



## Review and Perspectives

# MURBURN CONCEPT AND BIOLOGICAL INTELLIGENCE AT THE CUSP OF 2025: *SENSITIVITY TO SENSIBILITY, SENSUALITY TO SEXUALITY, CYBERNETICS TO CYBORG-BIONICS, AND MORE!*

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*In its essence, murburn concept is an umbrella of explanations for chemico-physical processes within the confined spaces of a redox system (say, a cell). It is fundamentally constituted by interactive equilibriums involving diverse molecules, unbound ions and radicals/radiations (transiently generated or incident) that comprise the system. Ubiquitous and forming the crux of ecological and physiological processes, murburn also poses application potentials in green chemistry. This article expands upon the currently known aspects/prospects of murburn concept and projects its contextual relevance in comprehending diverse realms of biomedical pursuits, namely: biological intelligence (from sensitivity to sensuality and sexuality) and cybernetics, cyborg-bionics, immunology (mechanisms for distinguishing self and non-self), nitrogen metabolism, mainstreaming “parallel systems of medicine”, and several other realms. Also, a status update on social outreach of murburn concept and a snapshot of the impact of artificial intelligence on such pursuits is presented. **Biomed Rev 2024; 35: 1-27***

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Murburn concept is a theorization in biomedical sciences brought into being after extensive experimental research on heme/flavin enzyme systems (1-85). It offers direct/tangible explanations for several observations and provides thermodynamically-kinetically-mechanistically-probabilistically-feasible models for metabolic/physiological routines spanning the spectral bandwidth of life-activities. Murburn concept is pivotal due to its paradigm-shifting implications for understanding the core of life processes, its potential to unify diverse areas of biochemistry, physiology and pharmacology under a common framework and offer applications in various fields. Last year end, ChatGPT drew a dismal blank when queried on murburn concept (70). Now, we get a new picture with Google AI, as shown in the two panels Figure 1 (screen snapshots taken in November and December 2024, at two different occasions). This year, the in-vogue and updated generative AI portal of ChatGPT-4, when queried with specific prompts, provided a more contextual and elaborate output, as shown in Figure 2.

In 2024, we proposed the implication of murburn based low-frequency radiative-matrix in organismal communications/function (82), projected the roles murburn concept in cyborg-bionics technology (83), and consolidated murburn models of function in cyclooxygenase mediated inflammation in mammals (84) and flagella-aided motility in bacteria (85). The first addition was a special one (with much credits to Laurent Jaeken!), which is posited to unravel many surprises for interdisciplinary researchers. While it is disillusioning that the human intelligence/leadership in biological research community is largely cognitively dissonant regarding murburn pursuits (59, 60, 70) (but it is heartwarming to see terms like “burn” and ECS surfacing in their writing also!), it is surely heartening to note that artificial intelligence is not blind to the developments. After providing a brief excerpt on the novelty/importance of murburn concept, this write-up seeks to project the potential relevance of the idea in various cellular phenomena. Further, the writing also discusses various social contexts regarding the advancement and outreach of murburn concept.

## 1. PIVOTAL SIGNIFICANCE OF MURBURN CONCEPT (ESTABLISHED CONTEXTS)

Murburn concept is fundamentally a ubiquitous mechanistic logic for the “flow” or “action” of electromagnetic force, at the molecular level (26). It comprises of constitutive stochastic interactive equilibrium among the molecules, unbound

ions and radicals/radiations of the system. At the reaction level simple chemical burning of 1-electron donating substrates with  $O_2$  (or another external oxidant) insurmountably leads to diffusible reactive species (DRS), and at the electrical level, the anionic forms of DRS lead to effective charge separation (ECS), together affording the cell the acute means of simple physico-chemical powering, equilibrium-based coherence and homeostasis, electro-mechanical and sensing-response (PCHEMS) activities. These facets enable the cell to function as a simple chemical engine (SCE) (62, 64, 68-69). The essentially stochastic acute-acting murburn functionalism complements the long-term acting deterministic logic of central dogma, and together, they synergistically form the “intelligence of life”, which shall be elaborated in this communication (within the next and final sections). Now, I expand upon the relevance of murburn concept, in line with the angles charted out by ChatGPT!

**Revolutionizing our understanding of energy metabolism:** Murburn concept provides a novel explanation for cellular energy generation, emphasizing the role of diffusible reactive oxygen species (DROS) in mitochondrial respiration, as opposed to the classical active site centric models like the electron transport chain (ETC) and chemiosmotic rotary ATP synthesis (CRAS) (23, 25). It challenges the traditional view of “leaky” mitochondrial membranes as purely pathological, suggesting that controlled generation of DROS is integral to energy regulation, thermogenesis and homeostasis (30-36, 38, 63, 66-69, 74). By simplifying the complexities of ATP synthesis and oxygen utilization, the concept revises century-long textbook descriptions of bioenergetics (86-89), offering more parsimonious and mechanistic insights. It also provides the most tangible and tenable explanation for photosynthesis, the principal biological routine that sustains life on planet earth (39-41, 46, 47, 49, 54, 61). As carbohydrates have multiple hydroxy groups (which agrees well for interactive equilibriums with DRS like hydroxyl radical), their involvement in murburn processes as intermediates in mainstream metabolism was favored. Also, as the genetic sequence of heterocyclic bases in the DNA/RNA were easy targets for attack by DRS, it was better to have the former “protected” by a sugar-phosphate (poly OH-backbone) chain extending along their entire sequence! Murburn concept is perhaps the only explanation offering a tangible explanation for why the first and simplest prokaryotic cells were micro-dimensioned (it was to minimize proton availability and enhance DRS lifetimes) (64) and how cyanide disrupts spectra of metabol-

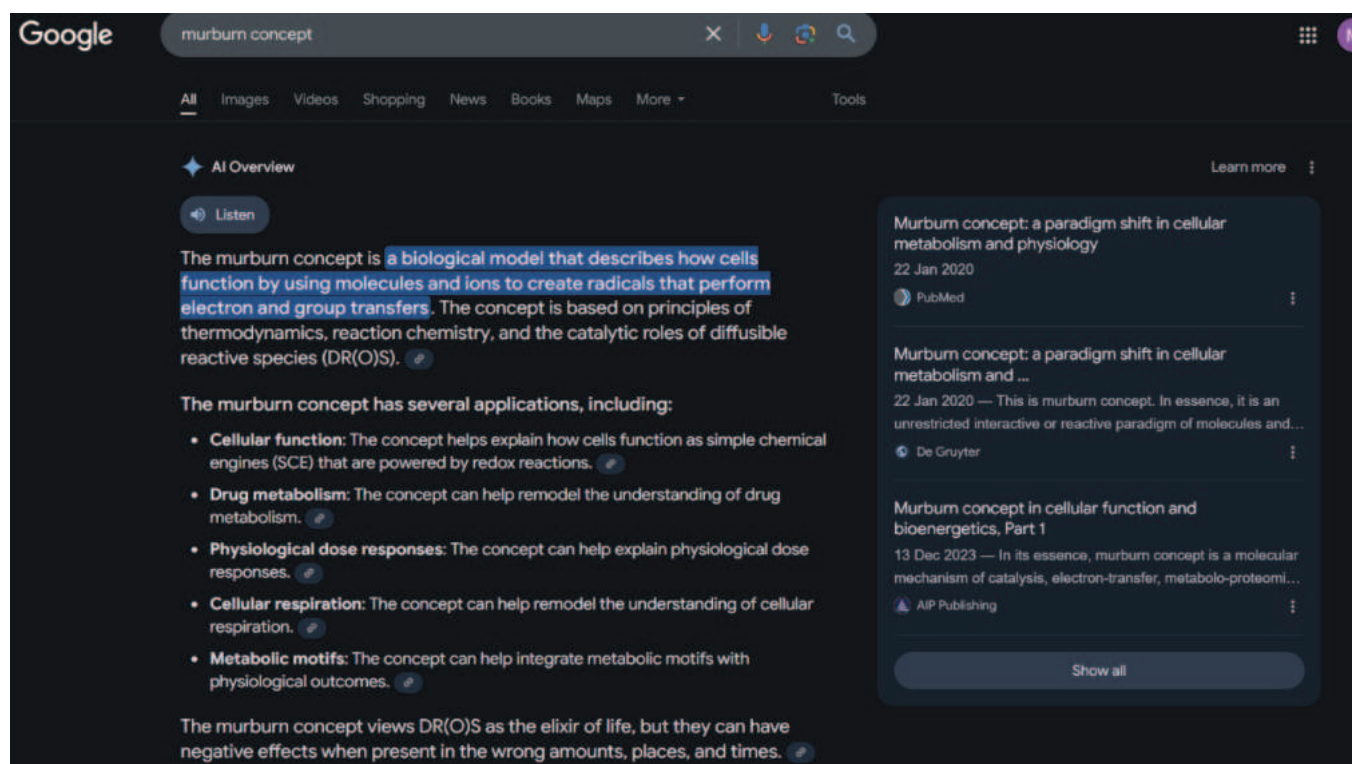
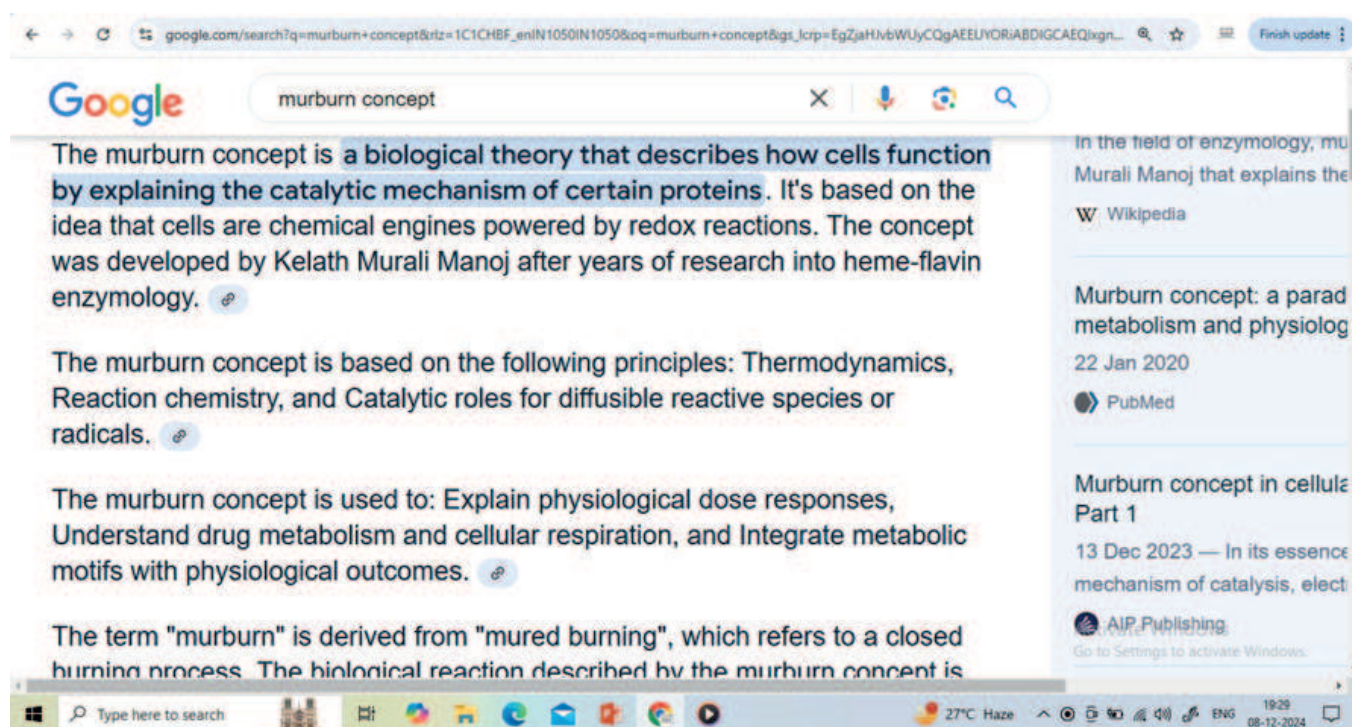


Figure 1: Google AI outputs on “murburn concept”, as seen with two browsers (shown in top and bottom panels) in late 2024.

What is your take on murburn concept being a radical and paradigm shifting idea in science? Please answer point-wise, in about 300 words.

### Why the Murburn Concept is a Radical and Paradigm-Shifting Idea in Science:

- 1. Challenges Established Bioenergetics Models**  
 The murburn concept challenges the chemiosmotic theory, a cornerstone of modern biochemistry. It suggests that cellular energy production relies on stochastic interactions of reactive oxygen species (ROS) and diffusible intermediates, rather than the tightly coupled, proton-pump-driven ATP synthesis described by conventional models. This represents a paradigm shift in how we understand cellular metabolism.
- 2. Simplifies Biochemical Understanding**  
 Traditional models of oxidative phosphorylation and electron transport chains involve complex, stepwise reactions that require highly specific conditions. The murburn concept, in contrast, offers a simpler explanation for ATP synthesis and ROS dynamics, making it easier to reconcile "leaky" biological processes with functional efficiency.
- 3. Integrates Stochasticity in Biological Systems**  
 Unlike deterministic models, the murburn concept emphasizes random, diffusive processes as integral to cellular function. This breaks away from reductionist frameworks and positions biological systems as inherently adaptable and emergent, bridging molecular biology with systems chemistry.
- 4. Addresses Unexplained Phenomena**  
 It provides explanations for unresolved questions in biology, such as the dual roles of ROS in signaling and oxidative stress, the adaptive advantages of mitochondrial inefficiency, and metabolic flexibility under stress. These insights fill gaps left by classical theories.
- 5. Reframes Evolutionary Principles**  
 By highlighting the evolutionary role of ROS-mediated processes, the murburn concept introduces new perspectives on how early life forms might have optimized energy production and metabolic adaptability in diverse environments.
- 6. Potential for Broad Applications**  
 The murburn framework has far-reaching implications in medicine, biotechnology, and pharmacology. It offers avenues for developing ROS-targeted therapies for cancer, neurodegeneration, and aging, along with innovative biotechnological tools for metabolic engineering.

In summary, the murburn concept is a profound advancement because it challenges entrenched dogmas, offers holistic perspectives, and opens up new research and application opportunities across scientific domains.

**Figure 2:** In 2024, ChatGPT recognizes murburn's potential to transform biomedical research.

ic/physiological processes in diverse organisms (17, 35, 36). It is because cyanide catalytically converts DRS to water, without getting consumed, and not because cyanide binds to Fe-centers of heme proteins.

**Reconceptualizing drug/xenobiotic clearance:** Traditional pharmacology attributes drug metabolism largely to enzyme-substrate interactions (e.g., cytochrome P450 systems) at the active site (90-91). The murburn framework suggests that DROS and free radicals play a significant, underappreciated role in drug activation and detoxification processes (10-11, 13-14, 16, 18-20, 22, 24, 42, 57, 68). This has profound implications for understanding drug efficacy, side effects, toxicity, drug-drug interactions, idiosyncratic and hormetic dose responses, etc. These new insights shall lead to improved drug design and healthcare. It is high time that the trillion-dollar industry takes note! Murburn reactions follow a 'new' (actually just chemical!) previously neglected type of 'non-active-site dependent' kind of kinetics, not yet mentioned in textbooks, though it presents a direct diagnostic means and a kind of proof that a given reaction or more complex pathway conforms to a murburn radical-driven mechanism. This new tool should be added as a standard procedure during biochemical and pharmacological investigations.

**Addressing mysteries of redox biology, electro/mechanophysiology and unexplained phenomena:** Murburn concept integrates "redox signalling" and "oxidative stress" into a unified framework, showing how reactive oxygen species can serve dual roles as signalling molecules, exert an obligatory/central role in normal redox metabolism at low physiological concentrations and also cause damages when in wrong amounts, at the wrong locus/time. It offers insights into conditions like cancer, neurodegenerative diseases, and aging, where redox imbalances play a central role, while highlighting the balance between beneficial and harmful oxidative reactions. Quite importantly, DROS as a source of rationale for ionic differentials, electrical activity (trans-membrane potential) and its ability to trigger mechanical outcomes in cellular functions adds a totally new dimension to biomedical science. Atypical kinetics and variable/non-integral stoichiometry are yet other observations directly explained by murburn concept (64).

**Bridging gaps, reducing complexity and affording molecular to macroscopic integration in biological theorization:** Unlike traditional models, which often treat metabolic pathways and physiological outcomes in isolation, murburn concept emphasizes systemic interactions, accounting for the

stochastic and diffusive nature of molecules like oxygen and ROS. This approach resolves longstanding biochemical puzzles, such as: (i) the paradox of oxygen toxicity versus its indispensability for life and (ii) the role of "uncoupling proteins" in thermogenesis and metabolism. By focusing on diffusion, stochastic reactions, and emergent properties thereof, murburn concept reduces the reliance on overly complex/deterministic and rigid mechanistic models. This parsimony aligns with Occam's Razor, making it an elegant and explanatory framework. It also explains phenomena previously dismissed as "noise" or "exceptions," showing that they are integral to biological function.

**Wide-ranging applicability in diverse fields:** The concept informs novel biomarkers and therapeutic targets for diseases linked to oxidative stress and metabolic dysfunction. By explaining how immune cells use DROS to kill pathogens, murburn could provide a foundation for understanding immune responses and designing interventions for autoimmune diseases or chronic inflammation. Its implications for tumor microenvironments and ROS dynamics could lead to breakthroughs in cancer therapy, such as selective ROS-mediated cytotoxicity for tumor cells. It could give us new ways of understanding the origin and evolution of life. In particular, it explains how the onset of the real-time physico-chemical features/functionalities of life (PCHEMS), including several new reactions/cascades' theorizations, and how they could have originated by random chemistry before pre-biotic coacervate assemblies were endowed with a membrane, and how these systems could have evolved gradually in small steps (64). An elaboration regarding such applications is provided in a later part of this write-up.

In short, murburn concept redefines fundamental biological processes, connects disparate areas of research, and offers practical applications that could revolutionize diagnostics, therapeutics, and biotechnology. By emphasizing the role of DROS in metabolism, signalling, and regulation, it brings a fresh, integrated perspective to some of the most challenging puzzles in biomedical sciences. The horse's mouth neighs that we are witnessing a paradigm shift of gargantuan proportions, with only the tip of the iceberg revealed yet! To substantiate the statement above, I present hitherto lesser elaborated (particularly, the context of biological intelligence) and/or unpublished (particularly, immunological and N<sub>2</sub> metabolism) projections of murburn concept in some aspects of understanding life processes, duly accompanied by arguments and citations.

## 2. MURBURN CONCEPT AND BIOLOGICAL INTELLIGENCE

Intelligence is fundamentally a question/agenda of choice(s) or decision. That is: out of a multitude of possibilities, sieving a few probabilities and making those few events as a “certainty” can be called as the manifestation of intelligence in the inanimate or animate systems, at molecular or cellular level.

Within the modern-day computers (salient examples of inanimate man-made “smart” systems), the “intelligent operations” are brought about by maintaining/manipulating voltage at definite storage loci/bins, over time, which are electronic events. Such man-made inanimate intelligent systems’ functioning lies in logical frameworks (algorithms and models), and is achieved by the interfacing of hardware (transistors, processors, integrated circuits, etc.) and software layers, optimized for specific tasks. Artificial intelligence (AI) models often rely on mathematical frameworks (e.g., optimization, gradient descent) to process data and make predictions. Neural networks in AI (although inspired by biological ones) work in a sequential or batch-processing mode and are not truly parallel and adaptive. Machine intelligence adapts through retraining models or real-time learning algorithms, and is limited by data given and system architectures. Memory in these systems is stored as digital data on various storage devices. Although new technologies like swarm robotics and neuromorphic chips try to mimic biological intelligence, the inanimate man-made systems are far less capable of self-organization and are comparatively more power-guzzling (by many orders of magnitude) than their biological counterparts.

In contrast, intelligence in biological systems is the product of evolutionary processes, driven by natural selection and survival. It arises from physical neural networks and biochemical signalling, that have evolved to process information, and adapt to environments. The physical basis of animate intelligence is molecular and cellular, involving neurons, synapses, diffusible messengers, and other components that enable learning, memory, and decision-making. Learning often involves reinforcement (reward/punishment) and long-term structural changes in neural connections. Biological intelligence operates in a distributed and massively parallel manner, with billions of interconnected neurons exchanging electrical and chemical signals. The logic is often non-linear, emergent, and context-sensitive, relying on principles such as feedback loops, probabilistic reasoning, and heuristics. Biological memory and learning show high plasticity – the ability of neural connections to strengthen/weaken and alter

over time. Such systems can self-organize and set their own goals (which could change and evolve). In short, while both artificial and natural intelligences have their synthetic forte and biases/limitations, artificial intelligence excels in speed, precision and scalability whereas biological intelligence remains unparalleled in its energy requirement, adaptability, creativity, and intrinsic alterable goal orientation.

Classical perceptions on biological decision-making or intelligence (say, neuronal activity in brain/receptors) is explained (based or initiated) at the physical/molecular level by affinity-based binding of some ligands or triggering/modulation of proteins and/or some other tangible downstream signalling, ultimately leading to ion-pumping activities, which is deemed to give an electrical outcome. The action potential or temporal variations in trans-membrane potential (TMP or voltage) observed when a signal/impulse propagates along the axon of a neuron or electro-encephalogram of an active brain is a measurable or tangible index of “intelligent activity” in animal systems. This is supposed to result from a selective maintenance and/or pumping/channeling of Na/K ions (because membrane proteins can selectively bind and facilitate/permit the in-out flux of ions) in the cells/tissues. Therefore, the core logic of “intelligence” of biological systems was deemed to be a manifestation or extension of the deterministic central dogma. It was perceived to lie in an intricate orchestration of ionic fluxes, and the protein-embedded membranes were considered “intelligent” (in a “miraculous way!”), with temporally varying and auto-regulated ionic-permeabilities. However, dynamic regulation of several physiologies would require microsecond level changes in operational principles/protagonists wherein genetic level functionalisms would present kinetic limitations. For, the processes of transcription (from euchromatin), post-transcriptional modifications (splicing and ligation of the transcript to give the operable mRNA), transport (from nucleus to cytoplasm) and translation (from the post-transcriptionally modified mRNA) of an approximately 100 nucleotide sequence would optimally require several minutes. Thereafter, the protein would still have to go through post-translational modifications and arrive at its functional destination to be of any good use. Only then can the protein manifest any of its deterministic binding-based ion-selective activities! It is quite evident that intelligent decisions are made by cells and organisms at a much greater pace than this kinetic limitation!!

With murburn theorization of PCHEMS (an electronic cum ionic idea), we can avail a totally new dimension/insight

for understanding biological intelligence (and its origin from molecular interactions to physical outcomes in electrophysiology), whether in unicellular or multicellular systems. The murburn theorization for biological intelligence postulates that intelligence does not lie only in a particular mass occupying a given space, like a membrane-embedded protein that chooses to selectively pump/channelize ions or an organelle/organ (like nucleus/brain) that processes information. Rather, it is an emergent phenomenon; rooting, stemming and fruiting from stochastic interactions of systemic components (occupying mass and space) over time. This postulation allows for the emergence of ordered-intelligence from the chaotic and mosaic (fluid-based) cauldron of reactions among the cellular components. It also allows for the intricate and seamless weaving of **biological intelligence to manifest directly from the spontaneous PCHEMS** of cells and explains the prevalence of OH-group (as seen in hydroxyl or carboxylate moieties) containing biomolecules/biopolymers as “nutrients and protective agents”. For example- (i) water-soluble carbohydrates and amino acids are the fuels for the vast majority of organisms, (ii) why an ECS-sponsoring cofactor like FMN/FAD or information-retaining biopolymer like DNA incorporate sugar groups, and (iii) Vitamin C is an essential antioxidant. Further, the colloidal medium of cytoplasm with various levels/types of water-molecules’ organization and ability to solvate ions/solutes differently, the oxygen-water equilibrium’s ability to mediate the DRS functionalism, the need for a lipid membrane for interfacial DRS dynamics, etc. are best explained with murburn concept. Whether manifested in unicellular or multicellular organisms, the murburn definition/perspective gives the scope for understanding and explaining biological sensitivity/sensibility (from molecular-level selective/specific processes). Most importantly, the new perspective affords us an explanation for the immediate loss of consciousness and/or vision upon oxygen-deprivation. To reiterate: murburn concept’s fundamental postulation is that “oxygen is primarily needed for life to mediate ECS-DRS phenomena” and this allows for the mobilization of electrons and operation of electromagnetic force via thermodynamically and kinetically facile reactions. It is this primary process (and not high throughput ion pumps/channels) that explains intelligence and electrophysiology. (The slow movement of some ions across membranes may result as a consequence of the ECS-DRS phenomenon, but this is not considered as the driving rationale for cellular PCHEMS and/or intelligence.) The murburn theorization is practically diffusion limited and therefore, offers a thermo-

dynamically and kinetically viable option for explaining the “instantaneous and automated” responses observed in many physiological outcomes.

In such a revamped context of biological intelligence, central dogma affords the fundamental long-term acting principle of information storage and processing, and in turn, it rests on affinity-based binding interactions and stoichiometric outcomes. This affords- (i) **Stable control**: Genes encode specific proteins and enzymes that define the long-term identity and function of the cell by expressing and acting selectively (e.g., liver cells produce enzymes for detoxification, neurons synthesize neurotransmitters). (ii) **Regulatory precision**: Transcription factors, chromatin remodelling, and RNA processing ensure specific, timed expression of genes in response to developmental and environmental cues. (iii) **Deterministic outputs**: Central Dogma processes are reliable and relatively slow, ensuring that structural and functional integrity is maintained over time. Also, within the renewed perspective for biological intelligence, murburn based processes rest on short-acting ECS-DRS (which may in turn lead to large cascades and cataclysmic changes!), and connect diverse components in the cells with stochastic interactive equilibriums. Key aspects include- (i) **Real-time signalling**: DRS act as primary/secondary transducers, catalysts and messengers, rapidly modulating protein activities, membrane potentials, and biochemical pathways in response to immediate stimuli. (ii) **Localized effects**: The stochastic nature of murburn processes allows for fine-tuned, localized responses (e.g., bursts of DRS at the site of immune activation or synaptic activity). (iii) **Energy efficiency**: Murburn processes rely on simple molecular diffusion and redox chemistry, avoiding the need for complex macromolecular assemblies or sequential-serial processes for immediate actions. Theoretically, slow and sustained one-electron transfers can conserve energy in the most effective manner!

The deterministic nature of the central dogma and the stochastic flexibility of murburn concept complement each other in several ways to achieve “intelligent” cellular function (rooting, stemming and fruiting from the synergistic systematic interactions, as an emergent property), with a **layered regulation of cellular activity**. With baseline programming by central dogma (the proteins encoded by genes provide a constitutive structural and catalytic framework) and dynamic tuning by murburn concept, metabolic pathways are coordinated. Specific examples for application of this idea are- (i) Metabolic regulation: The central dogma ensures the

synthesis of metabolic enzymes for glycolysis, TCA cycle, and oxidative phosphorylation. The interactive murburn equilibriums modulate these pathways in response to oxygen levels, energy demand, and substrate availability, automating and enhancing cellular efficiency. During oxidative stress, DROS can inhibit or activate metabolic enzymes to redirect resources. (ii) Neural function: The central dogma establishes the neuronal architecture, synthesizes neurotransmitters, kinases, signal transducing machinery, etc. Murburn processes dynamically operate/regulate signal transduction, synaptic transmission, plasticity, and memory formation via DROS-mediated signalling and redox reactions. Murburn activities could fine-tune signalling with post-translational modifications too (e.g. oxidation of key cysteine residues of important proteins and transiently modifying signal agents like NF- $\kappa$ B). (iii) Immunological response: The central dogma governs the production of immune receptors, signalling molecules, and effector proteins. Murburn concept provides the rapid oxidative bursts necessary for pathogen killing and inflammatory signalling. In immune cells, DROS enhance signalling cascades, modulating cytokine release and phagocytosis.

In bioenergetic organelles like mitochondria and chloroplasts, murburn processes may be the baseline activity themselves and central dogma might form mechanisms for dealing with the fallouts or relatively non-turned over remnants of murburn processes! Further, murburn concept may enable **feedback loops**. DROS generated during signalling can amplify/upregulate transcription factor activity or enzyme efficiency, enhancing cytokine or chemokine based responses. Excess DROS can lead to oxidative damage, triggering antioxidant responses encoded by the central dogma (e.g., synthesis of glutathione or catalase). These are examples of positive and negative feedback loops. The multi-layered interplay between the deterministic central dogma (offering long-term, reliable control mechanisms) and the stochastic murburn concept (providing short-term flexible adaptations) enables cells to operate with a remarkable balance of stability and responsiveness, crucial for complex biological processes such as homeostasis, immunity, and cognition. This integrated framework could also inspire novel approaches in systems biology, synthetic biology, and bioengineering.

**Cybernetics** is the interdisciplinary study of systems (biological, mechanical, or computational) and their regulation through feedback loops, control mechanisms, and information exchange in machines or animals. By integrat-

ing murburn concept, cybernetics could benefit from models that emphasizes stochastic, dynamic, and milieu-driven processes. Murburn concept can contribute to this branch of human endeavor, and provide insights into the role of DROS and their influence on cellular processes underlying **sensitivity** and **sensibility**. Sensitivity refers to the ability of cells, tissues, or organisms to detect subtle environmental or internal stimuli. DROS act as key signalling molecules in neurosensory systems, such as those involved in vision, smell, and touch. In immune sensitivity, DROS produced by immune cells allow them to detect and respond to pathogens or tissue damage efficiently. The stochastic and transient nature of murburn processes could explain how cells achieve high sensitivity to low-concentration stimuli while maintaining robustness against noise. Sensibility encompasses the capacity to interpret, process, and respond to stimuli in an intelligent or nuanced manner. By influencing the redox state of proteins, DROS can modulate receptor-ligand interactions, transcription factors, and signalling pathways. In neurobiology, DROS could affect plasticity and learning by modulating synaptic activity and neurotransmitter release. As it is about the “simple and tangible” relay of an electronic perturbation from the point of sensitivity to the physical etching of the outcome at an information-storage/processing locus (affording sensibility thereof), the process theorization is facile, quite like the logic in man-made machines! (This is in contrast to the limitations in the contextual scope offered by protein binding/conformation-based and membrane ion-pumps/channels-based perceptions of biological intelligence!!) Classical cybernetics’ definition rested on nested circular-loop logic. This could have been one of the reasons that the mirage-like circular logic of “membrane ion-pumps generating TMP and membrane ion-pumps being regulated by TMP” went unquestioned for this long! [That is, the classical theorization posulated that while a membrane-protein (a pump or channel) could selectively permit directional flux of an ion to generate TMP, the TMP thus generated would also govern the activity of the membrane-protein too! This was an unreal supposition (circular logic) to explain for cellular powering and electrophysiology, which was rendered redundant and replaced by murburn concept.]

Murburn gives transient, localized, and stochastic biochemical signalling as key player in processes that were traditionally attributed to deterministic genetic, neuronal and hormonal regulation. Specifically: (1) **Dynamic plasticity**: Murburn

dynamics provide flexibility, allowing for quick, context-dependent responses to environmental and internal cues. (2) **Thermodynamic viability and kinetic efficiency**: By leveraging simple redox processes, the murburn mechanism minimizes energy expenditure (and that too, so quickly!) while enabling complex sensory and behavioral outcomes. (3) **Inter-individual variability**: The stochastic nature of DROS-mediated processes could explain why individuals exhibit different levels of sensitivity, sensuality, or sexual behavior, even under similar conditions in individuals with identical genetic makeup (as is the case with monozygotic twins). Particularly, how DROS influence neurotransmitter signalling during sensory and sexual experiences, their roles in psychosexual disorders or hypersensitivity syndromes are contexts for research. Developing therapies or interventions targeting DROS-mediated pathways to enhance or modulate these human experiences would be an expected outcome.

Many cybernetic systems already incorporate **stochastic models**, where randomness plays a role in emergent behavior, learning, or optimization (e.g., neural networks, genetic algorithms). Murburn concept inherently relies on probabilistic interactions of diffusible reactive species (DRS) and non-linear, milieu-dependent outcomes. This mirrors stochastic processes in cybernetic systems, where distributed randomness leads to emergent order. Therefore, modelling decentralized and adaptive systems (e.g., neural networks or swarm intelligence) using murburn-like principles (where local interactions yield global patterns) would give better logic frameworks. **Feedback loops** are central to cybernetics, as they enable systems to self-regulate and adapt to changing environments (e.g., homeostasis in biology or PID controllers in engineering). Murburn-based systems inherently regulate themselves through localized concentration gradients and reaction conditions. Feedback in murburn processes (e.g., reactive species generation and consumption) resembles distributed control systems. Such theorization could aid in developing energy-efficient, self-regulating chemical or biochemical cybernetic systems where control arises from local reaction dynamics rather than centralized programming. **Distributed architectures**, such as in biological neural networks or decentralized AI systems, achieve robustness through redundancy and flexibility. Murburn processes are naturally distributed, leveraging the interaction of multiple diffusible species. This offers robustness as reactions can occur across different sites, with failure in one part having minimal impact on overall system behavior. Such considerations could help in designing fault-

tolerant networks or creating biochemical computing systems where radical-based stochasticity mimics neural adaptability. **Energy efficiency** is a critical factor in cybernetic systems, particularly in robotics, AI hardware, and biochemical modelling. Murburn models provide ways to conceptualize energy flow and utilization in systems with minimal structured constraints. It enables processes like mild uncoupling, where energy dissipation is controlled but not rigidly optimized. Such outlooks may potentially aid simulation or designing of adaptive energy management systems for robotics or biochemical networks that prioritize flexibility over maximal efficiency. Many cybernetic systems aim to replicate or harness **emergent behavior**, where simple local rules lead to complex global patterns (e.g., cellular automata, swarm intelligence). Murburn-driven interactions inherently give rise to emergent outcomes due to their dependence on concentration gradients, reaction kinetics, and environmental factors. Modelling based on murburn theorization for **non-linear dynamical** systems (e.g., ecosystems, metabolic networks, where emergent complexity plays a key role in system behavior) could provide new dimensions. Biological cybernetics also studies systems like neural signalling and metabolism. Immune responses involving DRS could inspire cybernetic designs for adaptive and distributed decision-making systems. As cybernetics increasingly deals with **biology-interfaces** (e.g., biohybrid systems, brain-computer interfaces), murburn offers an avenue to integrate natural stochasticity into artificial systems. In areas involving stochastic control, adaptive responses, and distributed processing, murburn theorization could be particularly relevant. Its emphasis on milieu-driven, probabilistic interactions could inspire new paradigms in the design of resilient, energy-efficient, and adaptable cybernetic systems. While the new perspectives may not replace traditional deterministic models outright, it offers a complementary framework for tackling complexity and unpredictability in dynamic systems. Some of the questions that remain to be answered are: Can murburn processes be mathematically modeled effectively in cybernetic terms (e.g., for simulation or control)? How can murburn-like stochasticity be controlled or utilized in practical cybernetic systems? Can murburn concepts scale from biochemical to macro-level cybernetic designs?

### 3. RELEVANCE OF MURBURN CONCEPT IN CYBORG-BIONICS TECHNOLOGY

One of the most salient applications of cybernetics is in the futuristic domain of cyborgs and bionics wherein achiev-

ing seamless communication between organic tissues and electronic devices is paramount. Murburn-based awareness would help us harness the roles of DROS serving as natural “electronic cum ionic” mediators in this interface (83). By tapping into the inherent reactivity and diffusibility of these species, it could become possible to design systems where biological signals are transduced into electronic outputs and vice versa. For instance, in neural interfaces, futuristic research could facilitate the development of electrodes that interact with neuronal tissues more naturally. By leveraging DROS-mediated pathways, these electrodes might detect neuronal activity with greater sensitivity and transmit signals back to the nervous system more effectively. This approach could lead to more responsive prosthetic limbs or advanced sensory devices that closely mimic natural human functions. Moreover, murburn concept’s emphasis on stochastic interactions aligns with the complex and variable nature of biological systems. Incorporating this understanding into bionic designs can result in devices that adapt to the dynamic environment of the human body, enhancing their functionality and longevity. For example, bioengineered tissues integrated with electronic sensors could monitor physiological changes in real-time, adjusting their responses based on fluctuating levels of DROS, thereby maintaining homeostasis.

The potential applications extend beyond medical devices. In robotics, murburn concept could inform the development of bio-hybrid robots that utilize biological components for energy production or sensory input. By integrating systems that operate on DROS-mediated mechanisms, such robots could achieve higher efficiency and adaptability, closely emulating living organisms. However, the practical implementation of murburn concept in cyborg and bionic technologies is still in its nascent stages. Further research is necessary to elucidate the precise mechanisms by which DROS can be generated and recruited in sustained, controlled and harnessed modalities in artificial systems. As research progresses, this approach holds the potential to revolutionize the design and functionality of prosthetics, neural interfaces, and bio-hybrid robots, bringing us closer to a future where the line between organic and synthetic becomes increasingly blurred. Challenges such as the potential cytotoxicity of DROS and the need for precise regulation within the human body must be addressed to ensure the safety and efficacy of such integrations.

#### 4. ORIGIN OF SENSUALITY AND SEXUALITY IN LIFE SYSTEMS, SOME MURBURN PERSPECTIVES

Sensuality, the ability to perceive and respond to environmental stimuli (with an attribution of positive and negative sensations of “pleasure and pain”), is a relatable and critical/crucial feature of animal life. At the outset, it is conceivable that such a facet most likely evolved as a means of detecting, interpreting and registering external cues with the long-term associated agenda of survival and self-perpetuation. In early life forms, simple redox reactions involving DRS likely facilitated the detection of environmental changes such as radiative or chemical gradients, enabling organisms to move toward favorable conditions (e.g., nutrients, light) or away from harmful stimuli (e.g., toxins). Such electro-mechanical responses to stimuli are best explained with murburn concept, which is compatible with the colloidal nature of cytoplasm (as opposed to the classical ion-pump/channel perception, which deems cellular interior as a dilute solution). The interaction of a photon or chemical could perturb the distribution equilibrium of oxygen-superoxide, setting forth a cascade. Over time, the stochastic but functional nature of DRS-equilibria likely contributed to the evolution of specialized sensory structures (e.g., eyes, with rhodopsin containing DROS generators responding to photon impingement (56)).

Sexuality, life activities encompassing reproductive mechanisms and behaviors thereof, emerged as an evolutionary strategy to ensure genetic diversity and species survival. The primary life forms could have been asexual, and tiding over unfavorable scenarios with spontaneously introduced modalities such as sporulation. When seeking for the “why” rationales in literature, diverse ideas were found that aim to explain the origin and evolution of sexuality: (A) *Red Queen hypothesis* (92) posits that sexual reproduction evolved to allow species to adapt rapidly in response to co-evolving parasites, pathogens, and environmental changes (93). (B) *DNA-repair and mutation-purging hypotheses* suggest that sexual reproduction may have originated as a mechanism for repairing DNA in early organisms and eliminate harmful mutations accumulated in populations. (C) *Gamete specialization and anisogamy* states that sexual reproduction stemmed from the differentiation of gametes (anisogamy), which paved the way for male and female sexes (sexual dimorphism and reproductive specialization). (D) *Energy allocation theory* argues that sexual reproduction evolved as a more energy-efficient means of ensuring reproductive success (quality over quantity in offspring) compared to asexual reproduction. (E) *Sexual*

*selection and other social/behavioral theories* say that sexual reproduction promotes the evolution of traits that enhance reproductive success, even at the cost of individual survival (e.g. highly colored large plumes and some apparently disadvantageous secondary sexual characters), also impacting social and ecological interactions in populations. (F) *Environmental variability hypothesis* attributes the evolution of sexual reproduction as a response to fluctuating environments. In my view, the evolution of sexuality is likely the result of multiple converging factors, some of them being listed above. In this regard, murburn perspective provides a biochemical basis for understanding the “how” aspect of evolution of sexuality as a stochastic and adaptive trait that could have spontaneously resulted. In the prokaryotes, the simple ECS-SCE operation would result in internal production of water due to respiratory/powering activities and the spontaneous outward movement/flux of the same (owing to turgor pressure) via various types of secretory mechanisms (which went on to be aided by various protein assemblies, as seen in the modern day toxin-injectors or motility-aiding flagella or the sexual pili in F<sup>+</sup> strains of *E.coli*) could have also transferred DNA into another similar cell nearby, which could have resulted in genetic recombination of the first kind. DRS could also have aided in cellular differentiation, sexual pheromones/hormones and secondary sexual characteristics thereof, and thereby, production of gametes. The production/secretion of mucopolysaccharides as DRS-sponging/trapping agents in pain-pleasure physiologies (including the ones during copulation in males and females) across the spectra of life-forms is testimony to the statement above. The role of nitric oxide in human sexual physiology has been well-charted in this regard. The interplay of sensuality and sexuality is evident in behaviors that promote reproduction, such as mating displays, courtship, and sensory-driven attraction. The integration of sensory inputs (e.g., visual, auditory, olfactory) with reproductive behaviors could be modulated and connected by DRS in neural and endocrine pathways. For example, DROS-mediated signalling in the brain could enhance the perception of pheromones, linking sensuality to reproductive success.

Murburn concept emphasizes stochastic, transient, and adaptive processes, which align with the trial-and-error nature of evolution. The randomness inherent in DRS mediated processes could afford a mosaic canvas to have driven evolutionary innovation, allowing organisms to explore new traits and adapt to changing environments. The biochemical

simplicity of DRS reactions suggests that murburn processes may have been universal across early life forms, providing a common foundation for the evolution and synergy of complex traits like sensuality and sexuality. The ability of some people to be “turned on” by pain signals is yet another testimony to the involvement of DRS in this context, as this is a two-edged sword. The murburn perspective is anticipated to provide fresh insights into how DROS influence: (1) The development of sensory and reproductive systems across species. (2) The emergence of behaviors linked to attraction and reproduction. (3) The redox mechanisms underlying evolutionary transitions.

From the murburn perspective, sensuality and sexuality likely originated as adaptive features driven by the stochastic dynamics of DRS-mediated processes, as they provided a concrete chemo-electrical connectivity to cause-consequence correlations within the scheme of cellular functioning. By bridging stochastic biochemical signalling with deterministic genetic programming, murburn mechanisms provide a unifying framework for understanding these fundamental aspects of life.

## 5. MURBURN CONCEPT IN IMMUNOLOGY AND IMMUNOCHEMISTRY

Immunology deals with the physiology of differentiation and defence of self (one’s own cells) from non-self (alien) or unwanted cells/elements. Murburn-mediated processes, such as the production of ROS/RNS in phagocytes, achieve pathogen destruction without relying on specific molecular targeting. The radical intermediates are inherently destructive to accessible macromolecules. My group’s works have recently confirmed via other articles published in BMR that cyclooxygenase (a heme-protein and the birthing mother of pain-hormones), the fundamental aide for recruiting immunological response, is a murzyme (52, 84). A fresh ‘murburn’ perspective on how immune responses can be understood and modulated is provided here.

**Vaccine development and immune activation:** DROS has been acknowledged as a key player in the development and manifestation of immunity (94-104). Aluminum-based adjuvants (e.g., alum) enhance immune responses by inducing local inflammation and promoting antigen uptake by dendritic cells. DROS could play a role in this process by generating localized oxidative stress that helps activate immune cells. DROS-mediated signalling is known to enhance the expression of cytokines and chemokines, critical for recruiting im-

immune cells to the site of antigen presentation. The oxidative burst is a well-established phenomenon observed during immune responses, stimulating the production of pro-inflammatory cytokines and chemokines, which are crucial for recruiting immune cells to the site of antigen presentation. These signalling molecules help amplify the immunogenicity of vaccines by creating a localized inflammatory environment conducive to immune activation. DROS might also contribute to the degradation of antigens into peptides suitable for presentation on major histocompatibility complex (MHC) molecules, a key step in initiating adaptive immunity. Aluminum ions have been shown to activate the inflammasome (such as NLRP3) pathway, leading to interleukin-1 $\beta$  production. Their presence could aid the production of DROS in antigen-presenting cells (APCs) and also could amplify their effects thereof by further triggering redox-sensitive transcription factors like NF- $\kappa$ B, promoting the inflammatory response. DROS can also influence B-cell activation and antibody production by modulating signalling cascades in lymphocytes. Understanding the interplay between adjuvants, DROS, and murburn concept could guide the development of safer and more effective vaccines. Optimizing DROS generation might help fine-tune immune activation while minimizing oxidative stress-related side effects. This perspective also opens up avenues for designing novel adjuvants inspired by controlled DROS dynamics.

**Non-specific redox-active antibodies/immunoglobulins:** Antibodies, or immunoglobulins, are specialized proteins produced by the immune system to identify and neutralize foreign pathogens. Traditionally, antibodies are understood to operate through topology-based specific interactions with antigens (following the lock & key type of transition state complex formation in classical enzyme mechanism), leading to confinement and denaturation/deactivation of the alien element. Since the late 1980s, some antibodies are known or engineered to have catalytic functions and they are called as abzymes. In recent years, the discovery of non-specific redox-active antibodies (herewith called ab-murzymes) has expanded the functional repertoire of these proteins. Ab-murzymes can catalyze redox reactions even in the absence of specific antigens, suggesting roles beyond conventional adaptive immunity (Figure 3).

Some antibodies exhibit intrinsic redox activity by modulating DROS dynamics or facilitating electron transfer reactions. These peroxidase/oxidase and oxidoreductase (even cytochrome P450 like!) activities, including the ability to

generate or neutralize reactive oxygen species (ROS) and catalyze reactions such as superoxide dismutation, peroxidation, oxygen atom insertion, and electron transfer (105-124). This activity is typically mediated by amino acid residues in the antibody's variable region (such as histidine, arginine or cysteine) and occasionally via chelated transition metal ions or even Se atom, which can act as reactive centres. Unlike traditional antibodies, which bind specific epitopes, redox-active antibodies could function in a non-specific manner, interacting with a range of molecular targets. This non-specificity aligns with the physicochemical nature of murburn redox or moiety-transfer/alteration reactions, which are not solely dependent on precise molecular recognition but rather on chemical attributes (such as redox potential). These relevance of ab-murzymes could justify the natural mandate inherent in response to immunological scenarios, which could fall under several contexts: (1) Pathogen neutralization: Redox-active antibodies may participate in innate-like immune responses, generating ROS to damage or neutralize pathogens dependent or independent of antigen specificity; their catalytic properties supplement traditional antibody-mediated functions, such as opsonization and antigen neutralization. (2) Tissue homeostasis: These antibodies may regulate redox balance within tissues, protecting against oxidative damage or modulating inflammatory responses. These antibodies may act as scavengers of excess ROS (quite akin to catalase or superoxide dismutase), protecting tissues from oxidative damage. (3) Autoimmune associations: Redox-active antibodies are often found in autoimmune conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (125). Their non-specific activity might contribute to tissue damage and chronic inflammation in these contexts. (4) Cancer: In tumor microenvironments, redox-active antibodies could influence oxidative stress, potentially impacting cancer progression or therapy resistance.

The awareness above could lead to new - (A) Therapeutics: Leveraging redox-active antibodies could lead to therapies that exploit their catalytic properties, such as ROS generation to target cancer cells. They could also be used as models to design synthetic catalytic antibodies or biomimetic materials. In diseases characterized by redox imbalances, such as neurodegenerative conditions, redox-active antibodies might serve as therapeutic modulators. Engineering antibodies with tailored redox properties could amplify their catalytic efficiency and specificity. (B) Diagnostics: The presence of redox-active antibodies in serum can serve as a biomarker for

certain pathological conditions, such as autoimmune diseases or chronic inflammation. Also, the redox activity of antibodies might be harnessed in biosensors to detect specific redox-active compounds or oxidative stress markers.

## 6. NITROGEN-FIXATION

Atmospheric biological nitrogen fixation (BNF) by symbiotic (*Rhizobium*, *Frankia*), free-living (*Azotobacter*, *Clostridium*, *Cyanobacteria*), associative (*Azospirillum*, *Herbaspirillum*), endophytic (*Gluconacetobacter*), and phototrophic (*Anabaena*, *Nostoc*) bacteria is a requirement for sustaining life forms and their ecosystems on our planet, as nitrogen is an

essential component of the most fundamental biomolecules. Essentially, it refers to the conversion of molecular nitrogen to ammonia using ATP, via the balanced equation:  $\text{N}_2 + 8\text{H}^+ + 8\text{e}^- + 16\text{ADPOP} \rightarrow 2\text{NH}_3 + \text{H}_2 + 16\text{ADPOH} + 16\text{POH}$  (where ADPOP, ADPOH and POH stand for ATP, ADP and inorganic phosphate, respectively). [It is known that- (i) atmospheric nitrogen can be converted abiotically by lightning into nitrogen-oxygen based ions like nitrate, (ii) ammonia can be oxidized to nitrite/nitrate biologically, and (iii) nitrites/nitrates from soil can be reduced to ammonium ion by their corresponding reductases which contain transition metal (like Cu/Mo/Fe) or flavin containing enzymes. However, such

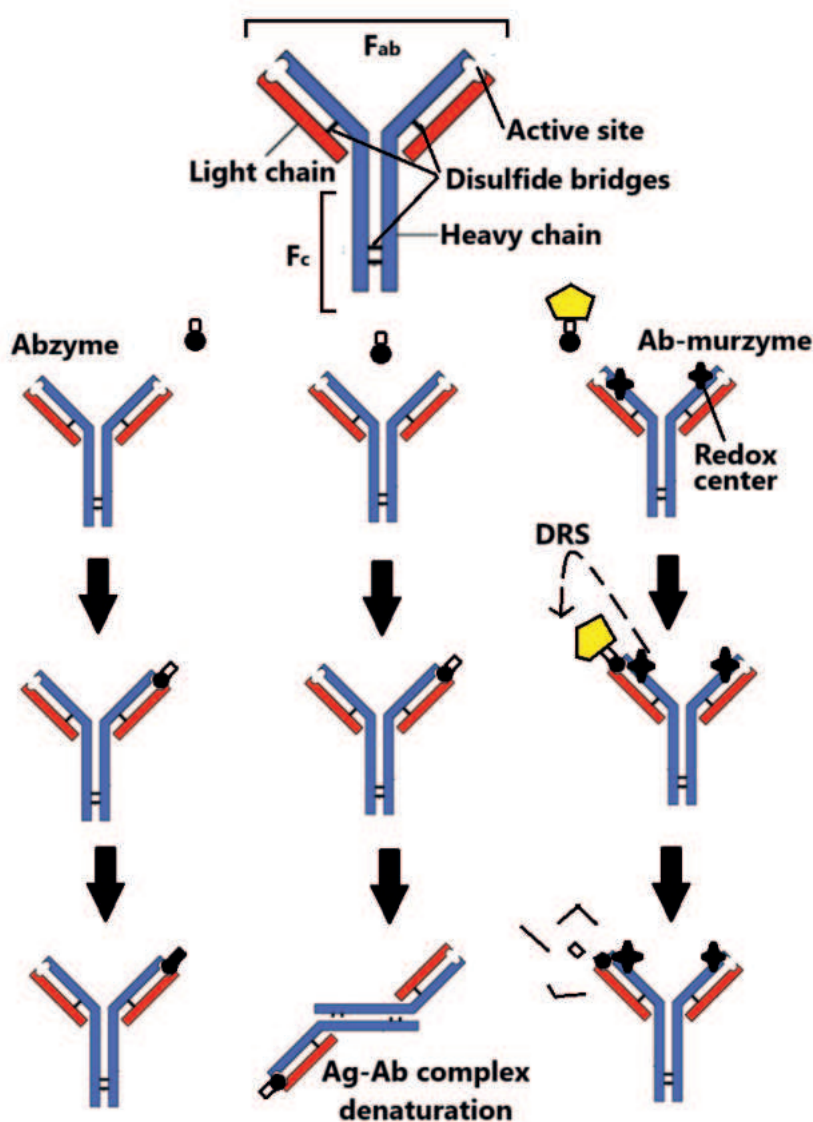


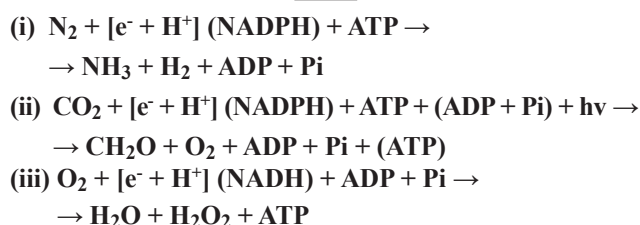
**Figure 3:** The functioning-schematic of normal antibodies (middle), abzymes (left) and ab-murzymes (right) is depicted.

processes are not the context of discussion here.] It is evident that the bioenergetic systems (demonstrated to work along murburn concept) of photosynthesis/respiration have several fundamental similarities with nitrogen fixation machinery, along the following summarized rationale:

*A. Structural aspects:* Evolutionarily conserved multi-component redox protein complexes evolved for ECS and electron transfer are present in both systems. Transition element (*d* block) metal centers (Fe/MoFe) in nitrogen-fixing nodules are similar to their equivalent counterparts (Fe/Cu or Fe/Mn) found in the mitochondrial systems (wherein the latter two systems are demonstrated to work via murburn principles). Further, prosthetic groups like the iron-sulfur clusters ([Fe-S]) or flavodoxin (containing flavin mononucleotide) that could serve as the reservoir of electrons for the reduction of nitrogen to DRNS (finally to ammonia) are also found to be similarly coordinated to the ones in NADH oxidoreductase (Complex I) used for the reduction of oxygen to DROS (finally to water).

*B. Functional aspects:* Both the bioenergetic systems and nitrogen-metabolism machinery, either directly or indirectly, deal with the “fixation” or redox reaction of gaseous reactants ( $\text{CO}_2/\text{O}_2$  and  $\text{N}_2$ ) with water’s dissociated product of protons. Both nitrogenase and bioenergetic complexes are involved in the uphill processes of nitrogen-fixing and ATP-synthesis, respectively. Both systems exhibit sensitivity to oxygen (albeit the effects are different!). Therefore, it is quite likely that they evolved from the same ancestral redox proteins involved in energy metabolism in primitive anaerobic environments. The DRS-involving conversion schemes shown in Box 1 (the equations are unbalanced, with water not shown on either side; and with only the minimal components represented!) of (i) nitrogen, (ii)  $\text{CO}_2$ , and (iii) oxygen reduction could potentially enable the transition to oxidative phosphorylation processes from such earlier types of anaerobic gas fixation/evolving mechanisms, as shown in scheme (ii).

#### Box 1



Therefore, a murburn model could potentially hold relevance for explaining the phenomenon of nitrogen-fixation premise also (particularly, considering the mandate that

has arisen under the premise that ion-pumping and affinity binding-based explanations in the bioenergetic systems have been proven to be untenable), and explain the survivability of diazotrophic species in diverse environments. Another fact is that DRNS are observed in nitrogen-fixation systems argue/evidence for the murburn model’s relevance in this system. Furthermore, we have also demonstrated that mobile proteins like cytochromes *c/b<sub>5</sub>* and ferredoxin are not specific electron relay agents but generic electron-sponges. Flavodoxins are known to be not only involved in nitrogen reduction, but also in nitrate/nitrite reduction. This is a fact which clearly argues for the non-specific murburn nature of the e-transfer mechanism. The ECS-DRS based murburn model for nitrogen-fixation is a far simpler and facile (thermodynamically, kinetically and mechanistically) model than the active-site centred affinity-based model for  $\text{N}_2$ -fixation. (Quite simply, molecular nitrogen would have little affinity for anything!) The new proposal needs to be empirically validated with more data and explorations. But for now, it surely helps explain the involvement of diffusible reactive species in nitrogenase activity (along the parallels in the bioenergetic routines).

## 7. MISCELLANEOUS FORESEEABLE APPLICATIONS OF MURBURN CONCEPT

The following appear to present scope for murburn-based explorations and applications in the future (some were suggested by ChatGPT!), from biological sciences to medicine to environmental engineering, cybernetics, and energy systems. It opines that future applications could transform how we approach problems in sustainability, and technology by embracing flexibility, robustness, and adaptability inherent in stochastic, milieu-driven processes.

**A. General metabolism, physiology, cell science, medicine and pharmacology:** Electron transfers in diverse physiologies would now need to be re-interpreted within the murburn scheme. Diseases like Alzheimer’s, Parkinson’s, and ALS involve disrupted mitochondrial function. Murburn models could provide insights into how DROS-driven pathways exacerbate or mitigate disease progression. Therapeutics targeting metabolic diseases like diabetes or neurodegeneration, where ROS play a role could be better understood with the advancement of awareness on murburn concept. ROS dynamics in neural signalling might better align with murburn principles, offering insights into synaptic activity and disorders like epilepsy or depression. Developing treatments for neuro-psychological disorders (e.g., depression, epilepsy) could be pursued by

modulating ROS-mediated pathways. The role of DROS in iodination and thyroid hormone synthesis remains poorly understood and could benefit from the murburn perspective. Exploring DROS-mediated signalling in stem cell differentiation, proliferation, and maintenance could improve regenerative therapies. Investigating how DROS influence microbial energy production and host-microbe signalling within the gastrointestinal tract could provide insights into inflammatory bowel disease, gut-brain axis interactions, nutrient absorption, and how pathogens and host cells leverage or counteract DROS during infections. With respect to the role of low-intensity DROS flux in cellular senescence or adaptive stress responses, the murburn framework might redefine theories of aging; and help contain oxidative damage while maintaining constructive signalling and catalytic physiology. Immune cells like neutrophils utilize DROS/DRNS for pathogen destruction and this fact could be exploited for designing drugs to modulate immune responses (e.g., in autoimmune diseases or chronic inflammation). Murburn reactions influence drug activation or degradation could refine pharmacokinetics and reduce side effects. Designing more predictable drug metabolism models that can accommodate and explain idiosyncracies, hormesis, and drug-drug interactions could be feasible. Development of drugs leveraging murburn-mediated pathways for controlled activation could be an avenue to explore, as well as designing therapies that either promote or inhibit murburn-mediated ROS production. Understanding DROS dynamics during oxygen fluctuations in cardiac and pulmonary tissues could aid in understanding endothelial oxidative stress and its role in atherosclerosis, managing heart attacks, strokes, and COPD. Also, engineers could find new ways to actively track DRS dynamics via various online methodologies, which could provide new avenues for diagnostics-aided therapy. Targeted ROS delivery or in situ generation for cancer treatment could be explored via oxidative stress induction in tumors, without harming normal cells. Murburn could help explain tumor metabolic plasticity, with respect to supporting or disrupting cancer growth. We could avail clarity on oxidative bursts during infections, allergies or chronic inflammations. Murburn concept could aid in developing biosensors for detecting pollutants or biomarkers. Most importantly, several observations/ideas and practices in parallel medicine (Chinese medicine, Accu-pressure/puncture, Ayurveda, Homeopathy, etc.) are currently sidetracked by the mainstream bio-medical researchers because such approaches don't seem to make apparent sense. They should be investigated in the context of a new bio-energetics in which murburn

primary energization, the colloid aspect of cells/tissues and their electromagnetic field are the main pillars. For example: (i) Curing of some symptoms with electrical cues (grounding the feet, for example!) has clinical evidence. (ii) The stabilization of epileptic seizures with the patient clutching on to iron is something the classical bio-medicine paradigm totally disregards. (iii) Some food items are deemed "hot" (capable of generating heat in the body) in several systems/cultures and there could be rationale for the same. (iv) Some drugs are more effective when dilute (which is not a support of homeopathic theories!). (v) Discomfort or issues at one part of the body may be addressed by "needling" or pressuring a suitable point.

**B. Engineering metabolic pathways for bioengineering or synthetic biology** could be envisaged by incorporating murburn principles into systems biology simulations for complex networks. Guided oxygen supply and understanding oxygen diffusion and metabolic energetic balance during organoid or tissue growth may enhance engineering protocols. Improving yields in fermentation or synthetic biology through controlled radical processes could be attempted. Engineering crops with optimized ROS-mediated resistance pathways is yet another angle. Developing energy-efficient nitrogen fixation technologies could be a target for sustainable agriculture. Designing fertilizers or soil treatments that exploit murburn-like radical reactions is another angle that could be pursued.

**C. Designing eco-friendly** water purification systems using murburn principles for oxidation of contaminants and advancing models of energy dissipation and entropy production in systems and advancing better models of energy dissipation and entropy production in biological and physical systems are yet other avenues for tapping the new insights. Development of self-regulating cybernetic systems mimicking murburn processes could be attempted.

**D. Environmental aspects:** Murburn insights could help understand how environmental toxins induce oxidative damage in biological systems. Low-cost renewable energy production and pollutant recycling could be made possible. Murburn-inspired mechanisms could be harnessed in enzyme-driven industrial applications or biofuel production and afford green chemistry routes for arriving at molecular synths.

**E. Philosophical and evolutionary questions:** Research into prebiotic chemistry and the origins of life with murburn perspective is warranted now. Explaining how primitive systems transitioned to structured cellular and tissue-organ-organ-

ism-level swarm processes could be attempted with murburn. Murburn concept also poses immense philosophical context, given that it is the very life-giving elixir that also takes life!

## 8. A SUMMARY OF THE FIRST SYMPOSIUM ON MURBURN CONCEPT

In the last week of May, the first international 3-day symposium was held at Amrita University's Coimbatore campus (<https://www.amrita.edu/events/three-day-symposium-on-how-do-cells-work-as-simple-chemical-engines>), with the patronage of the leadership of the institution, particularly Prof. K. P. Soman (Dean, School of Artificial Intelligence). About a hundred participants registered and attended in person, from the academic-industry spectrum of India. The event was inaugurated by Prof. George Chaldakov (Bulgarian Society for Cell Biology), with a keynote lecture (<https://www.youtube.com/watch?v=XaBaXrIEras>; <https://www.youtube.com/@satyamjayatu5613/videos>). Then, Prof. Laurent Jaeken (Karel de Grote Hogeschool, Belgium) and Prof. K. B. Venkatesh (IIT Bombay) delivered plenary lectures on the importance of murburn concept and cellular metabolic networks, respectively. Speakers (beside the above and KMM) elaborating on the metabolic/physiological and other aspects included: Dr. Daniel Andrew Gideon (St. Joseph's University, Bengaluru), Dr. Abhinav Parashar (CHARUSAT, Gujarat), and Dr. Surjith Ramasamy (Zero Cow Factory, Gujarat). Dr. Aravind Ranade, Director of National Science Foundation, Govt. of India, served as the Chief Functionary of the closing function (<https://www.youtube.com/watch?v=AaB2IIsmEvk>). He appreciated our group's (Amrit Subramanian, Pathange Omkareshwara Rao, Vinith Rejathalal) initiative in creating a web-based platform (<https://shark-app-tly4j.ondigitalocean.app/>) for the dissemination of information on murburn concept and providing an AI (artificial intelligence)-based query interface for parsing of proteins into classical catalysts and murzymes (for which the code base link is available at: <https://shark-app-tly4j.ondigitalocean.app/>). The sessions centred around the following types of holistic or specific questions:

1. Are all life-sustaining mechanisms purely deterministic? If so, why do living cells ultimately die?
2. How does a cell function at acute time scales, wherein genetic regulations are too slow to respond?
3. How are life forms powered, when most classical enzyme-catalyzed reactions have low yields?
4. How can two genetically identical living beings manifest different functional behaviour?

5. How could cyanobacteria carry out both respiration and photosynthesis, which are anti-parallel?

6. How could cyanide kill at such a low dosage at such short timescales?

7. Can there be a theory that could help us understand some "parallel medicine" ideas?

8. Can a theory better explain how diverse non-physiological drug molecules are metabolized?

9. How could erythrocytes function viably for 3-4 months, although lacking nucleus and mitochondria?

10. How could we explain a higher effectiveness of a lower concentration of drug?

11. How can we explain photosynthesis with the random-distribution of pigments in chloroplasts?

12. How can we prolong a healthy lifespan with new insights on life's origin, sustenance & evolution?

13. Can there be a better molecular/physical basis for explaining motility than mere changing of protein conformation-based explanations?

14. Does water have a greater role to play in cellular physiology than what cell biologists currently attribute it?

To address or answer the questions above (with the known yardsticks of thermodynamics, kinetics, reaction mechanism, probability-evolvability, structure-distribution-function correlations of molecules, etc.), it was argued that we need to go beyond highly recognized "theories" advocated in textbooks! (This statement does not mean that all of the following are misplaced. It merely implies that while some are redundant, murburn concept complements some earlier ideas, like the case of the celebrated Fischer's lock and key model or Marcus's outer sphere e-transfer theory.)

1. Emil Fischer (1902): Enzymes work by binding their substrates at a definite/unique 'active site' via lock-key model

2. Otto Warburg (~1920): Enzyme-catalyzed reactions are reversible and isozymes can work in different directions (e.g. as assumed for lactate dehydrogenase in prevailing scenarios)

3. Archibald Hill (1930): Cytoplasm is a dilute aqueous solution (and not colloid/coacervate!)

4. David Keilin (~1930): (a) Electron transport chain (dedicated protein and small molecule e-carriers and pit-stops, somewhat akin to a printed electronic circuit!) exists in mitochondria (b) cyanide toxicity results due to binding of the ion to the heme of cytochrome oxidase in mitochondria

5. Robert Dean (1941): Membrane proteins pump ions

6. D Harman & R Gerschman (~1950): One-electron ac-

tive oxygen-centred reactive species are wasteful/toxic metabolic products

7. Robert Emerson & William Arnold (1957): Z-scheme model of photosynthesis

8. J-P Wollman & P Joliot (1960s): Excitons are relayed from light harvesting complexes to photosystem reaction centers

9. Alan Hodgkin & Andrew Huxley (1963, Physiology): Neuronal impulse transmission occurs via trans-membrane ion-fluxes occurring through membrane protein channels

10. Ragnar Granit, Haldan Hartline & George Wald (1967, Physiology): Phototransduction occurs at rods/cones concomitant with geometrical transition of retinal (harbored in rhodopsin)

11. IC Gunzalus, JD Lipscomb, SG Sligar (1970s): P450cam mechanism for xenobiotic metabolism in liver (multi-molecular complexations sans definitive logic or evidence for affinity)

12. B Kok & P Joliot (1970s): Kok-Joliot water-photolysis model at Photosystem II

13. Howard Berg (1970s): Rotary flagellar motor as an explanation for bacterial mobility

14. Peter Mitchell (1978, Chemistry): (a) ET-coupled proton pumps lead to Chemiosmosis (trans-membrane chemoelectrical potential or proton motive force), which makes ATP, (b) proton-shuttlers (like fatty acids) uncouple ATP-synthesis, leading to thermogenesis

15. Erwin Neher & Bert Sakmann (1991, Physiology): Method to study single ion channels

16. Rudolph Marcus (1992, Chemistry): Application of outer-sphere inter-protein ET in redox enzymes

17. Paul Boyer (1997, Chemistry): Complex V (a naturally in vitro ATPase) channelizes protons for becoming rotary ATP-synthase in physiology

18. Jens Skou (1997, Chemistry): Electrogenic Na/K ion pumping explains ionic gradients in cells

19. Roderick MacKinnon (2003, Chemistry): Proteins facilitate cation fluxes at high-throughput rates

20. Metabolic reactions occur in well-defined integral stoichiometry (ratios of substrates and products) and the free energy yields lie near the midpoint equilibrium ( $\Delta G \approx 0$ ), capable of swinging both ways!

A visual demonstration of peroxidases functioning as murzymes was posted on YouTube as a follow-through exercise of the Symposium (<https://www.youtube.com/watch?v=9lShNfdlletg> <https://www.youtube.com/watch?v=m9VqMA553Xo>).

## 9. RECOGNITION AND ACCEPTANCE OF MURBURN CONCEPT AND THE WAY FORWARD

A small share of social recognition was received with invitation for plenary lecture titled “Murburn concept: a paradigm shift in biomedical science/technology” at Swadeshi Science Congress (CIFT, Cochin, Nov. 2024; <https://www.youtube.com/watch?v=SPprshMUfbs>) and invited lecture at the International School of Photonics (CUSAT, Cochin, Aug. 2024; <https://www.youtube.com/watch?v=MEw0gypern4>) highlighting murburn models for photosynthesis and photoreception (vision). Some media attention also came by, with a newspaper coverage in a science article featured at *Gujarat Samachar* (<https://www.gujaratsamachar.com/news/ravi-purti/ravi-purti-03-march-2024-k-r-choudhury-future-science>) and an interview on the auspices of *Science Talks* (Asianet), a south Indian YouTube/TV channel (<https://www.youtube.com/watch?v=LNhknsG15iI>).

I started this article by addressing the “artificial intelligence” perspectives on murburn concept. I end it with the same. Below are some of the issues and solutions that ChatGPT opined regarding the current social stature (low awareness and spread) of murburn concept.

**A. Paradigm inertia:** Established models such as “lock-and-key” enzymology and structured metabolic pathways dominate teaching and research, making it difficult for stochastic, milieu-dependent concepts like murburn to gain traction. Concepts like “lock-and-key” enzyme mechanisms and highly structured reaction pathways are well-evidenced. Murburn’s stochastic and milieu-driven perspective challenges these rigid frameworks, making it harder for scientists to accept a paradigm shift.

**B. Limited awareness in the scientific community:** Murburn concept is relatively not yet widely recognized across disciplines. Many researchers might not even be aware of it, let alone in a position to evaluate or critique it. In scientific culture, it is common for new ideas to be ignored (until it gets mentioned in ivy-league journals like *Nature*, *Cell*, *Science*, *PNAS*, etc.!) rather than actively opposed unless they directly contradict a widely held and proven model.

**C. Experimental design bias and misinterpretation of results:** Many experiments are tailored to confirm classical models, potentially overlooking or masking stochastic, unstructured dynamics predicted by murburn. Observations supporting murburn are often rationalized within existing frameworks (e.g., as anomalies or artifacts) rather than being

seen as evidence for a new paradigm. Observations such as ROS involvement in cellular processes or deviations from classical kinetics are often rationalized as “exceptions” or “artifacts” rather than evidence for a new framework. If murburn is viewed as explanatory rather than predictive, researchers may see it as supplementary, not confrontational. Validation and reproduction are difficult for chaos-based mechanisms, such as murburn.

**D. Communication and framing challenges:** Murburn concept (with terminologies like “stochastic” or “unstructured” or “simple chemical engine”) may be perceived as too radical or poorly integrated with existing knowledge, leading to skepticism. Murburn straddles multiple fields—chemistry, biology, biophysics—which can make it hard to place within a single discipline.

**E. Sociological and institutional resistance:** The scientific community often favors established theories and influential researchers. Concepts originating from less-prominent institutions or individuals may face greater scrutiny or dismissal. Lack of debate in peer-reviewed publications is yet another reasons that the community’s leaderships continue to stick on to inertial pursuits.

To overcome these challenges and unlock its full potential, ChatGPT proposes several strategies:

1. High-impact publications: Publish findings in prominent journals and focus on areas where murburn provides unique explanatory power.
2. Interdisciplinary collaboration: Engage researchers from systems biology, biophysics, and computational modelling to validate and extend the concept.
3. More experimental validation: Create specific experiments testing murburn predictions and use advanced tools (e.g., imaging or simulations) to observe stochastic dynamics in real-time.
4. Integration with existing models: Frame murburn as a complementary framework rather than a wholesale replacement for classical theories.
5. Public engagement: Increase visibility through conferences, workshops, and science communication to build broader awareness.

With respect to the above, my group remains open for any/all such possibilities and with this article, we earnestly and humbly seek global cooperation for the advancement of insightful research on cellular physiology, particularly with the application of murburn concept! However long the colleagues in diverse areas may choose to shun murburn concept, AI has

become a major level-playing force to reckon; as seen when queried to elaborate and compare the intelligence of inanimate and biological systems (Figure 4; edited and presented in Table 1).

I rest with the optimism/hope that such data/ideas can be globally availed using proper prompts with AI now, for those that really care about advancement of science and biomedical awareness.

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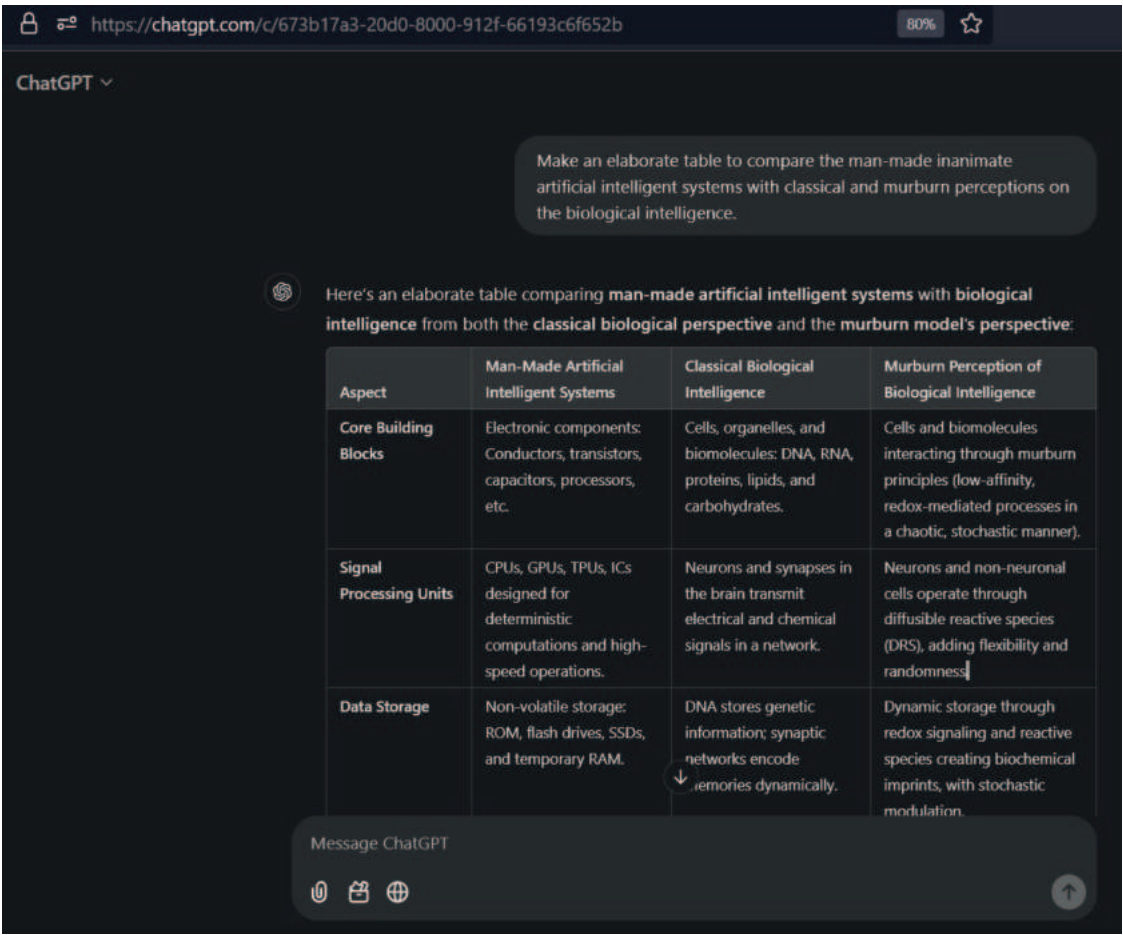


Figure 4. Screenshot of a query posed to ChatGPT on artificial and biological intelligence.

Table 1. A slightly edited version of ChatGPT's comparison of AI systems and classical and murburn perspectives on biological intelligence. It can be seen that the stochastic/acute facets of murburn complements and supplements the central dogma's deterministic/chronic control.

| Aspect                  | Man-Made Artificial Intelligent Systems                                                  | Classical Biological Intelligence                                                                                                                   | Murburn Perception of Biological Intelligence                                                                                                                 |
|-------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core Building Blocks    | Ordered electronic components: conductors, transistors, capacitors, processors, etc.     | Cells with organelles, and biomolecules: DNA, RNA, proteins, lipids, and carbohydrates. Proteins interact with diverse components via high affinity | Cellular molecules and ions interacting through redox equilibriums (low-affinity, in a chaotic, stochastic manner).                                           |
| Signal Processing Units | CPUs, GPUs, TPUs, ICs designed for deterministic computations and high-speed operations. | Neurons and synapses in the brain transmit electrical and chemical signals in a network.                                                            | Neurons and non-neuronal cells operate through effective charge separation (ECS) and diffusible reactive species (DRS), providing flexibility and plasticity. |
| Data Storage            | Non-volatile storage: ROM, flash drives, SSDs, and temporary RAM.                        | DNA stores genetic information; synaptic networks encode memories dynamically.                                                                      | Dynamic storage through redox signaling and reactive species creating biochemical imprints, with stochastic modulation.                                       |
| Energy Source           | Electricity from external power sources (batteries, power grids).                        | Biochemical energy: ATP generated by cellular respiration; proton-pumping and proton-gradient (pmf).                                                | ECS-DRS generate delocalized electro-motive force (emf).                                                                                                      |

| Aspect                             | Man-Made Artificial Intelligent Systems                                                                     | Classical Biological Intelligence                                                             | Murburn Perception of Biological Intelligence                                                                                  |
|------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <b>Energy Efficiency</b>           | Typically lower efficiency due to resistive losses and heat dissipation.                                    | Highly efficient, with near-optimal ATP generation per glucose molecule.                      | Moderately efficient but considers DRS as essential functional intermediates, not wastes.                                      |
| <b>Nature of Reactions</b>         | Deterministic and sequential processes, governed by algorithms and logic gates.                             | Enzyme-mediated highly specific, lock-and-key or induced fit interactions.                    | Low-affinity, probabilistic, redox-mediated reactions allow flexibility and adaptation.                                        |
| <b>Adaptability</b>                | Limited adaptability, requiring human intervention or pre-trained algorithms for updates and modifications. | Highly adaptable through natural selection and neuroplasticity.                               | Adaptability stems from stochastic biochemical processes and principles, enabling dynamic reactivity.                          |
| <b>Decision-Making Process</b>     | Pre-programmed algorithms based on input data; no true autonomy or consciousness.                           | Neural circuits dynamically integrate sensory input and past experiences to make decisions.   | Stochastic murburn signaling allows cells and systems to respond dynamically to stimuli in a probabilistic manner.             |
| <b>Fault Tolerance</b>             | Limited; redundancy in systems can mitigate some failures (e.g., RAID storage).                             | Robust fault tolerance via redundant pathways, feedback loops, and repair mechanisms.         | Enhanced robustness due to diffuse, overlapping roles of reactive species and redox equilibria in managing failures.           |
| <b>Communication</b>               | Binary signals (0 and 1), transmitted via electrical and optical signals in circuits or networks.           | Chemical and electrical signaling between cells, e.g., neurotransmitters, hormones, ions.     | Communication largely governed by DRS signaling and energy redistribution across cellular and systemic levels.                 |
| <b>Creation of New Structures</b>  | Requires external programming, manufacturing, or assembly by humans.                                        | Cells self-replicate via mitosis and meiosis, with information encoded in DNA.                | Redox states and murburn dynamics enable adaptive synthesis and spontaneous organization in response to environmental cues.    |
| <b>Self-Maintenance</b>            | Requires human maintenance, such as replacing parts or recharging batteries.                                | Homeostasis through feedback systems like insulin regulation and thermoregulation.            | Murburn mechanisms enable homeostasis through chaotic yet regulated DRS dynamics and energy redistribution.                    |
| <b>Scalability</b>                 | Physical constraints limit scalability; requires modular components for large systems.                      | Scales naturally with organismal size and complexity, e.g., neural networks in larger brains. | Murburn processes enable scaling by leveraging diffusible intermediates for energy and signaling over large systems.           |
| <b>Evolution Over Time</b>         | Upgrades depend on human innovation; obsolescence is common.                                                | Natural evolution through genetic mutations and environmental selection pressures.            | Evolution enhanced by stochastic signaling and murburn precepts, allowing non-linear adaptability over generations.            |
| <b>Error Correction Mechanisms</b> | Parity checks, error correction codes, or manual troubleshooting.                                           | DNA repair enzymes, immune responses, and neuroplasticity.                                    | Stochastic, redox-based adjustments that prevent overaccumulation of errors or oxidative stress.                               |
| <b>Speed of Operations</b>         | High computational speed (nanoseconds), limited by hardware constraints.                                    | Slower processes due to biochemical reaction rates and signal propagation.                    | Moderate speeds due to diffusible intermediates balancing flexibility and time scales.                                         |
| <b>Functionality in Chaos</b>      | Cannot function well in chaotic or unpredictable environments without robust programming.                   | Biological systems thrive in chaotic environments through adaptability and redundancy.        | Murburn systems excel in chaotic settings, using randomness and chaos as a functional advantage.                               |
| <b>Creation of Complexity</b>      | Built layer-by-layer through programming and physical assembly.                                             | Complexity arises through gene regulation, epigenetics, and environmental interactions.       | Complexity is a natural emergent property of stochastic redox systems and murburn mechanisms.                                  |
| <b>Consciousness or Awareness</b>  | No true awareness; operates solely based on input-output processes.                                         | Consciousness is a resident property of highly interconnected protein and neural networks.    | Consciousness is an emergent property owing to electron-exchange, and interactions of molecules, ions and radicals/radiations. |
| <b>Examples of Systems</b>         | Computers, robots, AI models, IoT devices, autonomous vehicles.                                             | Nervous systems, brains, immune systems, and multi-cellular organisms.                        | Overall acute PCHEMS of all cells.                                                                                             |

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