Editorial

Toward a unified theory of ATP synthesis/hydrolysis: Integrating physics, chemistry, and biology

1. Introduction

The synthesis and utilization of the universal biological energy currency, adenosine triphosphate (ATP) is a central and most prevalent chemical reaction in biomolecular systems. It is an area of basic research that has seen significant progress in our understanding resulting from both recent technological developments in instrumentation and reassessment of older theoretical studies. Our special issue "Toward a unified theory of ATP synthesis/hydrolysis: Integrating physics, chemistry, and biology" is devoted to theoretical developments in the field of ATP research with particular emphasis on various aspects of the mechanism of ATP synthesis and hydrolysis by F_OF_1-ATP synthase since the beginning of the millennium. During this period, older theories of ATP synthesis and hydrolysis proposed in the period 1950–1970 by a number of competing groups have undergone a thorough critical reassessment.

No special issue on ATP of this broad scope from a multidisciplinary perspective has appeared in more than 50 years. It is apparent from the current literature that several groups working in related research fields approach bioenergetic problems from their own perspectives. They might benefit from insights offered by unique systems approaches to solving complex problems in related areas of research. With this in mind as our guiding principle, we have sought contributions to our special issue of *BioSystems* from researchers in interrelated areas of ATP research that could offer novel insights and lead to a future, more holistic understanding of ATP-related phenomena.

2. Short presentation of each paper

The contributions to this special issue are categorized as follows:

Basis for a unified theory: Major reviews of the current status of ATP research (Four papers)

Individual reviews cover the research of Nath, an extensive account of a century of ATP research, ATP related to disease states, and organism classification and ATP in extreme environments.

Approaches to a unified theory: Original papers and mini-reviews

Thermodynamic aspects of ATP research are considered in seven papers, *experimental aspects* in four papers, *muscle contraction* in one paper, *models, modeling, mathematical aspects, and applications* in four papers.

2.1 Basis for a unified theory: Major reviews of the current status of ATP research

The first article in this special issue by Victor Wray (2025), "Field guide to Nath's research work on ATP synthesis and hydrolysis" provides a platform for the reader to follow the evolution since the late 1990s of Sunil Nath's publications that culminated in a detailed description of the molecular mechanism of ATP synthesis/hydrolysis in the F_O and F_1 potions of F_OF_1-ATP synthase. The new theory has become known in the literature as Nath's torsional mechanism of energy transduction and ATP synthesis, and Nath's two-ion theory of energy coupling. These, along with Nath's biothermokinetic theory, form one possible unified theory of ATP synthesis/hydrolysis. Biological thermodynamics has been applied to problems in comparative physiology, biochemistry and ecology. Most recently, strict mathematical methods have created new approaches to validate mechanistic events in biological systems. Nath's body of work on ATP (Wray, 2025, Fig. 1) has been regarded as a scientific *tour de force*.

Sunil Nath (2025) in "An account of a century of ATP research" provides a much needed historical review of the developments in the field of ATP research that provides a backcloth for our special issue. These are accompanied by an in-depth discussion of competing research groups that challenge the current dogma of metabolism. The subject matter is divided into five eras from its beginnings in the 1920s up to the current highly technical era. He aims to explain and interpret the cumulative experimental data and checks for consistency of theory with this data. Further, he explores novel explanations that could resolve longstanding molecular issues in muscle contraction, bioenergetics, and transport. The research has important ramifications for the treatment of disease, and applications of the ATP work to the Warburg Effect in cancer cells and to mitochondrial apoptosis and cell death are reviewed.

William D. Ehringer and Kristyn H. Smith's (2025) review "Coupling of the energetic and purinergic activities of ATP in ischemic and hypoxia disease states" covers an area of particular relevance to medical ATP research that complements the theoretical ATP research in the first publication in this special issue (Wray, 2025). The evolution of humans arising from environmental changes has resulted in the complex dependence on oxygen for the maintenance of cellular function. The regulation and consequences of the supply and consumption of ATP under various scenarios arising from ischemia and hypoxia are reviewed.

Brian Tindall (2025) in "Names, classification, structure and function and their inter-relationship to the Q cycle, photosynthesis and ATP synthesis" offers a cautionary tale, from first-hand experience, of the extensive problems biologists face in categorizing microorganisms in relation to structure and function, and in communicating this ever changing information in an orderly fashion to others in diverse fields of research. The review brings into focus three related phenomena: a) the evolutionary origin of mitochondria and chloroplasts, b) lipoquinones, the Q cycle, and photosynthesis, and c) ATP synthesis. In linking these phenomena, we are again reminded of the problems and issues for theoretical treatises on ATP functioning of neutrophilic and alkaliphilic microorganisms.

2.2 Approaches to a unified theory: Original papers and mini-reviews

2.2.1 Thermodynamic aspects of ATP research

Lee D. Hansen and Sunil Nath (2025) in the article "Thermodynamics of Nath's 2-ion model of ATP synthesis" show that earlier thermodynamic studies by one of the authors on the ionization of aliphatic organic acids are compatible with the more recently proposed requirements of a dicarboxylic acid in the 2-ion mechanism of ATP synthesis. Evolutionary considerations suggest that ATP synthesis in prokaryotes evolved in environments devoid of oxygen, which involved catabolic reactions with low enthalpy changes. As a consequence, it follows that ATP synthesis is powered by weak organic acids whose heat of ionization tends to zero, succinate being a prime example. These arguments are elucidated in some detail to convincingly show that ATP synthesis is powered by the potential energy associated with these ion concentration gradients.

Patricio Venegas-Aravena and Enrique G. Cordaro (2025) in their article "The Nath-Luxuriae principles: Unified thermodynamic framework for Molecular assembly and non-ergodicity via ATP synthesis/hydrolysis example," explore the relationship between Nath's thermodynamic principle concerning the constrained maximization of free energy dissipation in specific biological situations and a further principle, the Principium Luxuriae, describing how non-biological, multiscale systems dissipate energy in response to external forces. The work suggests a negative mathematical correlation between the free energy dissipation and the thermodynamic fractal dimension of the latter that satisfies both macroscopic and microscopic system changes. Comparison of the combined principles shows differences from Prigogine's work and suggests a possible application to the thermodynamic evolution of biological systems in the development of life on Earth.

In his article, Yoram Schiffmann (2025) tries to explain "How organisms decrease their entropy" within the framework of the thermodynamics of irreversible processes. He suggests that the condition for entropy reduction and for performing useful biological work arises from the far-from-equilibrium reaction of ATP hydrolysis in metabolism with its fixed, constant reaction affinity/standard free energy change (see Igamberdiev et al. (2024) for key papers that have covered this ground quantitatively). The author considers it a missing link in biology between the molecular and macroscopic levels.

In twin papers on least action in biology, Georgi Y. Georgiev (2025a,b) first develops the theoretical formalism and, in the companion article, explores how the physics-based least action principle can be applied to complex systems. He reviews and compares previous variational principles in nonequilibrium dynamics with his stochastic average action principle. He makes a strong case for the average action efficiency as a physically grounded unifying metric that drives the evolution of biosystems. Self-organization tends to increase the average action efficiency and guide the emergence of chemical reactions in molecular machines—with the F_OF_1-ATP synthase as a test case—and metabolic pathways. The work is important in the search for unifying variational principles in chemistry and biology.

In "A hybrid phase-synchronization framework for rotary motors: Discrete dynamics in ATP synthase and continuous dynamics in the bacterial flagellar motor," Carey Witkov (2025) examines how the mechanically mismatched rotors of ATP synthase maintain phase synchrony under physiological loads. A hybrid phase-synchronization equation is developed in which the elastic stalk acts as an adaptive filter, integrating discrete chemomechanical stepping with continuous torque transmission.

The same framework is extended to the bacterial flagellar motor, where multiple stator units must coordinate their torque pulses with a continuously rotating rotor. This unified approach reproduces essential experimental results and provides new insight into how rotary molecular machines achieve synchronization and efficiency despite structural asymmetry.

Davor Juretić and Branka Bruvo Mađarić (2025), in the article "Scale-invariant dissipation underlies enzyme catalytic performance," report a meta-analysis of a varied collection of literature data of enzyme-catalyzed reactions – primarily soluble enzymes – and find a relationship between total dissipated energy and the phenomenological biochemical kinetic parameters, specifically the catalytic constant and the specificity constant. An intriguing power law correlation is obtained that holds across a wide range of enzyme classes, biological domains, and natural or engineered enzymes. The work offers a unifying view of physical and biological evolutionary processes in the emergence of enzymatic function.

2.2.2 *Experimental aspects of ATP research*

Viktor V. Ivanishchev (2025) in the article "Problematic issues of ATP synthesis *in vivo*" revisits the differences in the nature of the processes that are required in the mitochondrion and chloroplast for the formation of the membrane electrochemical gradients during ATP synthesis *in vivo*. A mathematical flaw in the governing equations of the chemiosmotic theory and its removal by Nath's two-ion theory is discussed. It is concluded that the formation of the chemical gradients occurs only upon collapse of the electrical gradient by counterion translocation. The inverse relationship between the electrical and chemical gradients across the energy-transducing membrane in mitochondria versus chloroplasts is shown to find a ready explanation based on succinate and malate anions within the framework of Nath's two-ion theory.

Vitaly K. Koltover (2025) covers in "Energy transformation and nuclear spin catalysis: from magnetic isotope effects in chemical physics to ATP-dependent molecular motors in bioenergetics" the research, which the author has reported over the last two decades, published mostly in Russian journals, on magnetic isotope effects involving ATP-dependent molecular motors. This fascinating work centres on the rate enhancements observed in experiments monitoring enzymatic ATP hydrolysis of myosin in the presence of cofactors of the magnetic isotopes of magnesium and, more recently, zinc compared to their non-magnetic counterparts. There are a few other such reports in the biological literature and most are associated with rate enhancements of the magnetic ^{25}Mg isotope involved in phosphate group interactions. The data excludes any molecular mass effects on the rate of ATP hydrolysis and indicates that the effects arise purely from the magnetic moments of the atoms involved. Weak magnetic fields are also known to enhance isotope effects, perhaps suggesting the geomagnetic field of Earth plays such a role, as well as the overlap of the magnetic fields associated with other nuclear spins (^{31}P and ^{1}H) in the rate-limiting transition state.

In his paper, Gabi Drochioiu (2025a) has proposed a "Reinterpretation of Jagendorf's classic experiment on photophosphorylation" from the 1960s. The experiment was originally designed to confirm the chemiosmotic theory and proposed that the pH gradient is the driving force for ATP synthesis in plant chloroplasts. However, Drochioiu points out that this was a misinterpretation, and careful examination of Jagendorf's data shows that the driver of ATP synthesis was not ΔpH, but rather the "degradation of organic acids". The extracted data in their Table 1 shows that the maximum ATP yields by far were obtained with succinic acid as the incubation acid. The two-ion theory of energy coupling and the torsional mechanism of ATP synthesis are discussed as a viable alternative theory that is consistent with the cumulative photophosphorylation data of Jagendorf and colleagues.

In a second paper, a short communication, Drochioiu (2025b) considers bacteriorhodopsin of *Halobacterium salinarum* cells and the associated ATP synthesis by F_OF_1-ATP synthase, and especially the M_{412} amino acid intermediate and its transition to L_{550}/N_{560} in the cycle. The difference in infrared radiation energy of the transition of ~70 kJ/mol is considered sufficient to release bound ATP from the ATP synthase. However, the mechanism of how IR energy can release ATP from its binding site in a different complex remains to be elucidated.

2.2.3 Muscle contraction

Rama Krishna K., in his article "Kinematic linkage models of muscle contraction: A mechanical engineering perspective," compares the classical swinging lever arm (SLAM) and rotation-uncoiling-tilt (RUT) energy storage models of muscle contraction. It is shown that the primary drive, the distal effects, and the fulcrum of the power stroke are different in the two models (Wray, 2025). A novel 2D kinematic linkage model and mechanical perspective is employed to test which model reproduces the experimentally observed step size on actin.

2.2.4 Models, modeling, mathematical aspects, and applications

B. Vibishan, Mohit K. Jolly, and Akshit Goyal (2025) in the mini-review "Balancing the cellular budget: Lessons in metabolism from microbes to cancer" describe, using an extensive literature base, how cancer cell and microbial cell metabolism may undergo parallel shifts in resource allocation to optimize growth. Adaptation of the methodology and conceptual framework of resource allocation used in microbial contexts are then considered as an initial step for considering similar questions about metabolic states in cancer and their phenotypes.

Hirdesh Rohatgi (2025), in his article "The role of pure mathematics in resolving complex biological problems: Applications, achievements and future direction," proposes that pure mathematics should be a key component in addressing complex molecular-level problems in biological research. Various shortcomings in non-mathematical approaches are identified and commented upon. As an example of a real situation, the varied mathematical approaches used by Nath in his analysis of the molecular mechanism of ATP synthase that enables the choice between the 2-site binding change mechanism and the 3-site torsional mechanism in F_1-ATPase is highlighted. The section on economic losses in flawed and wasteful research is especially interesting and a mathematical framework to advance biological discovery is proposed.

Dhruba J. Mech and M. Suhail Rizvi (2025), in their article "Modeling the role of ATP metabolism in articular cartilage and osteoarthritis," offer a novel approach to explore the cross-talk between chondrocyte metabolism and the extracellular matrix of articular cartilage as well as its implications for osteoarthritis pathophysiology. Central to this process in the model is the role of ATP metabolism in chondrocytes regulated through a bistable switching between glycolysis and oxidative phosphorylation in response to various physiological factors. Simulations of stochastic fluctuations in oxygen and glucose levels successfully mimic the physiological conditions during mechanical loading, and their impact on articular cartilage dynamics. The consequences for therapeutic approaches are considered.

Sungchul Ji (2025), in his article "Chemiosmotic vs. conformational models of oxidative phosphorylation: Theory and mechanistic insights", carries out an in-depth analysis of oxidative phosphorylation mechanisms, Ji claims it has long been recognized that chemiosmotic theory alone is insufficient as it lacks a detailed molecular mechanism of ion gradient generation and coupling to ATP formation. The conformon model proposes that oxidative phosphorylation is powered by discrete packets of conformational energy—generated and transferred according to a generalized Franck–Condon principle—that couple electron transport to ATP synthesis. Ji analyzes logical errors in dismissing conformational change-based models in favor of chemiosmosis alone. Citing recent findings, he concludes that "non-chemiosmotic mechanisms such as the conformon or detailed conformational change-mediated mechanisms, such as Nath's torsional mechanism of energy transduction and ATP synthesis, are needed to explain the phenomenon of oxidative phosphorylation in enzymologically and quantum-mechanically realistic terms."

Our original intention of the special issue was to identify, as far as possible, the many biological interfaces through which ATP participates and to examine these from a variety of perspectives and approaches. Although several gaps remain in this endeavor, we believe that we have been successful in covering a fairly large area of current research through a number of reviews and original contributions.

References

Drochioiu, G., 2025a. Reinterpretation of Jagendorf's classical experiment on photophosphorylation. Biosystems 257, 105614. https://doi.org/10.1016/j.biosystems.2025.105614

Drochioiu, G., 2025b. Light-induced ATP production and proton translocation, two independent phenomena in *Halobacterium salinarum* archaea cells. Biosystems 258, 105633. https://doi.org/10.1016/j.biosystems.2025.105633

Ehringer, W. D., Smith, K. H., 2025. Coupling of the energetic and purinergic activities of ATP in ischemic and hypoxic disease states. Biosystems 255, 105544. https://doi.org/10.1016/j.biosystems.2025.105544

Georgiev, G. Y., 2026a. Stochastic–dissipative least-action framework for self-organizing biological systems. Part I: Variational rationale and Lyapunov-type behavior. Biosystems 259, xxxxxx. https://doi.org/10.1016/j.biosystems.2025.xxxxxx

Georgiev, G. Y., 2026b. Stochastic–dissipative least-action framework for self-organizing biological systems. Part II: Empirical estimation, average action efficiency, and applications to ATP synthase. Biosystems 259, xxxxxx. https://doi.org/10.1016/j.biosystems.2025.xxxxxx

Hansen, L. D., Nath, S., 2025. Thermodynamics of Nath's 2-ion model of ATP synthesis. Biosystems 254, 105505. https://doi.org/10.1016/j.biosystems.2025.105505

Igamberdiev, A. U., Müller, M., Elek, G., Mikhailovsky, G. E., Cottam, R., 2024. Biological thermodynamics: Bridging the gap between physics and life. Biosystems 242, 105258. https://doi.org/10.1016/j.biosystems.2024.105258

Ivanishchev, V. V., 2025. Problematic issues of ATP synthesis *in vivo*. Biosystems 254, 105493. https://doi.org/10.1016/j.biosystems.2025.105493

Ji, S., 2026. Chemiosmotic vs conformational models of oxidative phosphorylation: Theory and mechanistic insights. Biosystems 259, 105637. https://doi.org/10.1016/j.biosystems.2025.105637

Juretić, D., Mađarić, B. B., 2025. Scale-invariant dissipation underlies enzyme catalytic performance. Biosystems 258, 105568. https://doi.org/10.1016/j.biosystems.2025.105568

Koltover, V. K., 2026. Energy transformation and nuclear spin catalysis: from magnetic isotope effects in chemical physics to ATP-dependent molecular motors in bioenergetics. Biosystems 259, 105657. https://doi.org/10.1016/j.biosystems.2025.105657

Mech, D. J., Rizvi, M. S., 2025. Modeling the role of ATP metabolism in articular cartilage and osteoarthritis. Biosystems 257, 105597. https://doi.org/10.1016/j.biosystems.2025.105597

Nath, S., 2025. An account of a century of ATP research. Biosystems 256, 105527. https://doi.org/10.1016/j.biosystems.2025.105527

Rama Krishna, K., 2026. Kinematic linkage models of muscle contraction: A mechanical engineering perspective. Biosystems 259, 105658. https://doi.org/10.1016/j.biosystems.2025.105658

Rohatgi, H., 2025. The role of pure mathematics in resolving complex biological problems: Applications to F_1-ATPase, achievements and future directions. Biosystems 257, 105575. https://doi.org/10.1016/j.biosystems.2025.105575

Schiffmann, Y., 2025. How organisms decrease their entropy. Biosystems 257, 105592. https://doi.org/10.1016/j.biosystems.2025.105592

Tindall, B., 2025. Names, classification, structure and function and their inter-relationship to the Q cycle, photosynthesis and ATP synthesis. Biosystems 258, 105607. https://doi.org/10.1016/j.biosystems.2025.105607

Venegas-Aravena, P., Cordaro, E. G., 2025. The Nath-Luxuriae principles: Unified thermodynamic framework for Molecular assembly and non-ergodicity via ATP synthesis/hydrolysis example. Biosystems 253, 105481. https://doi.org/10.1016/j.biosystems.2025.105481

Vibishan, B., Jolly, M. K., Goyal, A., 2025. Balancing the cellular budget: lessons in metabolism from microbes to cancer. Biosystems 256, 105571. https://doi.org/10.1016/j.biosystems.2025.105571

Witkov, C. 2025. A hybrid phase-synchronization framework for rotary motors: Discrete dynamics in ATP synthase and continuous dynamics in the bacterial flagella motor. Biosystems 258, 105617. https://doi.org/10.1016/j.biosystems.2025.105617

Wray, V., 2025. Field guide to Nath's research work on ATP synthesis and hydrolysis. Biosystems 252, 105461. https://doi.org/10.1016/j.biosystems.2025.105461

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