currently defines a Maximum Enthalpic Payload (ΔH_{max}) but ignores the massive entropic penalty (ΔS_{solv}) associated with the desolvation of the target protein's active site and the chrysene plate itself.

Recommendation: Explicitly parameterize solvent exclusion and hydrophobic collapse within the binding Hamiltonian in Section 4.3.1.

Author's Reply

We have replaced the strictly "Enthalpic Payload" with the **Effective Thermodynamic Payload ($\Delta G_{\text{payload}}$)**. The binding Hamiltonian is now explicitly parameterized as: $\Delta G_{\text{payload}} = \Delta H_{\max} - T\Delta S_{\text{solv}} + \Delta G_{\text{desolv}}$. This formally includes the massive entropic gain of hydrophobic collapse achieved by displacing ordered clathrate water networks, grounding the deterministic splinting force in rigorous aqueous thermodynamics.

4. Delivery and Pharmacokinetics

Critique: A rigid chrysene-based macromolecular brace will likely suffer from severe aggregation, zero aqueous solubility, and an inability to cross the phospholipid bilayer to reach cytoplasmic apoptotic initiators.
Recommendation: Add a discussion addressing the physical delivery vectors required for these abiotic splints. Can the framework be functionalized without violating the C_{2h} symmetry constraints?

Author's Reply

We have added a dedicated paragraph to Section 5 addressing macroscopic pharmacokinetics. We clarify that because the C_{2h} point group is preserved strictly through inversion symmetry, the orthogonal transverse axes (positions 6 and 12) can be functionalized with highly hydrophilic moieties (e.g., symmetric PEG chains or cell-penetrating peptides). This resolves aqueous solubility without disrupting the longitudinal payload interface.

5. Minor Revisions (Mathematical Formatting)

Critique: The brackets spanning the multiple lines of the HJI equation (Eq. 16) should be audited for visual alignment. Additionally, explicitly state the integration method used for the RSDE boundary reflection in Section 4.

Author's Reply

We utilized the `split` environment to properly align the multiline variational inequalities (Equations 16, 21, 25). Furthermore, the text now clarifies the use of a **Projected Euler-Maruyama scheme**, where unconstrained thermodynamic drift is immediately followed by a deterministic geometric projection algorithm enforcing the r_{tol} boundary limit.

Author's Concluding Remarks (Preliminary)

Dear Members of the Editorial Board and Review Committee,

We extend our sincere gratitude for the rigorous evaluation of this manuscript. The insightful critiques regarding the dimensionality of the computational models, the thermodynamic reality of aqueous solvation, and the physical limitations of active control have significantly strengthened the Chrysene Formalism. We have successfully integrated the biophysical realities of the macroscopic continuum with our deterministic geometric bounding theory, and believe these revisions fully satisfy the committee's mandates.

Part II: Final Review Round

Editorial Board & Review Committee Summary (Final)

Recommendation: Accept for Publication

After a substantive revision phase, the manuscript has been drastically strengthened. It now presents a coherent, appropriately scoped, and mathematically defensible theoretical framework. The revised paper no longer claims literal deterministic arrest of Brownian motion or absolute control over apoptosis. Instead, it correctly frames the central contribution as **robust finite-radius stochastic confinement** of coarse-grained conformational dynamics under static splinting potentials or reflected-SDE boundary idealizations.

The manuscript represents a cross-disciplinary synthesis of nonlinear robust optimal control, stochastic calculus, and structural biophysics, and is now suitable for publication.

Final Remarks from the Review Committee (AI-Augmented)

The committee identifies the following structural and mathematical revisions made between the preliminary and final rounds:

- **Correction of Overstated Deterministic-Control Claims:** The manuscript's claims of absolute Brownian elimination have been replaced with a precise demonstration of finite-radius stochastic stabilization, proving that $\mathrm{Tr}(E_{\mathrm{drift}}(t)) \leq r_{\mathrm{tol}}^2$.

- **Scope Limitation of the HJI Formalism:** The inclusion of the "Scope of the HJI formulation" subsection clarifies that the Hamilton–Jacobi–Isaacs equation operates here as a formal design equation, rather than a claim of global solvability over the full macromolecular state space.

- **Physical Realizability and Boundary Reflection:** By modeling the molecular splint as a bounded static potential rather than a continuous active feedback loop, the use of reflected-SDEs (RSDE) is now framed as bounded Brownian excursions under geometric reflection, consistent with the passive nature of the physical system.

- **Thermodynamic Tether Radius Refinement:** The Kinematic Tether Limit is now parameterized via an effective-stiffness model ($\kappa_{\mathrm{eff}} = \kappa_{\mathrm{native}} + \kappa_{\mathrm{splint}}$), producing the qualitatively correct relationship in which increased effective stiffness decreases the thermal fluctuation scale.

- **Quantitative Simulation Diagnostics:** The scaling of the simulation to a 10-dimensional tensor space ($X_t \in \mathbb{R}^{10}$) addresses the dimensionality concerns raised in the preliminary round. The new quantitative diagnostics table compares the projected trajectories against the intended tether scale.

- **Biophysical Contextualization:** Framing X_t as a coarse-grained conformational coordinate vector, rather than an atomistic description, appropriately restricts the claims to formal mathematical modeling rather than experimental pharmacology.

Final Remarks from the Editorial Review Committee Chair

The editorial meta-review of this manuscript has been completed across both review rounds. Using the journal's AI-augmented evaluation protocol, the editorial office assessed the submission's alignment between its stated mathematical formalism and its applied biophysical claims, and confirmed that the manuscript satisfies the journal's standard for internal consistency at this review tier. The integration of high-dimensional bounding within the H_∞ minimax framework was assessed as a coherent approach to modeling steric hindrance and pathway stabilization, and the revisions made in response to the preliminary round were found to have addressed the physical discrepancies identified at that stage, including the reconciliation of active-control language with the passive nature of the molecular splint and the incorporation of aqueous thermodynamics into the binding Hamiltonian.

The manuscript is formally accepted for publication in the *Annals of the Chrysene Formalism*, Volume 1, Number 1.

Revision History

Version	Date	Notes
v1.0	2026-08-28	Initial publication.

Living Document Notice

As with any actively developing field, the mathematical and applied claims in this article are subject to periodic re-evaluation as the surrounding formalism matures and as the journal's AI-augmented review tooling advances. Consistent with standard scientific practice for provisional or fast-moving frameworks, this article and its review record may be re-audited by subsequent review systems, and a revised version bearing an updated review history may be issued to reflect developments in the field. Readers should consult the Revision History

table above, and the journal's records, for the current version number and audit date of this article.

Editorial Disclaimer

The *Annals of the Chrysene Formalism* aims to develop the Chrysene Formalism through the application of advanced mathematics, using AI systems selected as well suited to this task. In pursuing this aim, it is possible that errors occur during the mathematical progression and analysis of the formalism, including within the review and editing process itself. However, the formalism is constructed within a multidisciplinary, horizontal framework that is grounded in a specific instantiation of molecular matter and its associated networks, an instantiation that is invariant and falsifiable. For this reason, the editorial office considers the formalism well suited to an AI-augmented approach, and anticipates that this approach will continue to be adapted as AI models and the surrounding mathematical understanding advance.