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AI-AUGMENTED PEER-REVIEW:

Topological Spectral Inversion: Resolving Isomorphic Divergence in Inverse Generative Therapeutics via the Discrete Dirac Operator within the Chrysene Formalism

Compiled by the Editorial Office

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Schaper Systems Press

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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).

(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).

Review workflow: Single-model review.

> **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.

Editorial Board & Review Committee Summary

Recommendation: Accept with Minor Revisions

The manuscript presents a mathematically rigorous and highly innovative application of non-commutative spectral geometry to systems biology. By lifting classical graphs into non-commutative spectral triples $(\mathcal{A}, \mathcal{H}, \mathcal{D})$ over the Chrysene manifold $\mathcal{I}_C$, the author elegantly resolves the isomorphic divergence bottleneck. The correction of dimensional inconsistencies in the graph Laplacian via the $\mathbb{Z}_2$-graded Hilbert space and the grounding of non-commutative phase factors in classical non-equilibrium thermodynamics are exceptional contributions.

To finalize the manuscript for publication as a foundational pure mathematics treatise, the committee requests a few formal clarifications regarding the handling of spectral singularities, the empirical parameterization of thermodynamic phases, and the analytical scalability of the computational pipeline.

Reviewer 1 (AI-Augmented): Mathematical Physics and Spectral Geometry

1. Gauge Invariance and Degenerate Eigenspaces

Critique: While the text states that the objective function incorporates an eigenvector penalty to account for $U(1)$ gauge freedom, the exact Riemannian metric on the complex projective space is not explicitly defined. Furthermore, the use of the Feynman-Hellmann relation assumes non-degenerate perturbation theory, which is insufficient for symmetric or disconnected biological graphs that admit high-multiplicity eigenvalues.

Recommendation: Formally define the metric on the complex projective space (e.g., Fubini-Study) within the objective function. Additionally, introduce a lemma explicitly defining the spectral derivatives for perturbations within degenerate eigenspaces.

Author's Reply

Definition 6 has been revised to formally define the Gauge-Invariant Inverse Spectral Problem. The eigenvector penalty has been elevated to the complex projective space $\mathbb{CP}^{N-1}$, utilizing the trace of orthogonal rank-1 projection operators $(\mathrm{Tr}(\Pi_k \Pi_k^{healthy}))$, which precisely corresponds to the Fubini-Study metric distance to preserve homological phase-invariance unconditionally. Furthermore, Lemma 2 has been introduced to handle degenerate eigenspaces. It establishes that for a degenerate eigenvalue of multiplicity $m > 1$, the first-order shifts are unconditionally derived from the restricted perturbation matrix $\delta\Lambda_0 = \mathrm{Spec}(P_{\mathcal{V}_0}(\delta D)P_{\mathcal{V}_0})$.

Reviewer 2 (AI-Augmented): Systems Biology and Non-Equilibrium Thermodynamics

2. Empirical Parameterization and Pharmacological Mapping

Critique: The thermodynamic justification effectively associates the non-commutative holonomy with the thermodynamic affinity. However, for Inverse Generative Therapeutics (IGT) to function in vivo, the manuscript must mathematically establish how localized chemical potential gradients are empirically measured, and how an abstract phase perturbation geometrically maps to a physical therapeutic dosage.

Recommendation: Insert a formal definition demonstrating the derivation of the thermodynamic affinity from absolute multi-omics concentrations. Concurrently, define the strict mathematical mapping between the required topological phase shift $\delta\theta_{uv}$ and a physical fractional inhibition.

Author's Reply

Definition 4 has been added to establish Empirical Parameterization and Pharmacological Mapping. The manuscript now explicitly evaluates the non-conservative chemical potential gradient from empirically measured absolute concentrations $(\mathcal{E}_v, \mathcal{E}_u)$ utilizing the relation $\Delta\mu_{uv} = k_B T \ln(\mathcal{E}_v/\mathcal{E}_u)$. Concurrently, the text formalizes the exact physical mapping where the topological phase perturbation equates to Michaelis-Menten fractional inhibition via $\delta\theta_{uv} = \ln(1 - Y)$, uniquely determining the physical therapeutic dosage $[I] = IC_{50}(e^{-\delta\theta_{uv}} - 1)^{-1}$.

Reviewer 3 (AI-Augmented): Computational Methods and Optimization

3. Algorithmic Scalability and Topological Convexity

Critique: The finite-difference gradient computation in the optimization loop scales as $O(N^4)$, which will become intractable for high-dimensional biological networks. Additionally, the unconstrained optimization manifold is non-convex, and the methodology for balancing the regularization hyperparameters (α, β, λ) requires formal justification to prevent the structural penalty from overriding spectral alignment.

Recommendation: Replace the finite-difference approximation with an analytical gradient (e.g., the Adjoint State Method). Add formal remarks

outlining the Semi-Definite Programming (SDP) convex relaxation of the parameter space and the equilibration of hyperparameters via rigorous boundary principles.

Author's Reply

Proposition 3 has been added, defining the Analytical Gradient via the Adjoint State Method. By computing exact derivatives strictly via the trace operation $\nabla_p \mathcal{J} = \mathrm{Tr}(\dots)$, the computational complexity is formally reduced from $O(N^4)$ to $O(N^3)$, ensuring scalability. Additionally, Remark 2 has been incorporated to prove Topological Convexity, noting that lifting the optimization into the space of positive semi-definite matrices evaluates as a strictly convex Semi-Definite Program (SDP). Finally, Remark 1 specifies that hyperparameters α, β, and λ are rigorously bounded utilizing Morozov's Discrepancy Principle over a Pareto frontier, ensuring the structural penalty $\lambda\mathcal{R}(\delta D)$ does not exceed the native Dirichlet bornology τ_{max}.

Author's Concluding Remarks

Dear Members of the Review Committee, thank you for your meticulous evaluation and constructive feedback. I am pleased that the committee recognizes the theoretical rigor of lifting biological networks into non-commutative spectral triples over the Chrysene manifold $\mathcal{I}_C$. All requested mathematical recommendations have been incorporated into the revised manuscript to maximize categorical precision and biophysical validity.

Thank you again for the highly rigorous review. The finalized manuscript is submitted for your consideration.

Final Remarks from the Editorial Review Committee Chair

The editorial meta-review of this manuscript has been completed. Using the journal's AI-augmented evaluation protocol, the editorial office assessed the submission's alignment between its stated mathematical formalism and its applied engineering or scientific claims, and confirmed that the manuscript satisfies the journal's standard for internal consistency at this review tier. The manuscript's treatment of gauge invariance and degenerate eigenspaces, the empirical parameterization of the thermodynamic-to-pharmacological mapping, and the algorithmic scalability and convexity of the optimization pipeline was found to be consistent throughout. The formalization of the discrete Dirac operator as a topological probe of biological networks was noted as a central methodological contribution of the manuscript.

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	2026-08-14	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.